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Synthesis of macrocyclic precursors of lankacidins using Stille reactions of 4-(2-iodo-alkenyl)azetidinones and related compounds for ring closure

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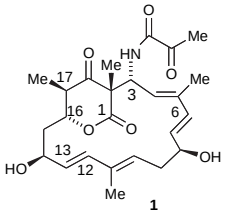
ABSTRACT

In the context of a proposed total synthesis of lankacidins, the synthesis of 4-(2-iodo-alkenyl)azetidinones and their participation in Stille coupling reactions have been investigated. 1-*tert*-Butyldimethylsilyl-4-(2-iodoethenyl)azetidinone was found to undergo a Stille coupling reaction with a 3-hydroxy-1-tributylstannylhepta-1,5-diene to give an acceptable yield of the corresponding conjugated diene but the analogous reaction with a 3-*tert*-butyldimethylsilyloxy-1-tributylstannylhepta-1,5-diene was unsuccessful. A series of 4-[(*E*)-2-iodoprop-1-enyl]azetidinones, a ring-opened ester and a lactone were also found to undergo Stille reactions with 3-tributylstannylprop-2-enol albeit with variable yields. Asymmetric syntheses of methyl (2*R*,3*R*,5*S*)-3-*tert*-butyldimethylsilyloxy-2-methyl-5-(2-trimethylsilylethoxy)methoxy-6-oxohexanoate, (3*R*,4*S*)-1-*tert*-butyldimethylsilyl-4-[(*E*)-2-iodoprop-1-enyl]-3-methylazetidin-2-one, and (5*S*,2*E*,6*E*)-5-*tert*-butyldimethylsilyloxy-2-methyl-1-phenylsulfonyl-7-tributylstannylhepta-2,6-diene and their incorporation into macrocyclic precursors of the lankacidins were then investigated. Key reactions were a Julia reaction between the aldehyde and the sulfone to form the 12,13-double-bond, a stereoselective acylation of the azetidinone, and formation of macrocycles using intramolecular Stille reactions in the presence of a free hydroxyl group at C(8) (lankacidin numbering).

1. Introduction

The lankacidins are a small group of macrocyclic natural products, which display antibiotic activity against Gram-positive bacteria.[1] They have also been found to enhance the survival times of mice with leukemia and solid tumours.[2] The structures of the lankacidins are unusual in that they have a 17-membered carbocyclic ring with a carbonyloxy bridge forming a six-membered lactone, see lankacidin C (**1**). A type of Favorskii reaction is believed to be involved in their biosynthesis.[3]



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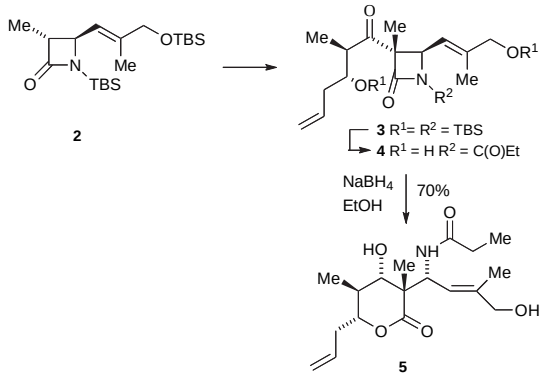
The lankacidins have interested synthetic organic chemists because of their unusual structures and biological activities.[4–7] An approach to the δ-lactone containing fragment, studied independently by Kende and ourselves, was based on the stereoselective acylation of an azetidinone followed by a ring-opening rearrangement of the acylated azetidinone with formation of a δ-lactone.[4,5] For example, acylation of azetidinone **2** gave the 3,3-disubstituted azetidinone **3**, which was taken through to the lactone **5** by reductive rearrangement of the *N*-acylazetidinone **4** using sodium borohydride see Scheme 1.[5] Lactone **5** corresponds to the C16–C6 fragment of lankacidin C (**1**) and has the required configuration at its stereogenic centres including the quaternary centre corresponding to C2 of the lankacidins. Using this approach, Kende completed a formal synthesis of lankacidin C (**1**).[4]



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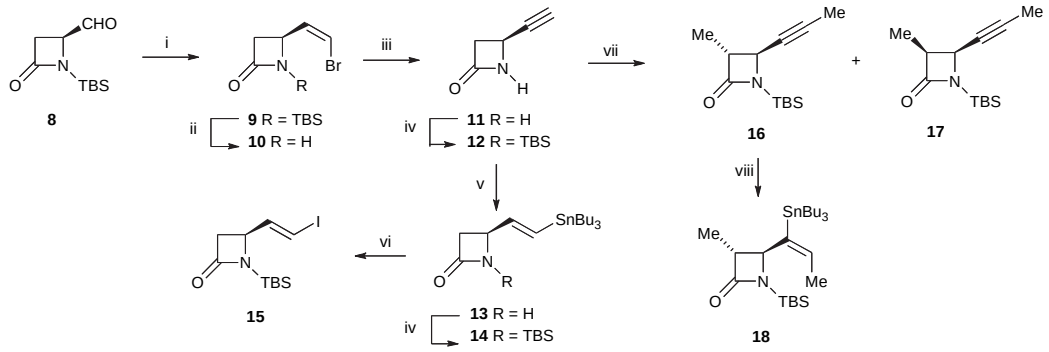
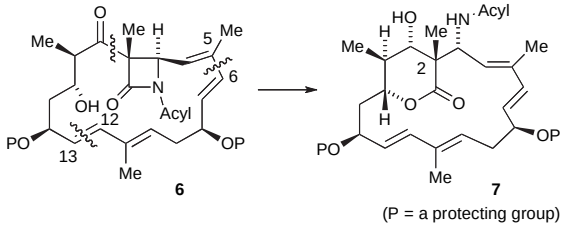


Scheme 1. Synthesis of 4-(2-iodoethenyl)azetidinones; reagents and conditions: (i) $Ph_3P{=}CHBr$, −78 °C to rt, 1 h (58%); (ii) HCl, H_2O, MeOH, rt, 1 h (70%); (iii) ^nBuLi, hexanes, THF, 0 °C, 1.5 h (77%); (iv) TBSCl, Et_3N, DMF, rt (**12**, 88%; **14**, 67%); (v) Bu_3SnH, AIBN (trace), 140 °C, 4 h (**13**, 62%; **14**, 64%); (vi) I_2, CCl_4, rt, 15 min (63%); (vii) 2 LDA, −78 °C, MeI, −78 °C to rt (**16**, 48%; **17**, 9%); (viii) Bu_3SnH, AIBN (trace), 100 °C, 6 h (73%).

Based on this work, a synthesis of lankacidin C (**1**) was planned in which an azetidinone-fused macrocycle **6** would be a key intermediate since reductive ring-opening of the azetidinone should lead to lactone **7**, which has the required configuration at the C2 quaternary carbon and the characteristic bicyclic structure of the lankacidins. A convergent synthesis of the azetidinone **6** was required and its assembly from three starting materials was considered, see structure **6**. At the time of planning the synthesis, the stereoselective acylation of azetidinones was precedented, e.g., by the synthesis of azetidinone **3**,[4,5] and several reactions could be envisaged for formation of the 12,13-double-bond although only modest yields had been obtained during preliminary studies of macrocyclisation via 12,13-double-bond formation using a Wadsworth–Emmons–Horner reaction.[7] It was recognised that late stage formation of the C5–C6 bond would provide a convergent synthesis and the use of a Stille reaction[8] was considered for this assembly step and for macrocyclisation.

In this paper, studies of Stille reactions of 4-(2-iodo-alkenyl) azetidinones and related compounds are described, which led to the use of this chemistry for the synthesis of advanced macrocyclic precursors of lankacidins.[9]



(P = a protecting group)

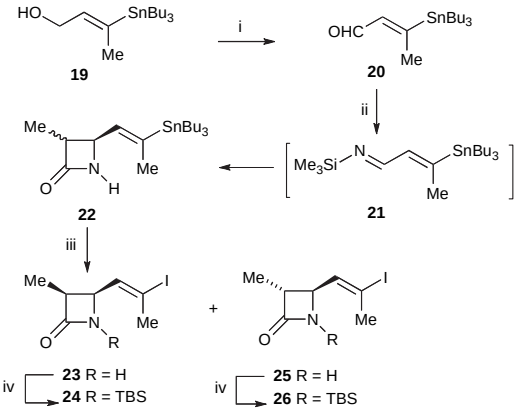
2. Results and discussion

2.1. Preliminary studies of Stille reactions of 4-(2-iodo-alkenyl)azetidinones and related compounds

(*S*)-4-Ethynylazetidinone (**11**)[10,11] was prepared from aldehyde **8**[12] by a modification of the published synthesis, see Scheme 1. A Wittig reaction using bromomethylidenetriphenylphosphorane[13] gave the (*Z*)-vinyl bromide **9**, which, after N-desilylation, was converted into the 4-ethynylazetidinone **11** on treatment with *n*-butyllithium. Following resilylation, addition of tributyltin hydride under free-radical conditions led to the 4-[(*E*)-2-tributylstannylethenyl]azetidinone **14**. Alternatively, addition of tributyltin hydride to the *N*H-azetidinone **11** gave the 4-ethenyl-*N*H-azetidinone **13**, which was N-silylated. Treatment of the vinylstannane **14** with iodine in carbon tetrachloride then provided the (*S*)-4-[(*E*)-2-iodoethenyl]azetidinone **15** ready for studies of Stille reactions.

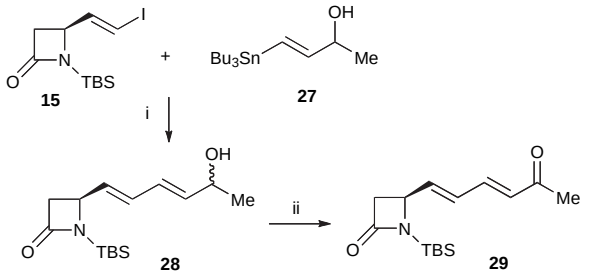
A 4-[(*E*)-2-iodoprop-1-enyl]azetidinone was required to provide the C5 methyl group of the lankacidins. However, although bis-methylation of the *N*-*tert*-butyldimethylsilyl-4-ethynyl-azetidinone **12** was achieved using lithium diisopropylamide and methyl iodide, addition of tributyltin hydride to the major 3,4-*trans*-disubstituted azetidinone **16** gave rise to the 4-[(*E*)-1-tributylstannylprop-1-enyl]-azetidinone **18** and not to the regioisomer required for a synthesis of a 4-(2-iodoprop-1-enyl)azetidinone.

To avoid this problem, the racemic 3,4-*cis*- and 3,4-*trans*-3-methyl-4-(2-iodoprop-1-enyl)azetidinones **24** and **26** were prepared from the open-chain imine **21** as outlined in Scheme 2. (*E*)-3-Tributylstannylbut-2-enal (**20**)[14] was obtained from the alcohol **19** by oxidation using manganese dioxide as under Swern conditions extensive isomerisation to the corresponding (*Z*)-aldehyde was observed. The imine **21** was then generated in situ by the addition of aldehyde **20** to lithium hexamethyldisilazide in tetrahydrofuran,[15] and addition of the lithium enolate of ethyl propanoate gave a mixture of the 3,4-*cis*- and -*trans*-azetidinones **22**. With iodine, this mixture gave the 4-[(*E*)-2-iodoprop-1-enyl]azetidinones **23** and **25**, which were separately converted into their *N*-silylated derivatives **24** and **26**, the *cis*/*trans*-configuration of the products being assigned on the basis of their 3,4-^{1}H-coupling constants.



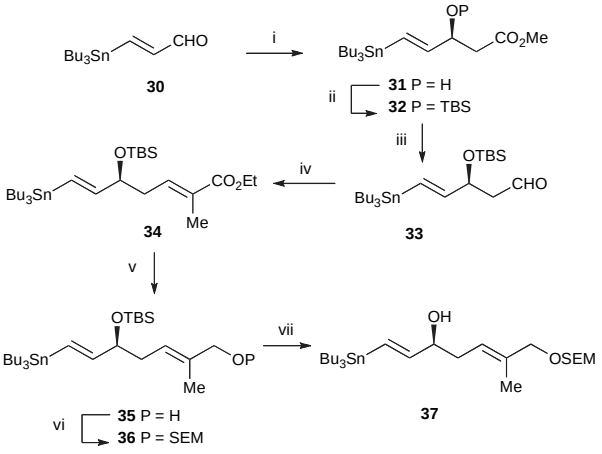
Scheme 2. Synthesis of racemic 4-(2-iodopropenyl)azetidinones; reagents and conditions: (i) MnO_2, acetone, rt, 12 h (100%); (ii) $LiN(SiMe_3)_2$, THF, −78 °C, 1 h, then $MeCHLiCO_2Et$, −78 °C, 45 min, rt, 1 h (49%; 3,4-*cis*:3,4-*trans*=75:25); (iii) I_2, CCl_4, rt, 1.5 h (**23**, 48%; **25**, 29%); (iv) TBSCl, Et_3N, DMF, rt, 2 h (**24**; 88%; **26**, 87%).

Stille reactions of the 4-(2-iodoethenyl)- and 4-(2-iodoprop-1-enyl)-azetidinones **15**, **24** and **26** were now investigated. Under standard conditions using bis(acetonitrile)palladium(II) chloride as the catalyst, (*S*)-4-(2-iodoethenyl)azetidinone **15** was coupled with racemic (*E*)-4-tributylstannylbut-3-enol **27** to give a mixture of the 5′-epimers of diene **28**. Oxidation then gave the ketone **29**, the *E*,*E*-geometry being confirmed by ^{1}H NMR, see Scheme 3.



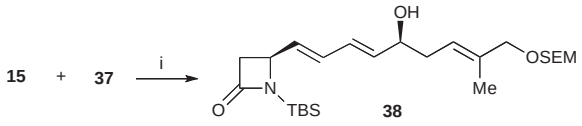
Scheme 3. A Stille reaction of a 4-(2-iodoethenyl)azetidinone; reagents and conditions: (i) $Pd(MeCN)_2Cl_2$, DMF, rt, 45 min (76%); (ii) TPAP, NMO, 4 Å sieves, rt 2 h (86%).

The formation of the dienyl azetidinone **28** was encouraging and so the Stille coupling of the (*S*)-4-(2-iodoethenyl)azetidinone **15** with more complex vinylstannanes was investigated. (*E*)-3-Tributylstannyl-prop-2-enal **30**[16] was converted into the (*S*)-aldol product **31** by reaction with (*S*)-2-hydroxy-1,2,2-(triphenyl)ethyl acetate followed by ester exchange using sodium methoxide, see Scheme 4.[17] The configuration at C3 in the ester **31** followed from the known stereoselectivity of aldol reactions of the chiral acetate,[17] and was confirmed using its (*R*)- and (*S*)-Mosher's derivatives, which indicated that the ee of the ester **31** was ca. 90%. Following O-silylation, reduction of the silyl ether **32** using di-isobutylaluminium hydride gave the aldehyde **33** together with a small amount of the corresponding alcohol, which was oxidized to the aldehyde under Swern conditions. A phosphonate condensation then gave the (*E*)-ester **34**, which was reduced to the alcohol **35**. Protection of the primary alcohol with triethylsilyethoxymethyl chloride gave the SEM-ether **36**, which was O-desilylated to give the secondary alcohol **37**.



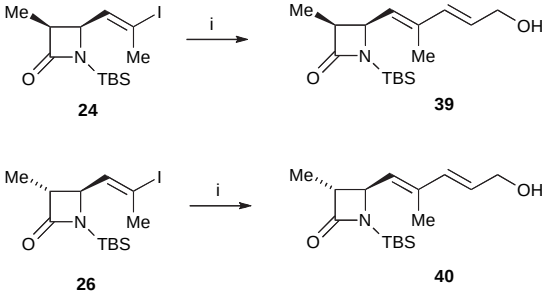
Scheme 4. Synthesis of a 1-tributylstannylhepta-1,5-dien-3-ol; reagents and conditions: (i) (a) (2-hydroxy-1,1,2-(triphenyl)ethyl acetate, LDA, −78 °C to rt, $MgBr_2$, −78 °C, 1 h, add **30**, −78 °C, 2 h (56%) (b) NaOMe, MeOH, rt, 15 min (73%); (ii) TBSOTf, 2,6-lutidine, DCM, −78 °C to rt, 30 min (99%); (iii) DIBAL-H, hexanes, THF, −78 °C, 20 min (79%); (iv) $(EtO)_2P(O)CHMeCO_2Et$, NaH, THF, 0 °C, 10 min, **33**, rt, 1.5 h (97%); (v) DIBAL-H, THF, 0 °C to rt, 1.25 h (65%); (vi), SEMCl, EtN^iPr_2, DCM, 0 °C to rt, 2.5 h (96%); (vii) TBAF, THF, 0 °C to rt, 3.5 h (66%).

The Stille reaction is sensitive to steric effects.[8] It was found that stannane **36** in which the allylic hydroxyl group is protected as its *tert*-butyldimethylsilyl ether, failed to undergo a Stille coupling with the 4-(2-iodoethenyl)-azetidinone **15** in the presence of either bis(acetonitrile)palladium(II) chloride or tetrakis(triphenylphosphine)palladium even after prolonged reaction times. In contrast, stannane **37** in which the secondary allylic hydroxyl group is unprotected, underwent a Stille coupling with the vinyl iodide **15** to give the conjugated diene **38** as a single diastereoisomer in a 50% yield see Scheme 5, the diene geometry again being consistent with ^1H NMR data.



Scheme 5. A further Stille reaction of a 4-(2-iodoethenyl)azetidinone; reagents and conditions: (i) $(MeCN)_2PdCl_2$, DMF, rt, 1 h (50%).

Stille reactions of the racemic *cis*- and *trans*-4-[(*E*)-2-iodoprop-1-enyl]azetidinones **24** and **26** with (*E*)-3-tributylstannylprop-2-enol[18] were now investigated. Using bis(acetonitrile) palladium(II) chloride as the catalyst, good yields of the dienes **39** and **40** were obtained so showing that the additional methyl group in the vinyl iodide was compatible with these Stille couplings, albeit with a relatively unhindered vinylstannane, see Scheme 6.



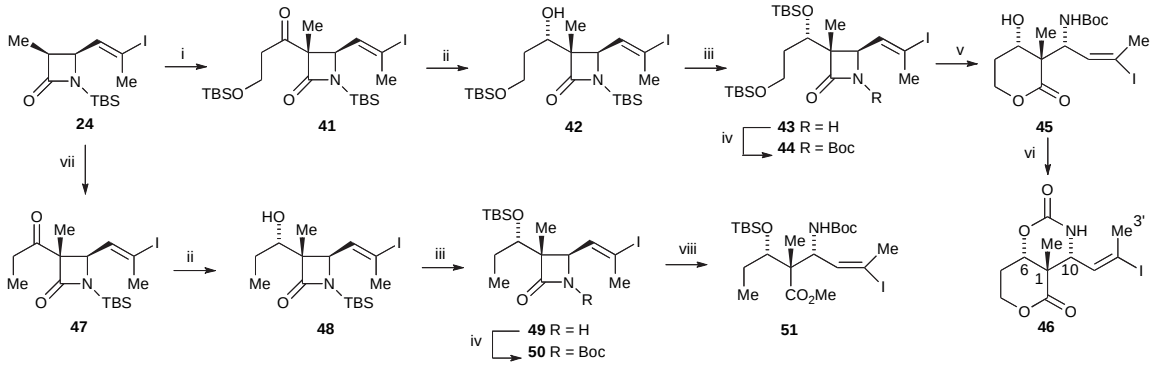
Scheme 6. Stille reactions of 4-(2-iodopropenyl)azetidinones; reagents and conditions: (i) (*E*)-$Bu_3SnCH{=}CHCH_2OH$, $(MeCN)_2PdCl_2$, DMF, rt, 45 min (**39**, 93%; **40**, 80%).

At this point, it was decided to study Stille reactions of other vinyl iodides prepared from azetidinone **24** with (*E*)-tributylstannylprop-2-enol to evaluate their potential for the introduction of the C4-C7-dienyl fragment of lankacidins.

The azetidinone **24** was converted into the 3-acylated azetidinone **41** by addition to 3-*tert*-butyldimethylsilyloxypropanal followed by oxidation, see Scheme 7. Reduction using the hindered reducing agent, potassium triethylborohydride, gave the alcohol **42** with excellent stereocontrol, the configuration at the newly formed stereogenic centre initially being assigned by analogy with earlier work[4,5] and was confirmed later in the synthesis. Following O-silylation using *tert*-butyldimethylsilyl triflate, selective N-desilylation was achieved using potassium fluoride in methanol and treatment of the resulting azetidinone **43** with Boc anhydride gave the carbamate **44**. Rearrangement to the lactone **45** was now achieved using tetrabutylammonium fluoride and the lactone was taken through to the bicyclic carbonate **46** by acid-catalysed removal of the *tert*-butyloxycarbonyl group followed by reaction with carbonyl di-imidazole.

The stereochemistry shown was assigned to the carbamate **46** on the basis of ^1H NMR observations. In particular the *cis*-ring fusion was confirmed by the observation of nuclear Overhauser enhancements between the quaternary methyl group and the *cis*-disposed bridgehead hydrogen. The relative configuration between the quaternary centre and the nitrogen bearing stereogenic centre followed the stereoselectivity of acylation of azetidinone **24**[4,5] and was confirmed by nuclear Overhauser enhancements between the 1,3-*cis*-disposed 6-H and 10-H. Nuclear Overhauser enhancements between the 3′-H_3 and 10-H also confirmed that the geometry of the double-bond, which had been assigned on the basis of the known geometry of aldehyde **20**, had not changed during the course of the synthesis.[14]

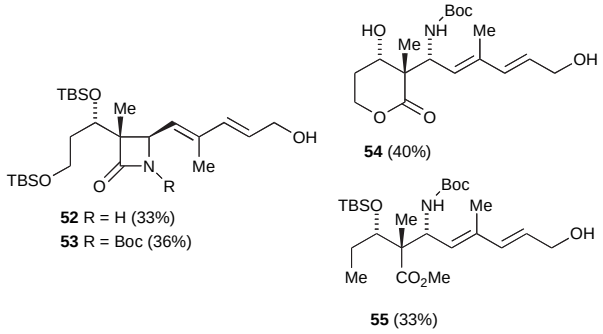
Azetidinone **24** was similarly taken through to the 3,3-disubstituted *N*-*tert*-butoxycarbonylazetidinone **50** and methanolysis,



Scheme 7. Further synthesis of 4-(2-iodopropenyl)azetidinones and analogues; reagents and conditions: (i) (a) $LiNEt_2$, −78 °C, 1 h, $TBSOCH_2CH_2CHO$, −78 °C, 30 min (b) PDC, DCM, 4 Å sieves, rt, 6 h (53%); (ii) $KBEt_3H$, THF, Et_2O, −78 °C, 10–20 min (**42**, 91%; **48**, 91%); (iii) (a) TBSOTf, 2,6-lutidine, DCM, rt, 3 h (b) KF, MeOH, rt, 30 min (**43**, 94%; **49**, 64%); (iv) NaHMDS, −78 °C, 15 min, $(^tBuO_2C)_2O$, −78 °C, 20 min (**44**, 98%; **50**, 89%); (v) TBAF, THF, rt, 45 min (62%); (vi) (a) TFA, rt, 15 min (b) Et_3N, rt, 20 min, Im_2CO, rt, 16 h 60%); (vii) (a) $LiNEt_2$, −78 °C, 1 h, EtCHO, −78 °C, 30 min (b) PDC, DCM 4 Å sieves (19%); (viii) KCN, MeOH, DMF, rt, 16 h (85%).

using potassium cyanide and methanol[19] in *N*,*N*-dimethylformamide, gave the methyl ester **51**, see Scheme 7.

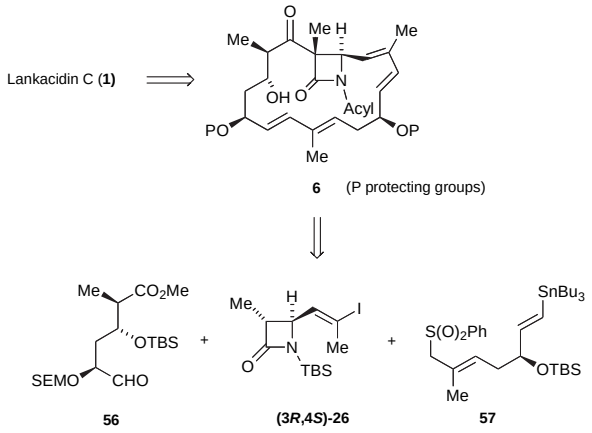
Stille reactions of the *N*H- and Boc-protected azetidinones **43** and **44**, the lactone **45** and the ester **51** with (*E*)-3-tributylstannylprop-2-enol catalysed by bis(acetonitrile)palladium(II) chloride were successful and gave the conjugated dienes **52**–**55** albeit in modest, unoptimised, yields. The use of other catalysts for these reactions was not investigated. Nevertheless, this work confirmed that Stille reactions could be used to assemble dienyl substituted esters, δ-lactones and azetidinones reminiscent of synthetic precursors of the C16–C7 fragment of lankacidins.



52 R = H (33%)
53 R = Boc (36%)
54 (40%)
55 (33%)

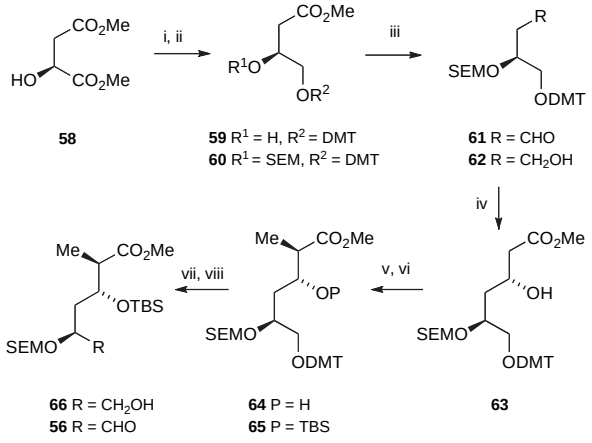
2.2. Synthesis of fragments for macrocycle assembly

Based on these preliminary studies, it was decided to study the use of a Stille reaction for formation of the macrocyclic ring of the lankacidins, and the convergent synthesis of azetidinone **6**, indicated above, was planned in more detail. The ester-aldehyde **56**, the azetidinone (3*R*,4*S*)-**26** and the vinylstannane-sulfone **57** were identified as key building blocks. A Julia reaction between the aldehyde **56** and sulfone **57** would give a long-chain ester, which would be converted into the corresponding thioester. Following acylation of the azetidinone **26** using the thioester, a ring-closing Stille reaction of the 4-(2-iodopropenyl)azetidinone would lead to a synthesis of the required bicyclic intermediate **6**. The end-game of a synthesis of lankacidin C could then include an azetidinone–lactone rearrangement, although the details of the later stages of the synthesis could only be worked out after the assembly steps had been completed.



6 (P protecting groups)
56 **(3*R*,4*S*)-26** **57**

The synthesis of aldehyde **56** started with dimethyl (*S*)-malate **58**, see Scheme 8. This was reduced regioselectively using the borane dimethyl sulfide complex together with sodium borohydride.[20] Selective protection of the resulting primary alcohol gave the mono(dimethoxytrityl) ether **59**, which was further protected as the (2-trimethylsilylethoxy)-methyl ether **60**. This was reduced to the aldehyde **61** using di-isobutylaluminium hydride, the small amount of alcohol **62**, which was obtained being oxidised to

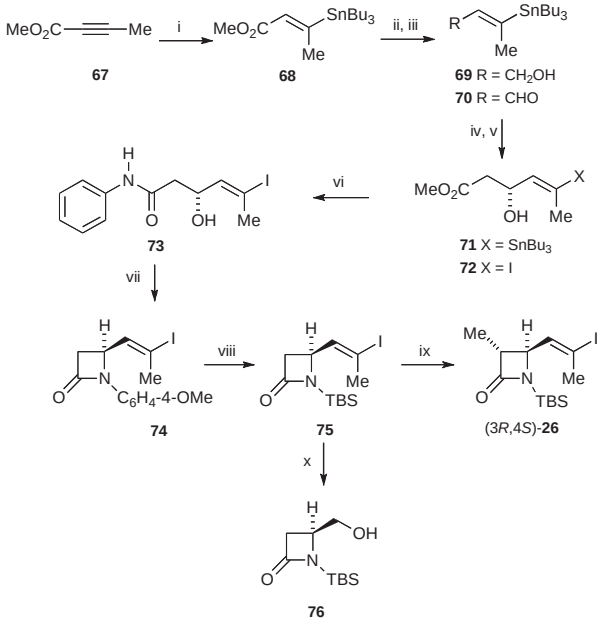


58
59 R^1 = H, R^2 = DMT
60 R^1 = SEM, R^2 = DMT
61 R = CHO
62 R = CH_2OH
63
64 P = H
65 P = TBS
66 R = CH_2OH
56 R = CHO

Scheme 8. Synthesis of aldehyde **56**; reagents and conditions: (i) BH_3·DMS, THF, rt, 30 min, $NaBH_4$, rt, 1 h, then DMTCl, DMAP, rt, 1.5 h (93%); (ii) SEMCl, EtN^iPr_2, DCM, rt, 14 h (99%); (iii) DIBAL-H, hexanes, THF, −78 °C, 2 h (75%); (iv) (a) (*S*)-2-hydroxy-1,1,2-(triphenyl)ethyl acetate, LDA, −78 °C to rt, $MgBr_2$, −78 °C, add **61**, −78 °C, 2 h (b) NaOMe, MeOH, rt, 3 h (68%); (v) 2 LDA, THF, −50 °C to −10 °C, TMEDA, MeI, −78 °C, 5 h (80%); (vi) TBSOTf, 2,6-lutidine, DCM, −78 °C, 1 h (93%); (vii) Cl_2CHCO_2H, DCM, rt, 2 h (74%); (viii) TPAP, NMO, 4 Å sieves, DCM, rt, 2 h (82%).

aldehyde **61** using the Swern procedure. A stereoselective aldol reaction of aldehyde **61** with (*S*)-2-hydroxy-1,2,2-(triphenyl)ethyl acetate[17] then gave the ester **63** after ester exchange with methanol together with ca. 25% of its epimer at C3, which were separated by chromatography. The configuration of the major product at C3 was assigned as shown in structure **63** by analogy with the literature.[17] An *anti*-selective methylation of hydroxy ester **63** was achieved using Frater's procedure[21] to give the *tert*-butyldimethylsilyl ether **65** after silylation of the resulting alcohol **64** using *tert*-butyldimethylsilyl triflate. Selective removal of the dimethoxytrityl group was carried out using dichloroacetic acid and oxidation using tetrapropylammonium perruthenate[22] gave the aldehyde-ester **56**.

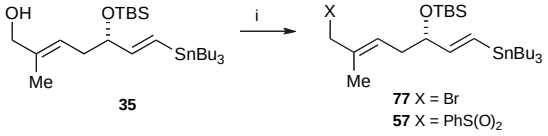
The racemic 3,4-*cis*- and -*trans*-azetidinones **24** and **26** had been prepared earlier, see Scheme 2, but it was now necessary to develop an asymmetric synthesis for the synthesis of advanced lankacidin intermediates. Stereoselective conjugate addition of a tributyltin cuprate to methyl but-2-ynoate **67** gave the (*E*)-adduct **68**,[23] which was taken through to the aldehyde **70** by reduction–oxidation with manganese dioxide being the preferred oxidant to prevent (*E*)/(*Z*)-isomerisation, see Scheme 9. Aldol addition with lithiated (*R*)-2-hydroxy-1,2,2-(triphenyl)ethyl acetate mediated by magnesium dibromide followed by ester exchange using sodium methoxide[17] gave the (3*R*)-aldol adduct **71**, which was converted into the iodide **72** by a tin–iodine exchange. Reaction of this methyl ester with lithium 4-methoxyanilide gave the hydroxyamide **73** and cyclisation with inversion of configuration under Mitsunobu conditions[24] formed the azetidinone **74**.



Scheme 9. Synthesis of azetidinone (3*R*,4*S*)-**26**; reagents and conditions: (i) Li($Bu_3SnCuBr$)·DMS, −78 °C, 3 h (91%); (ii) DIBAL-H, hexanes, −78 °C to 0 °C, 1 h (98%); (iii) MnO_2, acetone, rt, 12 h (100%); (iv) (a) (*R*)-2-hydroxy-1,1,2-(triphenyl)ethyl acetate, LDA, −78 °C to rt, $MgBr_2$, −78 °C, add **70**, −78 °C, 2 h (b) NaOMe, MeOH, rt (96% from **70**); (v) I_2, CCl_4, rt, 20 min (98%); (vi) 4-$MeOC_6H_4NHLi$, THF, −78 °C, 40 min (73%); (vii) Ph_3P, DEAD, THF, rt, 1 h (83%); (viii) CAN, MeCN, H_2O, rt, 20 min then TBSCl, Et_3N, DMF, rt, 30 min (78% from **74**); (ix) LDA, −78 °C, 30 min, then MeI, −78 °C, 2 h (85%); (x) O_3, −78 °C, then $NaBH_4$, MeOH.

Oxidative N-deprotection and silylation then delivered the azetidinone **75**, which was ozonolyzed with reduction using sodium borohydride to the 4-(hydroxymethyl)-azetidinone **76**. Comparison of azetidinone **76** with a sample prepared from L-aspartic acid following the literature procedure[12,25] showed that it had an enantiomeric excess of ca. 90% and confirmed its absolute configuration which had been assigned on the basis of the known stereoselectivity of aldol reactions of (*R*)-2-hydroxy-1,2,2-(triphenyl)ethyl acetate.[17] Azetidinone **75** was then methylated stereoselectively to give the (3*R*,4*S*)-azetidinone **26**, the 3,4-*trans*-stereochemistry being assigned by ^{1}H NMR; $J_{3,4}$=2.5 Hz.

The vinylstannane-sulfone **57** was prepared from (5*S*,2*E*,6*E*)-5-*tert*-butyldimethylsilyloxy-7-tributylstannyl-2-methylhept-2,6-dien-1-ol (**35**). Conversion to the bromide **77** and substitution using sodium benzenesulfinate gave the required sulfone **57**, see Scheme 10.



Scheme 10. Synthesis of sulfone **57**; reagents and conditions: (i) (a) MsCl, Et_3N, THF, −78 °C, 1 h then LiBr, rt, 12 h (81%); (b) $PhSO_2Na$, DMF, rt, 12 h (88%).

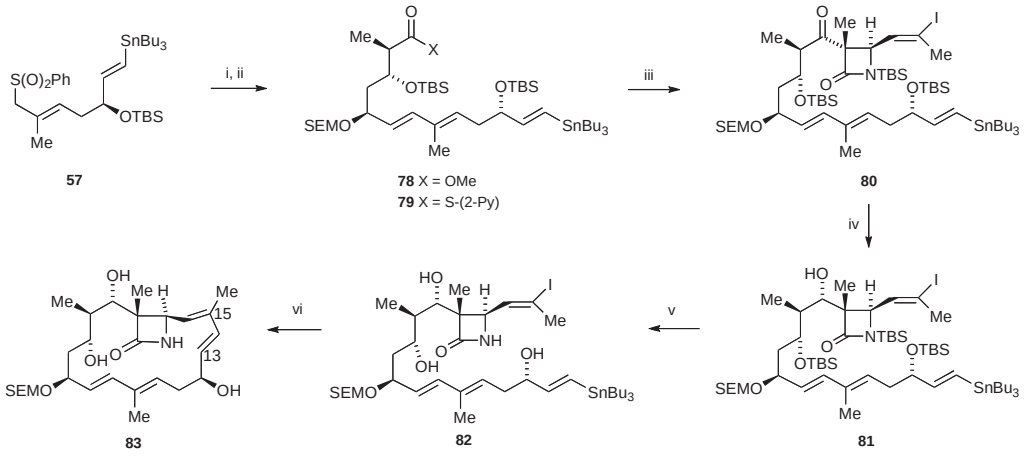
2.3. Assembly of macrocyclic precursors of lankacidins

A Julia olefination between the aldehyde **56** and sulfone **57** gave the conjugated diene **78**, the (*E*)-configuration across the newly formed double-bond being assigned on the basis of the H(6)–H(7) coupling constant of 15.7 Hz. Saponification of the methyl ester and coupling of the resulting carboxylic acid with 2-mercaptopyridine gave the thioester **79**. Following the procedure developed in earlier work,[5] deprotonation of the (3*R*,4*S*)-azetidinone **26** using lithium diethylamide followed by the addition of the thioester **79** gave the 3-acylated azetidinone **80**. This was reduced stereoselectively to the alcohol **81** using potassium triethylborohydride, the configuration shown at the newly introduced hydroxyl bearing stereogenic centre being assigned by analogy with earlier work.[4,5]

The earlier studies on Stille reactions of 4-(2-iodo-alkenyl)azetidinones with (*E*)-1-(tributylstannyl)-alkenes had shown that better results were obtained if a 3-hydroxyl group was unprotected. Therefore before the attempted macrocyclisation, the tris-silylated azetidinone **81** was desilylated using tetrabutylammonium fluoride to give the triol **82**. Initial studies into the cyclisation of this vinylstannane using a Stille reaction were carried out using bis(acetonitrile)palladium(II) chloride as the catalyst, which had given useful results in the intermolecular Stille reactions of 3-hydroxyalk-1-enylstannanes and 4-(2-iodo-alkenyl)azetidinones, but only modest, ca. 27%, yields of the required macrocyclic product **83** were obtained. However, when tris(dibenzylideneacetone)bis-palladium(0)[26] in the presence of triphenylarsine was used as the catalyst, a significantly better yield, 52%, of the macrocyclic intermediate **83** was isolated, see Scheme 11.

The structure assigned to the Stille product **83** was consistent with spectroscopic data. In particular, the 15-CH_3 substituent was observed as a singlet at δ 1.69 in its ^{1}H NMR, whereas the analogous methyl group in the vinyl iodide **82** was seen as a narrow doublet at δ 2.48 (J 1.3), cf. analogous chemical shifts observed during the earlier intermolecular Stille reactions. The (13*E*)-geometry was consistent with $J_{13,14}$ (15.5 Hz).

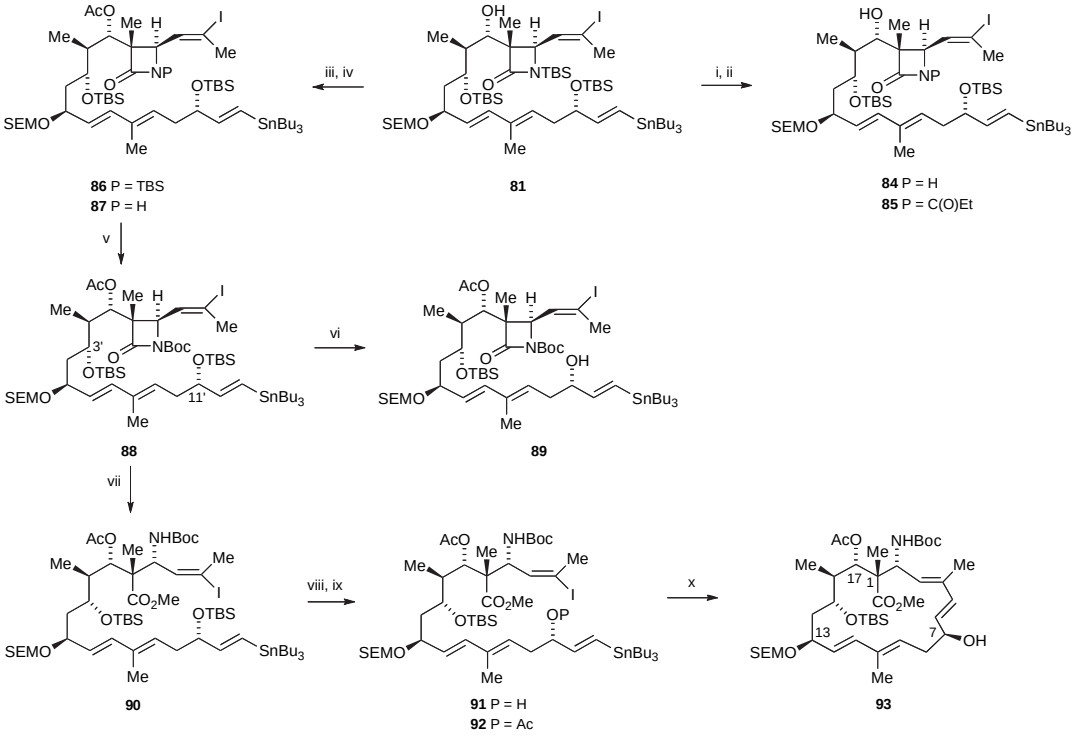
As an improved yield had been obtained from the intramolecular Stille reaction of the iodostannane **82** using tris(dibenzylideneacetone)bis-palladium(0) as the catalyst, the use of this catalyst to promote a Stille cyclisation of the (*E*)-*tert*-butyldimethylsilyloxyalkenylstannane **81** was studied. However, as had been observed during the earlier studies of intermolecular Stille reactions, only mixtures of unidentifiable compounds were obtained. It appeared that in this system the hydroxyl group, which is allylic to the vinylstannane cannot be silylated. The compatibility of other hydroxyl protecting groups with the Stille reaction was not investigated.



Scheme 11. Synthesis of the azetidinone-fused macrocycle **83**; reagents and conditions: (i) (a) $LiN^{i}Pr_2$, −78 °C, THF, −78 °C, 10 min, add **56**, 2 h (b) Ac_2O, Et_3N, DCM, DMAP (trace), −20 °C, 30 min then rt, 1 h (c) Na/Hg, MeOH, EtOAc, 20 °C, 1 h (54%); (ii) (a) NaOH, MeOH, THF, H_2O, rt, 32 h (b) 2-mercaptopyridine, DCC, DCM, DMAP (cat), 0 °C, 4 h (91%); (iii) (3*R*,4*S*)-**26**, $LiNEt_2$, −78 °C, 15 min, add **79**, 3 h (57%); (iv) KEt_3BH, Et_2O, −78 °C, 15 min (79%); (v) TBAF, THF, 0 °C to rt, 12 h (84%); (vi) $(MeCN)_2PdCl_2$, DMF, rt 12 h (27%) or $Pd_2(dba)_3$, $AsPh_3$, DMF, THF, rt, 22 h (52%).

Although the bicyclic structure of the azetidinone-macrocycle **83** corresponded to the azetidinone **6** identified as a possible intermediate for a synthesis of lankacidin C (**1**), the presence of three unprotected secondary hydroxyl groups, as well as the unprotected azetidinone, meant that several selective functional group interconversions would be necessary if a total synthesis were to be completed. It was therefore decided to study additional chemistry of the azetidinone **81** to see whether some of these selective functional group transformations could be carried out before macrocyclisation.

Reaction of the azetidinone **81** with potassium fluoride in methanol resulted in the selective removal of the *N*-silyl group and gave the *N*H-azetidinone **84**, which was acylated on nitrogen to give the *N*-propanoyl azetidinone **85**, see Scheme 12. The 3-(1-acetoxyalkyl)azetidinone **88** was also prepared from the azetidinone **81** by acetylation of the 1′-hydroxyl group to give the acetate **86**, selective N-desilylation, and *tert*-butoxycarbonyl N-protection of the resulting *N*H-azetidinone **87**. Interestingly, O-desilyation of the bis-*tert*-butyldimethylsilyl ether **88** under mild conditions proceeded by selective deprotection of the 11′-hydroxyl group and gave the azetidinone **89** in which the 3′-silyloxy group was intact.[27] Moreover treatment of the *N*-acylated azetidinone **88** with potassium cyanide and methanol in *N*,*N*-dimethylformamide resulted in ring-opening and gave the methyl ester **90**.[19] Monodesilylation of this acetoxy-substituted intermediate was also selective for the remote allylic silyl ether and gave alcohol **91**, the regioselectivity of this desilylation being confirmed by conversion to the bis-acetate **92**. Finally, an intramolecular Stille reaction of the hydroxyvinylstannane **91**



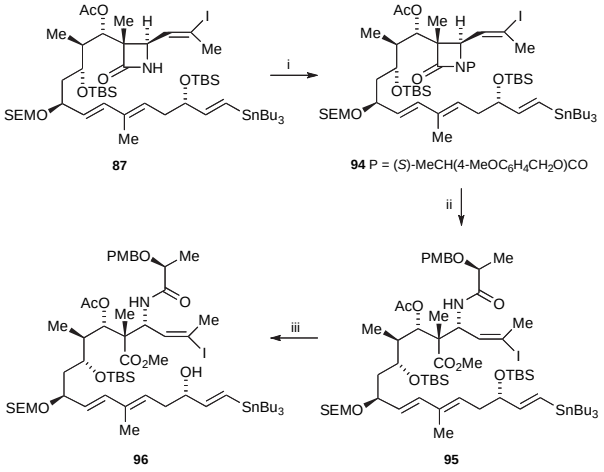
Scheme 12. Further macrocyclisation studies; reagents and conditions: (i) KF, MeOH, 0 °C, 20 min (92%); (ii) NaHMDS, −78 °C, 15 min then EtCOCl −78 °C, 30 min (78%); (iii) Ac_2O, Et_3N, DMAP (trace), rt, 3 h (89%); (iv) KF, MeOH–THF, rt, 30 min (93%); (v) Boc_2O, DMAP, MeCN, rt, 16 h (84%); (vi) TBAF, THF, rt, 16 h (48%); (vii) MeOH, KCN, DMF, rt, 48 h (88%); (viii) TBAF, THF, rt, 4 h (84%); (ix) Ac_2O, Et_3N, DMAP (cat), rt, 24 h (52%); (x) $Pd_2(dba)_3$, $AsPh_3$, DMF, THF, rt, 18 h (48%).

using tris(dibenzylideneacetone)bis-palladium(0) as the catalyst was successful and gave the 17-membered macrocycle **93** in a 48% isolated yield. In this macrocyclic intermediate, all four of the hydroxyl groups are already differentiated, which will facilitate future regiospecific functionalisation.

2.4. Introduction of a *N*-(2-alkoxy)propanoate

Having prepared the macrocyclic intermediate **93**, it was of interest to prepare analogous compounds with an *N*-substituent, which could be converted into the *N*-(2-hydroxy)propanoyl and *N*-pyruvyl groups found in natural lankacidins.[1]

N-Acylation of the *N*H-azetidinone **87** was carried out using (*S*)-2-(4-methoxy)benzyloxypropanoyl chloride, which was prepared from the corresponding ethyl ester,[28] to give the *N*-acylazetidinone **94** in a 70% yield, see Scheme 13. Selective methanolysis of the azetidinone was again achieved using potassium cyanide in methanol and gave the open-chain methyl ester **95** in which the *N*-[(*S*)-2-(4-methoxy)benzyloxypropanoyl] group was intact. As before, selective deprotection of the 13-hydroxyl group could now be carried out using tetrabutylammonium fluoride and provided the hydroxy ester **96** ready for macrocyclisation via an intramolecular Stille reaction. Preliminary studies of this reaction were promising and gave a product, which had the expected molecular ion in its mass spectrum, but which could not be formally characterised because of insufficient material. Nevertheless, this study showed that advanced intermediates with *N*-2-(4-methoxy)benzyloxypropanoyl substituents are accessible and compatible with late-stage transformations. Moreover, the 4-methoxybenzyloxy protecting group should be orthogonal to those to be used for the hydroxy groups of the macrocyclic ring, cf. ester **93**.



Scheme 13. Introduction of an *N*-(2-alkoxy)propanoyl substituent; Reagents and conditions: (i) KHMDS, THF, −78 °C, 15 min, (*S*)-2-(4-methoxybenzyloxy)propanoyl chloride, THF, −78 °C, 4 h (70%); (ii) MeOH, KCN, DMF, room temperature, 5 h (87%); (iii) TBAF, THF, room temperature, 4 h (81%).

3. Summary and conclusions

A range of 4-(2-iodoalk-1-enyl)azetidinones and related compounds have been shown to participate in intermolecular Stille coupling reactions with (*E*)-1-(tributylstannyl)alk-1-en-3-ols. These studies were followed by a study of macrocycle-forming intramolecular Stille reactions, which led to the completion of convergent syntheses of the azetidinone-fused macrocycle **83** and the 17-membered macrocyclic ester **93**. These are advanced intermediates for a proposed total synthesis of lankacidins.

Interestingly, the (*E*)-3-hydroxyalkenyl stannane **37** was shown to participate in an intermolecular Stille reaction with the 4-(2-iodoethenyl)azetidinone **15** but the analogous 3-*tert*-butyldimethylsilyloxyalkenylstannane **35** did not. An analogous discrepancy was also noticed in the reactivities of the more complex (*E*)-vinylstannanes **81** and **82** towards intramolecular Stille reactions.

cis-Disposed allylic hydroxyl groups, which can co-ordinate to the trialkyltin moiety are known to accelerate Stille reactions,[14,29] but this is not possible for the (*E*)-3-hydroxyalkenylstannanes discussed here. Stille reactions can be sensitive to steric effects[8] and it may be that the different reactivities of (*E*)-3-hydroxy- and their *tert*-butyldimethylsilyl protected derivatives towards Stille reactions are due to steric hindrance from the bulky allylic silyloxy groups. However, the (*E*)-geometry of the vinylstannanes means that this must be a rather subtle effect perhaps influenced by the hindered nature of the palladium complexes involved in Stille processes.

The stereoselective acylation of suitably functionalised azetidinones has again proved useful for the synthesis of advanced intermediates for a synthesis of lankacidins. Several other potentially useful selective transformations have also been developed during the course of this work including the selective cleavage of *N*-silyl groups in the presence of analogous *O*-silylated derivatives, and the regioselective monodeprotection of 3′,11′-bis-*tert*-butyldimethylsilyl ethers in the presence of a 1′-acetoxy group.[27]

To complete the synthesis of a lankacidin, it remains to effect a macrocyclisation of the Stille precursor **96**. Formation of the δ-lactone, oxidation of the 18-hydroxyl group, and deprotection should then deliver lankacidinol and further selective oxidation to introduce the pyruvyl group would complete a total synthesis of lankacidin C (**1**).

4. Experimental

4.1. General procedures

Melting points were recorded on a Gallenkamp apparatus, and optical rotations measured on an AA-100 polarimeter at 589 nm. Proton NMR spectra were recorded using Varian Unity A300 and 500 spectrometers. Coupling constants are given in hertz and chemical shifts relative to Me_4Si. IR spectra were recorded on a Perkin–Elmer 1710FT or an ATI Mattson Genesis FTIR spectrometer and were run as liquid films unless otherwise stated. Low resolution mass spectra were measured on a Micromass Trio 200 spectrometer and high resolution spectra on a Kratos Concept IS spectrometer.

Chromatography refers to flash chromatography using Merck silica gel 60H (40–63 nm^3, 230–400 mesh). Light petroleum refers to the fraction boiling at 40–60 °C and ether to diethyl ether. All solvents and reagents were purified by standard techniques and all non-aqueous reactions were performed under an atmosphere of dry argon or nitrogen.

Racemic (*E*)-4-tributylstannylbut-3-enol **27**[30] was prepared by the addition of tributyltin hydride to but-3-ynol under free-radical conditions (catalytic azobis-isobutyronitrile, toluene, 100 °C, 4 h). (*S*)-2-(4-Methoxy)benzyloxypropanoyl chloride was prepared from the corresponding ethyl ester[28] by hydrolysis to the acid (lithium hydroxide, THF–water, ambient temperature, 1 h; acidified using glacial acetic acid) followed by treatment with oxalyl chloride (benzene–DMF, ambient temperature, 3 h), and was used without purification.

4.1.1. (S)-1-tert-Butyldimethylsilyl-4-[(5SR,1E,3E)-5-hydroxyhexa-1,3-dienyl]azetidin-2-one ***28***. Bis(acetonitrile) palladium(II) chloride (ca. 2 mg, 5 mol %) was added to the vinyl iodide **15** (39 mg, 0.11 mmol) and the vinylstannane **27** (62 mg, 0.17 mmol) in degassed DMF (1 ml) and the mixture was stirred in the dark at room temperature for 45 min. Saturated aqueous ammonium chloride (2 ml) was added and the suspension filtered through Celite. The filtercake was washed with ethyl acetate and the organic

and aqueous phases were separated. The aqueous phase was extracted with ethyl acetate (3×2 ml) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (2:1+2% triethylamine) gave the *title compounds* **28** (24 mg, 86 mmol, 76%) as a colourless oil (found: M^++H, 282.1881; $C_{15}H_{28}NO_2Si$ requires M, 282.1889); ν_{max} 3413, 1742, 1627, 1471, 1411, 1364, 1255, 1189, 1128, 988 and 968 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.16 and 0.21(each 3H, s, $SiCH_3$), 0.94 [9H, s, $SiC(CH_3)_3$], 1.28 (3H, d, *J* 6.9, 6′-H_3), 1.74 (1H, s, OH), 2.75 (1H, dd, *J* 3.1, 16.1, 3-H), 3.29 (1H, dd, *J* 5.8, 16.1, 3-H′), 4.03 (1H, ddd, *J* 3.1, 5.8. 8.7, 4-H), 4.36 (1H, quin, *J* 6.9, 5′-H) and 5.71 and 6.19 (each 2H, m, vinylic H); *m*/*z* (CI) 282 (M^+, 32%), 280 (26), 264 (24), 222 (70) and 107 (100).

4.1.2. (S)-1-tert-Butyldimethylsilyl-4-[(1E,3E)-5-oxohexa-1,3-dienyl]azetidin-2-one ***29***. *N*-Methylmorpholine-*N*-oxide (18 mg, 0.15 mmol), tetrapropylammonium perruthenate (ca. 5 mg, 16 mol %) and powdered activated 4 Å molecular sieves (ca. 20 mg) were added to the alcohol **28** (24 mg, 86.5 mmol) in dichloromethane (1 ml) and mixture stirred at room temperature for 2 h. Ethyl acetate (5 ml) was added and the mixture filtered through Celite. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate (3:2) gave the *title compound* **29** (21 mg, 74.2 mmol, 86%) as a yellow oil (found: M^++H, 280.1726; $C_{15}H_{26}NO_2Si$ requires M, 280.1732); $[\alpha]_D^{18}$ −61 (*c* 1.36 in CH_2C1_2); ν_{max} 1746, 1667, 1599, 1363, 1253, 1184, 989 and 841 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 0.16 and 022 (each 3H, s, $SiCH_3$), 0.95 [9H, s, $SiC(CH_3)_3$], 2.29 (3H, s, 6′-H_3), 2.81 (1H, dd, *J* 2.7, 15.5, 3-H), 3.36 (1H, dd, *J* 5.6 and 15.5, 3-H′), 4.11 (1H, ddd, *J* 2.7, 5.6, 9.0, 4-H), 6.13 (1H, dd, *J* 9.0, 15.2, 1′-H), 6.16 (1H, d, *J* 15.4, 4′-H), 6.36 (1H, dd, *J* 10.7, 15.2, 2′-H) and 7.09 (1H, dd, *J* 10.8, 15.7, 3′-H); δ_C (75 MHz, $CDCl_3$) −5.62, −5.42, 18.36, 26.22, 27.52, 45.78, 50.57, 130.58, 131.42, 141.23, 143.57, 171.64 and 198.31; *m*/*z* (EI) 280 (M^++H, 48%), 222 (100), 180 (94), 148 (41), 123 (73) and 122 (43).

4.1.3. (4S)-1-tert-Butyldimethylsilyl-4-[(5S,1E,3E,7E)-5-hydroxy-8-methyl-9-(2-trimethylsilylethoxy)methoxy-nona-1,3,7-trienyl]azetidin-2-one ***38***. Bis(acetonitrile)palladium(II) chloride (ca. 0.5 mg, 5 mol %) was added to the vinyl iodide **15** (10 mg, 30 μmol) and the vinylstannane **37** (14 mg, 26 μmol) in degassed DMF (0.2 ml) and the mixture stirred at room temperature in the dark for 0.5 h. More catalyst (ca. 0.5 mg) was added and the mixture was stirred for a further 0.5 h. Ethyl acetate (2 ml) and brine (2 ml) were added and the aqueous phase was extracted with ethyl acetate (3×2 ml). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (4:1+2% triethylamine) as eluant gave the *title compound* **38** (6 mg, 13 μmol, 50%) as a yellow oil (found: M^++H, 482.3123; $C_{25}H_{48}NO_4Si_2$ requires M, 482.3122); $[\alpha]_D^{21}$ −15 (*c* 0.51 in CH_2Cl_2); ν_{max} 3424, 1746, 1467, 1290, 1251, 1188, 1056, 989 and 838 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.002 [9H, s, $Si(CH_3)_3$], 0.141 and 0.181 (each 3H, s, $SiCH_3$), 0.919 [11H, m, $SiC(CH_3)_3$ and CH_2Si], 1.628 (1H, br s, OH), 1.670 (3H, s, 8′-CH_3), 2.311 (2H, m, 6′-H_2), 2.730 (1H, dd, *J* 2.8, 15.4, 3-H), 3.281 (1H, dd, *J* 5.6, 15.4, 3-H′), 3.608 (2H, m, OCH_2CH_2Si), 3.945 (2H, s, 9′-H_2), 4.005 (1H, ddd, *J* 2.8, 5.6, 8.7, 4-H), 4.208 (1H, m, 5′-H), 4.645 (2H, s, OCH_2O), 5.450 (1H, t, *J* 7.1, 7′-H), 5.641 (1H, dd, *J* 9.2, 14.3, 1′-H), 5.725 (1H, dd, *J* 6.2, 14.5, 4′-H) and 6.194 (2H, m, 2′-H and 3′-H); δ_C (75 MHz, $CDCl_3$) −5.62, −5.40, −1.39, 14.39, 18.13, 18.32, 26.27, 35.93, 45.76, 50.98, 65.27, 71.79, 73.50, 93.99, 122.76, 129.00, 132.02, 134.46, 135.87, 136.57 and 172.20; *m*/*z* (CI) 499 (M^++18, 80%), 482 (M^++1, 53), 369 (21), 107 (46), 91(53), 90 (73) and 69 (100).

4.1.4. (3RS,4SR)-1-tert-Butyldimethylsilyl-4-(5-hydroxy-2-methyl-penta-1,3-dienyl)-3-methylazetidin-2-one ***39***. Bis(acetonitrile)palladium(II) chloride (2 mg, 7 mmol) was added to the vinyl iodide **24** (37 mg, 0.10 mmol) and (*E*)-3-tributylstannylprop-2-enol (55 mg, 0.16 mmol) in degassed DMF (1 ml) in the dark. The reaction was stirred for 45 min, saturated aqueous ammonium chloride (10 ml) was added, and the mixture filtered through Celite, eluting with ethyl acetate. The aqueous layer was extracted with ethyl acetate (3×10 ml) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate–triethylamine (60:40:1) as eluant gave the *title compound* **39** (28 mg, 93%) as a colourless oil, R_f 0.30 (3:2 light petroleum–ethyl acetate) (found: M^++H, 296.2050; $C_{16}H_{30}O_2NSi$ requires M, 296.2046); ν_{max} 3261, 1752, 1255, 1095 and 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01 and 0.06 (each 3H, $SiCH_3$), 0.80 [9H, s, $SiC(CH_3)_3$], 0.93 (3H, d, *J* 7.7, 3-CH_3), 1.62 (1H, s, OH), 2.02 (3H, br s, 2′-CH_3), 3.35 (1H, m, 3-H), 4.11 (2H, d, *J* 5.5, 5′-H_2), 4.33 (1H, dd, *J* 9.6, 5.9, 4-H), 5.31 (1H, d, *J* 9.6, 1′-H), 5.71 (1H, dt, *J* 15.6, 5.9, 4′-H) and 6.17 (1H, d, *J* 15.6, 3′-H); δ_C (75 MHz, $CDCl_3$) −5.69, −5.61, 9.87, 12.76, 18.24, 26.18, 50.26, 50.94, 63.42, 127.84, 129.99, 134.74, 136.37 and 176.64; *m*/*z* (CI) 296 (M^++1, 30%) and 121 (100).

4.1.5. (3RS,4RS)-1-tert-Butyldimethylsilyl-4-(5-hydroxy-2-methyl-penta-1,3-dienyl)-3-methylazetidin-2-one ***40***. Following the procedure outlined for the synthesis of the diene **39**, bis(acetonitrile) palladium(II) dichloride (2 mg, 7 mmol), the vinyl iodide **26** (40 mg, 0.11 mmol) and (*E*)-3-tributylstannylprop-2-enol (58 mg, 0.17 mmol) gave the *title compound* **40** (25 mg, 80%) as a colourless oil, R_f 0.30 (3:2 light petroleum–ethyl acetate) (found: M^++H, 296.2052; $C_{16}H_{30}O_2NSi$ requires M, 296.2045); ν_{max} 3261, 1750, 1255, 1093 and 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.08 and 0.13 (each 3H, $SiCH_3$), 0.86 [9H, s, $SiC(CH_3)_3$], 1.25 (3H, d, *J* 7.6, 3-CH_3), 1.41 (1H, t, *J* 5.5, OH), 1.76 (3H, d, *J* 1.2, 2′-CH_3), 2.82 (1H, qd, *J* 7.4, 2.5, 3-H), 3.91 (1H, dd, *J* 9.7, 2.6, 4-H), 4.19 (2H, t, *J* 5.5, 5′-H_2), 5.41 (1H, d, *J* 9.7, 1′-H), 5.77 (1H, dt, *J* 15.6, 5.5, 4′-H) and 6.17 (1H, d, *J* 15.6, 3′-H); *m*/*z* (CI) 296 (M^++1, 25%) and 121 (100).

4.1.6. Methyl (2R,3R,5S,11S,6E,8E,12E)-3,11-di-tert-butyldimethylsilyloxy-2,8-dimethyl-13-tributylstannyl-5-(2-trimethylsilylethoxy)methoxytrideca-6,8,12-trienoate ***78***. Butyllithium (2.7 ml; 1.34 M in hexane, 3.61 mmol) was added to *N*,*N*-di-isopropylamine (0.51 ml, 3.63 mmol) in THF (20 ml) at 0 °C and the solution stirred for 15 min. After being cooled to −78 °C, the sulfone **57** (2.2 g, 3.3 mmol) in THF (5 ml) was added dropwise and the resulting solution was stirred at −78 °C for 10 min before the aldehyde **56** (1.43 g, 3.3 mmol) in THF (5 ml) was added. The mixture was stirred for 2 h before being allowed to warm to room temperature. Saturated aqueous ammonium chloride (30 ml) was added and the aqueous phase was extracted with ether (2×30 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a residue (3.58 g), which was dissolved in DCM (20 ml) and the solution cooled to −20 °C. Triethylamine (1.85 ml, 13.2 mmol), DMAP (ca. 10 mg) and acetic anhydride (0.63 ml, 6.6 mmol) were added and the mixture was stirred for 30 min before being warmed to room temperature. After 1 h, saturated aqueous sodium hydrogen carbonate (10 ml) and ether (50 ml) were added and the aqueous phase was extracted with ether (2×15 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a residue (3.76 g), which was dissolved in anhydrous methanol/ethyl acetate (40 ml of a 2:1 mixture). The solution was cooled to −20 °C, sodium amalgam (15.0 g; ~5% Na w/w, ~32.4 mmol) was added portionwise, and the mixture was stirred for 1 h at −20 °C. After warming to room temperature, the liquid phase was poured into a mixture of water (25 ml) and ether (50 ml). The aqueous phase was extracted with ether (2×30 ml) and the organic extracts were washed with brine and dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with ether in light petroleum (1:20) afforded the *title*

compound **78** as a colourless oil (1.7 g, 54%); $[\alpha]_D^{24}$ −47.5 (*c* 1.1 in $CHCl_3$) (found: M^++Na, 969.5263; $C_{46}H_{94}NO_6Si_3{}^{120}SnNa$ requires M, 969.5278); ν_{max} 1742, 1646, 1601, 1463, 1251, 1098, 1056, 1028, 836 and 775 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.06–0.11 (21H, overlapping s, 7×$SiCH_3$), 1.18 (3H, d, *J* 7.1, 2-CH_3), 1.77 (3H, s, 8-CH_3), 0.90–1.99 [49H, m, Sn(C_4H_9)$_3$, −CH_2Si, 2×$SiC(CH_3)_3$ and 4-H_2], 2.37 (2H, m, 10-H_2), 2.81 (1H, m, 2-H), 3.54 (1H, m, O*H*CHCH_2Si), 3.68 (3H, s, OCH_3), 3.76 (1H, m, OHC*H*CH_2Si), 4.01–4.15 (2H, m, 5-H and 11-H), 4.31 (1H, m, 3-H), 4.62 and 4.72 (each 1H, d, *J* 7.5, O*H*CHO), 5.33 (1H, dd, *J* 8.4, 15.7, 6-H), 5.56 (1H, br t, *J* 7.0, 9-H), 5.99 (1H, dd, *J* 5.2, 19.0, 12-H), 6.12 (1H, d, *J* 19.0, 13-H) and 6.26 (1H, d, *J* 15.7, 7-H); δ_C (75 MHz, $CDCl_3$) −4.74, −4.41, −4.28, −1.42, 9.48, 12.08, 12.73, 13.72, 17.98, 18.17, 18.31, 25.80, 25.90, 27.24, 29.11, 37.37, 40.02, 45.29, 51.31, 65.33, 70.93, 73.71, 76.28, 91.56, 126.13, 126.85, 129.70, 134.03, 138.59, 151.25 and 174.80; *m*/*z* (FAB) 969 (M^++23, 2%), 742 (4), 171 (100) and 136 (65).

4.1.7. S-(2-Pyridinyl) (2R,3R,5S,11S,6E,8E,12E)-3,11-di-tert-butyldimethylsilyloxy-2,8-dimethyl-13-tributyl-stannyl-5-(2-trimethylsilylethoxy)methoxytrideca-6,8,12-trienethioate ***79***. Sodium hydroxide (1.45 g, 36 mmol) in methanol (15 ml) and water (5 ml) were added to the methyl ester **78** (1.7 g, 1.8 mmol) in THF (20 ml) and the solution stirred at room temperature for 32 h. Water (20 ml) and ether (40 ml) were added and the solution was acidified with glacial acetic acid. The aqueous phase was extracted with ether (3×30 ml) and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to leave a viscous oil (1.67 g), which was dissolved in DCM (20 ml). Dicyclohexylcarbodi-imide (740 mg, 3.6 mmol), DMAP (10 mg, cat.) and 2-mercaptopyridine (300 mg, 2.7 mmol) were added at 0 °C and the yellow suspension stirred at room temperature for 4 h. The mixture was diluted with ether (20 ml) and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure and column chromatography of the residue eluting with ether in light petroleum (1:9) gave the *title compound* **79** (1.69 g, 91%) as a colourless viscous oil; $[\alpha]_D^{21}$ −76.5 (*c* 1.1 in CHCl); ν_{max} 2120, 1705, 1660, 1573, 1518, 1463, 1250, 1092, 1027, 836 and 776 cm^{-1}; δ_H (300 MHz, $CDCl_3$) −0.05–0.15 (21H, overlapping s, 7×$SiCH_3$), 0.88–1.61 [50H, m, Sn(C_4H_9)$_3$, −CH_2Si, 2×$SiC(CH_3)_3$ and 2-CH_3], 1.75 (3H, s, 8-CH_3), 1.94 (2H, m, 4-H_2), 2.35 (2H, m, 10-H_2), 3.16 (1H, m, 2-H), 3.55 and 3.78 (each 1H, m, OHC*H*CH_2Si), 4.12 (2H, m, 5-H and 11-H), 4.37 (1H, m, 3-H), 4.63 and 4.74 (each 1H, d, *J* 7, O*H*CHO), 5.34 (1H, dd, *J* 8.4, 15.7, 6-H), 5.55 (1H, br t, *J* 7.0, 9-H), 5.97 (1H, dd, *J* 5.2, 19.0, 12-H), 6.10 (1H, d, *J* 19.0, 13-H), 6.26 (1H, d, *J* 15.7, 7-H), 7.30 (1H, t, *J* 7.8, 5′-H), 7.63 (1H, d, *J* 7.8, 6′-H), 7.76 (1H, dt, *J* 1.8, 7.8, 4′-H) and 8.65 (1H, m, 3′-H); δ_C (75 MHz, $CDCl_3$) −4.73, −4.52, −4.40, −4.28, −1.32, 9.46, 12.60, 12.76, 13.77, 18.07, 18.21, 18.33, 24.73, 25.91, 27.27, 29.12, 37.94, 37.17, 39.64, 54.59, 65.48, 70.88, 73.49, 76.29, 91.59, 123.30, 125.95, 126.82, 129.90, 134.03, 136.92, 138.82, 150.35, 151.24, 151.96 and 198.65; *m*/*z* (ES^+) 1048 (M^++23, 13%), 969 (30), 761 (30), 497 (31), 388 (100), 247 (33) and 227 (28).

4.1.8. (3S,4R)-1-tert-Butyldimethylsilyl-3-[(2R,3R,5S,11S,6E,8E,12E)-3,11-di-tert-butyldimethylsilyloxy-2,8-dimethyl-13-tributylstannyl-5-(2-trimethylsilylethoxy)-methoxy-1-oxotrideca-6,8,12-trienyl]-4-((E)-2-iodoprop-1-enyl)-3-methylazetidin-2-one ***80***. Butyllithium (1.41 ml; 1.36 M in hexane, 1.9 mmol) was added to *N*,*N*-diethylamine (0.20 ml, 1.9 mmol) in THF (10 ml) at 0 °C. The solution was stirred for 15 min then cooled to -78 °C and added to the (3*S*,4*R*)-azetidinone **26** (0.65 g, 1.77 mmol) in THF (5 ml) dropwise at −78 °C. The solution was stirred for 15 min before the thioester **79** (1.52 g, 1.48 mmol) in THF (5 ml) cooled to −78 °C was added, and the mixture stirred for 3 h. Saturated aqueous ammonium chloride (2 ml) and ether (10 ml) were added and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with ether (2×5 ml) and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with ether in light petroleum (1:20) gave the *title compound* **80** (1.08 g, 57%) as a viscous colourless oil; $[\alpha]_D^{20}$ −55 (*c* 0.8 in $CHCl_3$); ν_{max} 1750, 1703, 1633, 1464, 1252, 1021, 836 and 776 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.05 (3H, s, $SiCH_3$), 0.08 [15H, s, $Si(CH_3)_3$ and 2×$SiCH_3$], 0.09, 0.18 and 0.27 (each 3H s, $SiCH_3$), 0.88–2.00 [56H, m, Sn(C_4H_9)$_3$, −CH_2Si and 3×$SiC(CH_3)_3$], 1.05 (3H, d, *J* 6.7, 2′-CH_3), 1.40 (3H, s, 3-CH_3), 1.74 (3H, s, 8′-CH_3), 1.74 and 1.94 (each 1H, m, 4′-H), 2.35 (2H, m, 10′-H_2), 2.54 (3H, d, *J* 1.3, 3″-H_3), 3.48 (1H, m, 2′-H), 3.60 and 3.79 (each 1H, m, OHC*H*CH_2Si), 4.08 (2H, m, 5′-H and 11′-H), 4.34 (1H, m, 3′-H), 4.64 and 4.74 (each 1H, d, *J* 7, O*H*CHO), 4.81 (1H, d, *J* 9.4, 4-H), 5.35 (1H, dd, *J* 8.5, 15.6, 6′-H), 5.54 (1H, br t, *J* 7.4, 9′-H), 5.98 (1H, dd, *J* 5.2, 19.0, 12′-H), 6.11 (1H, d, *J* 19.0, 13′-H), 6.14 (1H, dd, *J* 1.4, 9.3, 1″-H) and 6.23 (1H, d, *J* 15.6, 7′-H); δ_C (75 MHz, $CDCl_3$) −5.64, −4.63, −4.52, −4.52, −4.30, −4.21, −1.26, 9.55, 12.80, 13.81, 14.49, 18.11, 18.25, 18.38, 18.61, 26.11, 26.17, 27.29, 28.36, 29.02, 29.29, 37.40, 38.19, 40.19, 48.49, 54.04, 65.47, 71.07, 72.74, 73.74, 76.26, 91.90, 98.77, 126.47, 126.69, 129.61, 133.81, 137.94, 138.72, 151.09, 172.14 and 208.68; *m*/*z* (ES^+) 1302 (M^++23, 45%), 1176 (6), 1012 (5), 830 (6), 761 (26), 515 (9), 461 (34), 339 (23), 227 (41) and 121 (100).

4.1.9. (3S,4R)-1-tert-Butyldimethylsilyl-3-[(1S,2S,3R,5S,11S,6E,8E,12E)-3,11-di-tert-butyldimethylsilyloxy-2,8-dimethyl-1-hydroxy-13-tributylstannyl-5-(2-trimethylsilylethoxy)methoxytrideca-6,8,12-trienyl]-4-((E)-2-iodoprop-1-enyl)-3-methylazetidin-2-one ***81***. Potassium triethylborohydride (0.54 ml; 1.0 M in THF, 0.54 mmol) was added to the ketone **80** (0.63 g, 0.49 mmol) in ether (10 ml) dropwise at −78 °C and the mixture stirred for 15 min. Saturated aqueous ammonium chloride (5 ml) was added and, after being warmed to room temperature, the mixture was extracted with ether (3×10 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with ether in light petroleum (1:9) afforded the *title compound* **81** (0.49 g, 79%) as a colourless gum; $[\alpha]_D^{22}$ −42 (*c* 1.03 in CH_2Cl_2) (found: M^++Na, 1124.5232; $C_{54}H_{107}NO_6ISi_4{}^{120}SnNa$ requires M, 1124.5243); ν_{max} 3463, 1748, 1630, 1464, 1252, 1092, 1069, 1022, 836 and 776 cm^{-1}; δ_H (500 MHz, $CDCl_3$) −0.01 (3H, s, $SiCH_3$), 0.00 [9H, s, $Si(CH_3)_3$], 0.01, 0.09, 0.10, 0.13 and 0.21 (each 3H, s, $SiCH_3$), 0.83–1.50 [56H, m, Sn(C_4H_9)$_3$, −CH_2Si, 3×$SiC(CH_3)_3$], 1.04 (3H, s, 3-CH_3), 1.20 (3H, d, *J* 7.0, 2′-CH_3), 1.74 (3H, s, 8′-CH_3), 1.84 (3H, m, 2′-H and 4′-H_2), 2.34 (2H, m, 10′-H_2), 2.44 (3H, d, *J* 1.5, 3″-H_3), 3.42 and 3.67 (each 1H, m, OHC*H*CH_2Si), 3.89–4.45 (5H, m, 1′-H, 3′-H, 5′-H, 11′-H and OH), 4.45 (1H, d, *J* 9.4, 4-H), 4.49 and 4.62 (each 1H, d, *J* 7, O*H*CHO), 5.28 (1H, dd, *J* 5.0, 15.6, 6′-H), 5.51 (1H, m, 9′-H), 5.92 (1H, dd, *J* 5.56, 19.0, 12′-H), 6.05 (1H, dd, *J* 1.0, 19.0, 13′-H), 6.12 (1H, d, *J* 15.6, 7′-H) and 6.17 (1H, dd, *J* 1.5, 9.6, 1″-H); δ_C (75 MHz, $CDCl_3$) −5.59, −5.50, −4.80, −4.60, −4.28, −4.04, −1.27, 9.57, 12.86, 13.28, 13.83, 14.07, 17.97, 18.22, 18.40, 18.81, 25.89, 26.14, 26.25, 27.31, 28.43, 29.17, 34.89, 37.48, 41.64, 54.85, 65.02, 65.64, 72.61, 73.91, 76.16, 76.36, 91.54, 97.04, 125.80, 126.80, 130.19, 133.79, 137.91, 140.65, 150.98 and 175.79; *m*/*z* (FAB) 1224 (M^++23, 0.6%), 1076 (1.0), 508 (0.6), 405 (10), 289 (8) and 227 (100).

4.1.10. (3S,4R)-3-[(1S,2R,3R,5S,11S,6E,8E,12E)-2,8-di-methyl-13-tributylstannyl-5-(2-trimethylsilylethoxy)-methoxy-1,3,11-trihydroxytrideca-6,8,12-trienyl]-4-((E)-2-iodoprop-1-enyl)-3-methylazetidin-2-one ***82***. Tetrabutylammonium fluoride (250 μl; 1.0 M in THF, 250 mmol) was added to the azetidinone **81** (36 mg, 30 mmol) in THF (250 ml) at 0 °C and the solution was stirred a ambient temperature for 15 h. Saturated aqueous ammonium chloride (2 ml) and ethyl acetate (10 ml) were added and the aqueous phase was extracted with ethyl acetate (3×5 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with ethyl acetate in light petroleum (3:2) afforded the *title compound* **82**

(22 mg, 84%) as a colourless gum; $[\alpha]_D^{20}$ −35 (*c* 0.65 in CH_2Cl_2) (found M^++Na, 962.3240; $C_{40}H_{74}NO_6ISi^{120}SnNa$ requires M, 962.3251); ν_{max} 3401, 3054, 1753, 1627, 1463, 1265, 1218, 1056 and 738 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.00 [9H, s, $Si(CH_3)_3$], 0.80–1.60 [35H, m, $Sn(C_4H_9)_3$, $-CH_2Si$, 2′-H, 2′-CH_3 and 4′-H_2], 1.17 (3H, s, 3-CH_3), 1.74 (3H, s, 8′-CH_3), 2.40 (3H, m, 10′-H_2 and OH), 2.48 (3H, d, *J* 1.3, 3″-H_3), 3.48 and 3.63 (each 1H, m, OH*CH*CH_2Si), 3.67 (1H, s, OH), 3.86 (1H, dd, *J* 3.2, 9.6, 1′-H), 4.03–4.15 (3H, m, 5′-H, 11′-H and OH), 4.35 (1H, m, 3′-H), 4.56 (1H, d, *J* 9.2, 4-H), 4.58 and 4.72 (each 1H, d, *J* 7, O*H*CHO), 5.36 (1H, dd, *J* 8.1, 15.6, 6′-H), 5.53 (1H, br t, *J* 7.0, 9′-H), 5.74 (1H, s, NH), 6.01 (1H, dd, *J* 5.13, 19.0, 12′-H), 6.16 (1H, dd, *J* 0.8, 19.0, 13′-H), 6.19 (1H, dd, *J* 1.5, 9.6, 1″-H) and 6.23 (1H, d, *J* 15.6, 7′-H); δ_C (75 MHz, $CDCl_3$) −1.39, 9.48, 12.15, 12.76, 13.74, 13.91, 18.18, 27.27, 28.58, 29.08, 36.15, 39.45, 41.36, 53.25, 65.31, 65.78, 72.56, 74.731, 77.25, 78.02, 91.52, 99.02, 125.49, 128.33, 129.39, 134.99, 138.33, 138.49, 150.00 and 171.50; *m*/*z* (FAB) 962 (M^++23, 11%), 446 (6), 196 (84) and 177 (100).

4.1.11. (1S,2S,3R,4R,6S,12S,17R,7E,9E,13E,15E)-1,3,9,15-Tetramethyl-6-(2-trimethylsilylethoxy)methoxy-19-oxo-18-azabicyclo[15.2.0]nonadeca-7,9,13,15-tetraene-2,4,12-triol ***83****.* (Bisacetonitrile)palladium (II) chloride (1 mg, ~30 mol %) was added to a degassed solution of the iodostannane **82** (10 mg, 10 mmol) in DMF (4 ml) and the mixture stirred in the dark for 12 h. Saturated aqueous ammonium chloride (2 ml) and ethyl acetate (20 ml) were added, and the organic phase washed with brine and dried ($MgSO_4$). Concentration under reduced pressure and column chromatography of the residue using gradient elution with ethyl acetate in light petroleum (4:1 then 3:2) afforded the *title compound* **83** (1.5 mg, 27%) as a colourless gum (found M^++Na, 544.3093; $C_{28}H_{47}NO_6SiNa$ requires M, 544.3070); ν_{max} 3389, 1742, 1620, 1461, 1379, 1249, 1088, 1023, 966 and 836; δ_H (500 MHz, $CDCl_3$) −0.006 [9H, s, $Si(CH_3)_3$], 0.90 (2H, m, CH_2Si), 1.06 (3H, d, *J* 7, 3-CH_3), 1.24 (3H, s, 1-CH_3), 1.32 (1H, m, 3-H), 1.66 and 1.69 (each 3H, s, 9- and 15-CH_3), 1.90–2.00 (2H, m, 5-H_2), 2.40–2.50 (2H, m, 11-H_2), 3.30 (1H, s, OH), 3.44 (1H, m, O*H*CHCH_2Si), 3.66 (2H, m), 3.88, 3.97 and 4.30 (each 1H, m), 4.45 (1H, d, *J* 7, O*H*CHO), 4.58 (1H, d, *J* 9.8, 17-H), 4.61 (1H, d, *J* 7, OHC*H*O), 5.09 (1H, m 10-H), 5.28 (1H, dd, *J* 9.4, 15.6, 13-H), 5.36 (1H, dd, *J* 9.4, 15.8, 7-H), 5.46 (1H, d, *J* 9.8, 16-H), 5.70 (1H, s, NH), 6.015 and 6.025 (each 1H, d, *J* 15.6, 8-H and 14-H); δ_C −1.69, 12.33, 12.68, 12.77, 13.84, 17.79, 29.41, 35.74, 37.25, 42.18, 51.75, 64.47, 64.93, 72.55, 73.79, 74.12, 91.06, 126.24, 127.06, 129.18, 131.05, 133.59, 134.94, 138.02, 138.06 and 173.04; *m*/*z* (FAB) 544 (M^++23, 100%).

Triphenylarsine (7 mg, 23.26 μmol) was added to bis(benzylideneacetone)palladium (5 mg, 5.82 μmol) in DMF–THF (8 ml; 1:1) at ambient temperature followed by the iodostannane **82** (18 mg, 19.39 μmol) in DMF–THF (4 ml; 1:1) and the mixture stirred in the dark (wrapped in aluminium foil) for 22 h. Water (5 ml) and ethyl acetate (10 ml) were added and the aqueous phase extracted with ethyl acetate (3×10 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (3:2; with 1% triethylamine) as eluant gave the macrocycle **83** (4.5 mg, 52%) as an oil with spectroscopic data identical to those obtained earlier.

4.1.12. (3S,4R)-3-[(1S,2S,3R,5S,11S,6E,8E,12E)-3,11-Di-tert-butyldimethylsilyoxy-2,8-dimethyl-1-hydroxy-13-tributylstannyl-5-(2-trimethylsilylethoxy)methoxytrideca-6,8,12-trienyl]-4-((E)-2-iodoprop-1-enyl)-3-methylazetidin-2-one ***84****.* Solid anhydrous potassium fluoride (75 mg, 1.29 mmol) was added to the *N*-silylazetidinone **81** (0.55 g, 0.43 mmol) in MeOH–THF (10 ml; 4:1) at 0 °C and the mixture stirred at room temperature for 20 min. Saturated aqueous ammonium chloride (5 ml) and ether (20 ml) were added and the aqueous phase was extracted with ether (3×5 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with ether in light petroleum (1:4) afforded the *title compound* **84** (0.46 g, 92%) as a viscous oil; $[\alpha]_D^{21}$ −28 (*c* 0.85 in CH_2Cl_2) (found: M^++Na, 1190.5028; $C_{52}H_{102}NO_6ISi_3{}^{120}SnNa$ requires M, 1190.4980); ν_{max} 3473, 3287, 1758, 1632, 1463, 1250, 1069, 1021 and 836 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.00 [15H, s, $Si(CH_3)_3$ and 2×$SiCH_3$], 0.09 and 0.11 (each 3H, s, $SiCH_3$), 0.78–1.51 [50H, m, $Sn(C_4H_9)_3$, $-CH_2Si$, 2′-CH_3 and 2×$SiC(CH_3)_3$], 1.10 (3H, s, 3-CH_3), 1.70 (3H, s, 8′-CH_3), 1.90 (3H, m, 2′-H and 4′-H_2), 2.35 (2H, m, 10′-H_2), 2.45 (3H, d, *J* 1.28, 3″-H_3), 3.43 and 3.68 (each 1H, m, OH*CH*CH_2Si), 3.94–4.10 (5H, m, 1′-H, 3′-H, 5′-H, 11′-H and OH), 4.49 (1H, d, *J* 7, O*H*CHO), 4.56 (1H, d, *J* 8.9, 4-H), 4.61 (1H, d, *J* 7, OHC*H*O), 5.28 (1H, dd, *J* 8.1, 15.6, 6′-H), 5.52 (1H, t, *J* 7.2, 9′-H), 5.76 (1H, br s, NH), 5.92 (1H, dd, *J* 5.5, 19.0, 12′-H), 6.05 (1H, dd, *J* 1.0, 19.0, 13′-H), 6.13 (1H, d, *J* 15.6, 7′-H) and 6.20 (1H, dd, *J* 1.5, 8.9, 1″-H); δ_C (125 MHz, $CDCl_3$) −4.84, −4.76, −4.43, −4.38, −1.39, 9.42, 12.75, 13.02, 13.74, 13.94, 17.84, 18.09, 18.30, 25.85, 27.22, 28.57, 29.07, 34.53, 37.39, 41.59, 53.18, 65.41, 65.65, 72.23, 73.85, 76.12, 76.37, 91.36, 98.50, 125.67, 126.89, 130.45, 133.82, 138.13, 138.74, 151.02 and 170.72; *m*/*z* (FAB) 1190 (M^++23, 2%), 259 (19), 227 (100) and 171 (48).

4.1.13. (3S,4R)-3-[(1S,2S,3R,5S,11S,6E,8E,12E)-3,11-Di-tert-butyldimethylsilyoxy-2,8-dimethyl-1-hydroxy-13-tributylstannyl-5-(2-trimethylsilylethoxy)methoxytrideca-6,8,12-trienyl]-4-((E)-2-iodoprop-1-enyl)-3-methyl-1-propanoylazetidin-2-one ***85****.* Sodium hexamethyldisilylamide (0.46 ml; 1.0 M in THF, 0.46 mmol) was added to azetidinone **84** (0.235 g, 0.20 mmol) in THF (4 ml) dropwise at −78 °C and the solution stirred for 15 min. Propionyl chloride (0.22 ml; 1.0 M in THF, 0.22 mmol) was added dropwise and the mixture stirred at −78 °C for 30 min. Triethylamine (0.2 ml), saturated aqueous sodium hydrogen carbonate (5 ml) and ether (10 ml) were added and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with ether (2×5 ml) and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with ether in light petroleum (1:9) afforded the *title compound* **85** (0.192 g, 78%) as a colourless viscous oil; $[\alpha]_D^{22}$ −47 (*c* 0.95 in $CHCl_3$) (found M^++Na, 1246.5260); $C_{55}H_{106}NO_7ISi_3{}^{120}SnNa$ requires M, 1246.5242); ν_{max} 3449, 1787, 1710, 1638, 1462, 1376, 1251, 1067, 1021 and 836 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.00 (3H, s, $SiCH_3$), 0.01 [12H, s, $Si(CH_3)_3$], 0.10 and 0.15 (each 3H, s, $SiCH_3$), 0.83–1.48 (48H, m, $Sn(C_4H_9)_3$, $-CH_2Si$, 2′-H and 2×$SiC(CH_3)_3$], 1.12 (3H, s, 3-CH_3), 1.12 (3H, t, *J* 7.4, CH_2CH_3), 1.18 (3H, d, *J* 7.0, 2′-CH_3), 1.70 (3H, s, 8′-CH_3), 1.90 (2H, m, 4′-H_2), 2.32 (2H, m, 10′-H_2), 2.50 (3H, d, *J* 1.5, 3″-H_3), 2.60–2.78 (2H, m, CH_2CH_3), 3.43 and 3.68 (each 1H, m, OH*CH*CH_2Si), 3.92–4.10 (5H, m, 1′-H, 3′-H, 5′-H, 11′-H and OH), 4.50 and 4.63 (each 1H, d, *J* 7, O*H*CHO), 4.86 (1H, d, *J* 8.7, 4-H), 5.28 (1H, dd, *J* 8.1, 15.6, 6′-H), 5.53 (1H, t, *J* 7.3, 9′-H), 5.93 (1H, dd, *J* 5.3, 19.0, 12′-H), 6.06 (1H, dd, *J* 0.8, 19.0, 13′-H), 6.12 (1H, dd, *J* 1.5, 8.9, 1″-H) and 6.12 (1H, d, *J* 15.6, 7′-H); *m*/*z* (FAB) 1246 (M^++23, 1%), 259 (37), 227 (100), 171 (78) and 136 (145).

4.1.14. (3S,4R)-1-tert-Butyldimethylsilyl-3-[(1S,2S,3R,5S,11S,6E,8E,12E)-1-acetoxy-3,11-di-tert-butyldimethylsilyloxy-2,8-dimethyl-13-tributylstannyl-5-(2-trimethylsilylethoxy)methoxytrideca-6,8,12-trienyl]-4-((E)-2-iodoprop-1-enyl)-3-methylazetidin-2-one ***86****. N,N*-Dimethylaminopyridine (1 mg, ca. 7 μmol), triethylamine (45 μl, 0.32 mmol) and acetic anhydride (30 μl, 0.20 mmol) were added to the alcohol **81** (23 mg, 18 mmol) in dry dichloromethane (0.20 ml) and the reaction stirred for 3 h. Saturated aqueous ammonium chloride (5 ml) and ether (5 ml) were added and the aqueous layer extracted with ether (2×5 ml). The organic extracts were washed with brine (5 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with light petroleum–ether (10:1) gave the *title compound* **86** (21 mg, 89%) as a colourless oil, R_f 0.21 (6:1 light petroleum–ethyl acetate); $[\alpha]_D^{24}$ −80 (*c* 0.25 in $CHCl_3$); ν_{max} 1748, 1250, 1071, 1024 and 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) −0.01 [18H, s,

3×$SiCH_3$ and $Si(CH_3)_3$], 0.00, 0.04 and 0.16 (each 3H, s, $SiCH_3$), 0.80–1.00 [44H, 3×$SiC(CH_3)_3$, 3×$CH_2CH_2CH_2CH_3$ and $SiCH_2$], 1.11 (3H, d, *J* 7.0, 2′-CH_3), 1.15 (3H, s, 3-CH_3), 1.20–1.60 [12H, m, 3×$CH_3CH_2CH_2CH_2Sn$], 1.72 (3H, s, 8′-CH_3), 1.62–1.85 (2H, m, 4′-H_2), 2.04 (1H, m, 2′-H), 2.06 (3H, s, CH_3CO), 2.32 (2H, m, 10′-H_2), 2.42 (3H, d, *J* 1.0, 3″-H_3), 3.45 (1H, m, OHC*H*CH_2Si), 3.65 (2H, m, 3′-H and OHC*H*CH_2Si), 4.00–4.18 (3H, m, 4-H, 5′-H and 11′-H), 4.53 and 4.65 (each 1H, d, *J* 6.9, OHC*H*O), 5.20 (1H, br s, 1′-H), 5.27 (1H, dd, *J* 15.6, 8.5, 6′-H), 5.52 (1H, t, *J* 7.0, 9′-H), 5.95 (1H, dd, *J* 19.1, 5.2, 12′-H), 6.06 (1H, d, *J* 19.0, 13′-H), 6.13 (1H, m, 1″-H) and 6.15 (1H, d, *J* 15.6, 7′-H); *m*/*z* (ES^+) 1346 (M^++23, 4%), 305 (100) and 123 (95).

4.1.15. (3S,4R)-3-[(1S,2S,3R,5S,11S,6E,8E,12E)-1-Acetoxy-3,11-di-tert-butyldimethylsilyloxy-2,8-dimethyl-13-tributylstannyl-5-(2-trimethylsilylethoxy)methoxytrideca-6,8,12-trienyl]-4-((E)-2-iodoprop-1-enyl)-3-methylazetidin-2-one ***87***. Potassium fluoride (9 mg, 0.15 mmol) was added the azetidinone **86** (70 mg, 52 μmol) in MeOH–THF (3:1, 1.6 ml) and the reaction stirred for 30 min. Saturated aqueous ammonium chloride (5 ml) and ether (5 ml) were added and the aqueous layer extracted with ether (2×5 ml). The organic extracts were washed with brine (5 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with light petroleum–ethyl acetate (4:1) gave the *title compound* **87** (60 mg, 93%) as a colourless oil, R_f 0.09 (2:1 light petroleum–ether); $[\alpha]_D^{24}$ +12 (*c* 0.30 in $CHCl_3$); ν_{max} 1760, 1247, 1071, 1024 and 835 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [15H, s, 2×$SiCH_3$ and $Si(CH_3)_3$], 0.06 (6H, s, 2×$SiCH_3$), 0.8–1.00 [35H, 2×$SiC(CH_3)_3$, 3×$CH_3CH_2CH_2CH_2Sn$ and $SiCH_2$], 1.08 (3H, d, *J* 6.9, 2′-CH_3), 1.17 (3H, s, 3-CH_3), 1.26 [6H, hex, $CH_3CH_2CH_2CH_2Sn$], 1.47 (6H, m, $CH_3CH_2CH_2CH_2Sn$), 1.66 (1H, m, 4′-H), 1.72 (3H, s, 8′-CH_3), 1.82 (1H, m, 4′-H′), 2.02 (1H, m, 2′-H), 2.08 (3H, s, CH_3CO), 2.31 (2H, m, 10′-H_2), 2.46 (3H, d, *J* 1.0, 3″-H_3), 3.46 (1H, m, OHC*H*CH_2Si), 3.65 (2H, m, 3′-H and OHC*H*CH_2Si), 4.10 (2H, m, 5′-H and 11′-H), 4.20 (1H, d, *J* 8.8, 4-H), 4.54 and 4.64 (each 1H, d, *J* 6.9, OHC*H*O), 5.27 (2H, m, 1′-H and 6′-H), 5.51 (1H, t, *J* 6.6, 9′-H), 5.71 (1H, br s, NH), 5.94 (1H, dd, *J* 19.1, 5.2, 12′-H), 6.07 (1H, d, *J* 19.1, 13′-H), 6.16 (1H, m, 1″-H) and 6.19 (1H, d, *J* 15.6, 7′-H); *m*/*z* (ES^+) 1232 (M^++23, 15%), 839 (95) and 305 (100).

4.1.16. (3S,4R)-3-[(1S,2S,3R,5S,11S,6E,8E,12E)-1-Acetoxy-3,11-di-tert-butyldimethylsilyloxy-2,8-dimethyl-13-tributylstannyl-5-(2-trimethylsilylethoxy)methoxytrideca-6,8,12-trienyl]-1-tert-butoxycarbonyl-4-((E)-2-iodoprop-1-enyl)-3-methylazetidin-2-one ***88***. Di-*tert*-butyl dicarbonate (105 mg, 0.48 mmol) and *N*,*N*-dimethylaminopyridine (30 mg, 0.24 mmol) were added to the azetidinone **87** (197 mg, 0.16 mmol) in dry acetonitrile (3 ml) and the reaction stirred for 16 h. Saturated aqueous ammonium chloride (5 ml) and ether (5 ml) were added and the aqueous layer extracted with ether (2×5 ml). The organic extracts were washed with brine (5 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with light petroleum–ether (6:1) gave the *title compound* **88** (180 mg, 84%) as a colourless oil, R_f 0.50 (2:1 light petroleum–ether); $[\alpha]_D^{24}$ +35.2 (*c* 0.25 in $CHCl_3$); ν_{max} 1814, 1730, 1638, 1463, 1328, 1249, 1154, 1072, 1064, 1024, 836 and 776 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [15H, s, 2×$SiCH_3$ and $Si(CH_3)_3$], 0.06 and 0.07 (each 3H, s, $SiCH_3$), 0.85–0.95 [35H, 2×$SiC(CH_3)_3$, 3×$CH_3CH_2CH_2CH_2$ and $SiCH_2$], 1.05 (3H, d, *J* 7.0, 2′-CH_3), 1.19 (3H, s, 3-CH_3), 1.30–1.59 (12H, 3×$CH_3CH_2CH_2CH_2$), 1.58 [9H, s, $OC(CH_3)_3$], 1.74 (3H, s, 8′-CH_3), 1.85 (2H, m, 4′-H_2), 1.97 (1H, m, 2′-H), 2.06 (3H, s, CH_3CO), 2.33 (2H, m, 10′-H_2), 2.49 (3H, d, *J* 1.2, 3″-H_3), 3.46 and 3.65 (each 1H, m, OHC*H*CH_2Si), 3.69 (1H, m, 3′-H), 4.09 (1H, m, 11′-H), 4.13 (1H, m, 5′-H), 4.44 (1H, d, *J* 9.3, 4-H), 4.53 and 4.64 (each 1H, d, *J* 6.9, OHC*H*O), 5.28 (1H, dd, *J* 15.5, 8.4, 6′-H), 5.30 (1H, br s, 1′-H), 5.51 (1H, t, *J* 7.1, 9′-H), 5.94 (1H, dd, *J* 18.9, 5.2, 12′-H), 6.06 (1H, d, *J* 18.9, 13′-H), 6.12 (1H, m, 1″-H) and 6.15 (1H, d, *J* 15.5, 7′-H); δ_C (75 MHz, $CDCl_3$) −4.81, −4.46, −4.36, −1.46, 9.37, 10.94, 12.66, 13.27, 13.66, 18.03, 18.07, 18.23, 20.92, 25.83, 25.98, 27.16, 27.91, 28.48, 29.02, 37.29, 39.18, 40.50, 55.91, 62.15, 65.30, 72.73, 73.99, 76.17, 83.35, 91.44, 100.38, 125.86, 126.74, 129.91, 133.89, 135.12, 138.46, 147.31, 151.92, 166.96, 170.32; *m*/*z* (ES^+) 1327 (M^++18, 10%) and 816 (65).

4.1.17. (3S,4R)-3-[(1S,2S,3R,5S,11S,6E,8E,12E)-1-Acetoxy-3-tert-butyldimethylsilyloxy-2,8-dimethyl-11-hydroxy-13-tributylstannyl-5-(2-trimethylsilylethoxy)-methoxytridec-6,8,12-trienyl]-1-tert-butoxycarbonyl-4-((E)-2-iodoprop-1-enyl)-3-methylazetidin-2-one ***89***. Tetrabutylammonium fluoride (20 ml; 1.0 M in THF, 21 mmol) was added dropwise to the bis-*tert*-butyldimethylsilyl ether **88** (7 mg, 5 mmol) in dry THF (0.1 ml) and the mixture stirred for 16 h. Saturated aqueous ammonium chloride (5 ml) and ethyl acetate (5 ml) were added and the aqueous layer extracted with ethyl acetate (2×5 ml). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue eluting with light petroleum–ethyl acetate (6:1) gave the *title compound* **89** (3 mg, 48%) as a colourless oil, R_f 0.45 (3:1 light petroleum–ethyl acetate); $[\alpha]_D^{24}$ +5 (*c* 0.20 in $CHCl_3$); ν_{max} 3423, 1809, 1733, 1651 and 1064 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [9H, s, $Si(CH_3)_3$], 0.06 and 0.07 (each 3H, s, $SiCH_3$), 0.85–0.95 [29H, $SiC(CH_3)_3$, 3-CH_3, 3×$CH_3CH_2CH_2CH_2$ and $SiCH_2$], 1.06 (3H, d, *J* 7.0, 2′-CH_3), 1.30–1.59 (12H, 3×$CH_3CH_2CH_2CH_2$), 1.57 [9H, s, $OC(CH_3)_3$], 1.78 (3H, s, 8′-CH_3), 1.82 (2H, m, 4′-H_2), 1.97 (1H, m, 2′-H), 2.05 (3H, s, CH_3CO), 2.33 (2H, t, *J* 6.5, 10-H_2), 2.49 (3H, br s, 3″-H_3), 3.48 (1H, m, OHC*H*CH_2Si), 3.66 (2H, m, OHC*H*CH_2Si and 3′-H), 4.15 (2H, m, 5′-H and 11′-H), 4.44 (1H, d, *J* 8.9, 4-H), 4.53 and 4.65 (each 1H, d, *J* 6.8, OHC*H*O), 5.28 (1H, br s, 1′-H), 5.34 (1H, dd, *J* 15.6, 8.3, 6′-H), 5.54 (1H, t, *J* 7.1, 9′-H), 6.04 (1H, dd, *J* 19.3, 4.6, 12′-H), 6.08–6.12 (2H, m, 1″-H and 13′-H) and 6.18 (1H, d, *J* 15.6, 7′-H).

4.1.18. Methyl (2S,3S,4S,5R,7S,13S,8E,10E,14E)-3-acetoxy-2-[(1R,2E)-1-tert-butoxycarbonylamino-3-iodobut-2-enyl]-5,13-di-tert-butyldimethylsilyloxy-2,4,10-trimethyl-7-(2-trimethylsilylethoxy)methoxy-15-tributylstannylpentadeca-8,10,14-trienoate ***90***. Methanol (102 μl, 2.52 mmol) and potassium cyanide (164 mg, 2.52 mmol) were added to the azetidinone **88** (178 mg, 0.13 mmol) in dry DMF (2 ml) and the reaction stirred for 2 days. Saturated aqueous ammonium chloride (5 ml) and ethyl acetate (5 ml) were added and the aqueous layer extracted with ethyl acetate (2×5 ml). The organic extracts were washed with brine (5 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with light petroleum–ether (15:1) gave the *title compound* **90** (160 mg, 88%) as a colourless oil, R_f 0.76 (4:1 light petroleum–ethyl acetate); $[\alpha]_D^{24}$ −48 (*c* 1.25 in $CHCl_3$); ν_{max} 1747, 1721, 1465, 1248, 1162, 1076, 1025 and 835 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [18H, s, 3×$SiCH_3$ and $Si(CH_3)_3$], 0.09 (3H, s, $SiCH_3$), 0.85–0.92 [38H, 2×$SiC(CH_3)_3$, 4-CH_3, 3×$CH_3CH_2CH_2CH_2$ and $SiCH_2$], 1.14 (3H, s, 2-CH_3), 1.10–1.55 (12H, 3×$CH_3CH_2CH_2CH_2$), 1.40 [9H, s, $OC(CH_3)_3$], 1.73 (2H, m, 6-H_2), 1.78 (3H, s, 10-CH_3), 2.04 (3H, s, CH_3CO), 2.10–2.40 (3H, 4-H and 12-H_2), 2.50 (3H, br s, 4′-H_3), 3.47 (2H, m, 5-H and OHC*H*CH_2Si), 3.63 (3H, s, OCH_3), 3.65 (1H, m, OHC*H*CH_2Si), 4.07 (1H, m, 13-H), 4.20 (1H, m, 7-H), 4.55 (1H, m, 1′-H), 4.57 and 4.68 (each 1H, d, *J* 6.9, OHC*H*O), 5.17 (1H, br s, 3-H), 5.32 (1H, dd, *J* 15.7, 8.8, 8-H), 5.52 (1H, t, *J* 6.3, 11-H), 5.63 (1H, d, *J* 10.0, NH), 5.95 (2H, m, 2′-H and 14-H), 6.07 (1H, d, *J* 19.1, 15-H) and 6.22 (1H, *J* 15.8, 9-H); δ_C (75 MHz, $CDCl_3$) −4.83, −4.47, −3.81, −1.50, 9.14, 9.36, 12.81, 13.63, 17.99, 18.02, 18.20, 20.88, 25.81, 25.92, 27.14, 28.24, 28.55, 29.00, 37.30, 38.59, 39.58, 52.23, 53.15, 64.85, 72.33, 73.52, 74.11, 76.23, 91.23, 125.92, 126.81, 129.47, 134.15, 137.55, 139.46, 151.17, 154.91, 169.58 and 173.89; *m*/*z* (ES^+) 1364 (M^++23, 60%), 847 (20), 659 (30) and 460 (100).

4.1.19. Methyl (2S,3S,4S,5R,7S,13S,8E,10E,13R,14E)-3-acetoxy-2-[(1R,2E)-1-tert-butoxycarbonylamino-3-iodo-but-2-enyl]-5-tert-butyldimethylsilyloxy-13-hydroxy-2,4,10-trimethyl-7-(2-trimethylsilylethoxy)methoxy-15-tributylstannylpentadeca-8,10,14-trienoate ***91***. Tetra-*n*-butylammonium fluoride (0.16 ml; 1.0 M in THF) was added to the bis-*tert*-

butyldimethylsilyl ether **90** (70 mg, 50 μmol) in dry THF (0.4 ml) and the reaction stirred for 4 h. Water (0.1 ml) was added and the mixture extracted with ether. The ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with light petroleum–ethyl acetate (4:1) gave the *title compound* **91** (54 mg, 84%) as a colourless oil, R_f 0.25 (4:1 light petroleum–ethyl acetate); $[\alpha]_D^{24}$ −36 (*c* 1.80 in $CHCl_3$); ν_{max} 3458, 1722, 1654, 1482, 1367, 1248, 1163, 1074, 1024 and 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [9H, s, $Si(CH_3)_3$], 0.03 and 0.08 (each 3H, s, $SiCH_3$), 0.85–0.95 [29H, $SiC(CH_3)_3$, 4-CH_3, 3×$CH_3CH_2CH_2CH_2$ and $SiCH_2$], 1.13 (3H, s, 2-CH_3), 1.26–1.55 (12H, 3×$CH_3CH_2CH_2CH_2$), 1.39 [9H, s, $OC(CH_3)_3$], 1.73 (2H, m, 6-H_2), 1.81 (3H, s, 10-CH_3), 2.04 (3H, s, CH_3CO), 2.14 (2H, m, 4-H), 2.39 (2H, m, 12-H_2), 2.51 (3H, br s, 4′-H_3), 3.47 (2H, m, 5-H and $OHCHCH_2Si$), 3.68 (3H, s, OCH_3), 3.68 (1H, m, $OHCHCH_2Si$), 4.15 (2H, m, 7-H and 13-H), 4.58 (1H, m, 1′-H), 4.58 and 4.70 (each 1H, d, *J* 6.9, OHCHO), 5.19 (1H, br s, 3-H), 5.38 (1H, dd, *J* 15.7, 8.8, 8-H), 5.57 (1H, t, *J* 6.3, 11-H), 5.64 (1H, d, *J*10.0, NH), 5.95 (1H, d, *J* 8.4, 2′-H), 6.04 (1H, dd, *J* 18.8, 4.9, 14-H), 6.20 (1H, d, *J* 18.8, 15-H) and 6.26 (1H, *J* 15.7, 9-H); δ_C (75 MHz, $CDCl_3$) −4.68, −3.83, −1.51, 9.14, 9.38, 12.83, 13.61, 17.99, 18.03, 20.88, 25.91, 27.15, 28.24, 28.57, 28.96, 29.10, 36.25, 38.55, 39.57, 52.25, 53.21, 64.88, 72.31, 73.48, 74.08, 74.61, 76.49, 79.53, 91.44, 126.67, 128.01, 135.65, 137.53, 138.78, 150.04, 154.91 and 169.58; *m*/*z* (ES^+) 1249 (M^++23, 60%), 734 (60), 142 (100).

*4.1.20. Methyl (2S,3S,4S,5R,7S,13S,8E,10E,13R,14E)-3,13-diacetoxy-2-[(1R,2E)-1-tert-butoxycarbonylamino-3-iodobut-2-enyl]-5-tert-butyldimethylsilyloxy-2,4,10-trimethyl-7-(2-trimethylsilylethoxy)methoxy-15-tributylstannylpentadeca-8,10,14-trienoate **92**.* Triethylamine (15 μl, 0.11 mmol) and acetic anhydride (10 ml, 0.10 mmol) were added to the alcohol **91** (4 mg, 3 mmol) in dry dichloromethane (0.1 ml) and the reaction stirred for 24 h. Saturated aqueous ammonium chloride (5 ml) and ethyl acetate (5 ml) were added and the aqueous layer extracted with ethyl acetate (2×5 ml). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with light petroleum–ethyl acetate (4:1) gave the *title compound* **92** (2 mg, 52%) as a colourless oil, R_f 0.45 (4:1 light petroleum–ethyl acetate); $[\alpha]_D^{24}$ −31.6 (*c* 0.25 in $CHCl_3$); ν_{max} 1744, 1722, 1480, 1247, 1073 and 1024 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01 (3H, $SiCH_3$), 0.09 [12H, s, $Si(CH_3)_3$ and $SiCH_3$], 0.85–0.95 [29H, $SiC(CH_3)_3$, 4-CH_3, 3×$CH_3CH_2CH_2CH_2$ and $SiCH_2$], 1.10–1.55 (15H, 3×$CH_3CH_2CH_2CH_2$ and 2-CH_3), 1.59 [9H, s, $OC(CH_3)_3$], 1.76 (2H, m, 6-H_2), 1.81 (3H, s, 10-CH_3), 2.08 (6H, s, 2×CH_3CO), 2.16 (1H, m, 4-H), 2.44 (2H, m, 12-H_2), 2.52 (3H, br s, 4′-H_3), 3.51 (1H, m, 5-H), 3.52 (1H, m, $OHCHCH_2Si$), 3.68 (3H, s, OCH_3), 3.69 (1H, m, $OHCHCH_2Si$), 4.19 (1H, m, 7-H), 4.54 (1H, m, 1′-H), 4.57 and 4.69 (each 1H, d, *J* 6.8, OHCHO), 5.17 (1H, *J* 1.7, 3-H), 5.25 (1H, q, *J* 5.8, 13-H), 5.37 (1H, dd, *J* 15.7, 8.9, 8-H), 5.45 (1H, t, *J* 7.3, 11-H), 5.64 (1H, d, *J* 10.6, NH), 5.94 (1H, dd, *J* 19.2, 5.8, 14-H), 5.96 (1H, br d, *J* 10.8, 2′-H), 6.19 (1H, dd, *J* 19.2, 0.8, 15-H) and 6.22 (1H, *J* 15.7, 9-H); *m*/*z* (ES^+) 1287 (M^++18, 40%), 1274 (30), 1121 (56), 1062 (60), 242 (70), 150 (100).

*4.1.21. Methyl (1S,2R,7S,13S,15R,16S,17S)-17-acetoxy-2-tert-butoxycarbonylamino-15-tert-butyldimethylsilyl-oxy-7-hydroxy-1,4,10,16-tetramethyl-13-(2-trimethylsilylethoxy)methoxycycloheptadeca-3,5,9,11-tetraenecarboxylate **93**.* Triphenylarsine (5 mg, 15.64 μmo1) was added to bis(dibenzylideneacetone)palladium (3.5 mg, 3.9 μmol) in a degassed mixture of DMF and THF (8 ml; 1:1) at room temperature followed by the vinylstannane **91** (16 mg, 13 μmol) in a degassed mixture of DMF and THF (4 ml; 1:1) over 5 min. The resulting dark-green solution was stirred, wrapped in aluminium foil in the dark, at room temperature for 18 h. Water (5 ml) and ethyl acetate (10 ml) were added and the aqueous phase extracted with ethyl acetate (3×10 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue eluting with light petroleum and ethyl acetate (4:1+1.0% triethylamine) gave the *title compound* **93** (5 mg, 48%) as a pale yellow oil, $[\alpha]_D^{24}$ −130.66 (*c* 0.3 in CH_2C1_2) (found M^++Na, 832.4855. $C_{42}H_{75}O_{10}NSi_2Na$ requires M, 832.4827); ν_{max} 3426, 1727, 1498, 1367, 1249, 1166, 1091, 1023, 909 and 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [9H, s, $Si(CH_3)_3$], 0.09 and 0.12 (each 3H, s, $SiCH_3$), 0.89 (2H, m, $SiCH_2$), 0.90 (3H, d, *J* 7, 16-CH_3), 0.93 [9H, s, $SiC(CH_3)_3$], 1.27 (3H, s, 1-CH_3), 1.39 [9H, s, $OC(CH_3)_3$], 1.57 (2H, m, 14-H_2), 1.70 (3H, s, 10-CH_3), 1.87 (3H, s, 4-CH_3), 2.00 (3H, s, CH_3CO), 2.01 (1H, m, 16-H), 2.49 (2H, m, 8-H_2), 3.28 (1H, dd, *J* 9.5, 2.5, 15-H), 3.45 and 3.64 (each 1H, m, $OHCHCH_2Si$), 3.70 (3H, s, CH_3O), 4.09–4.15 (2H, m, 7-H and 13-H), 4.46 (1H, br, OH), 4.55 and 4.67 (each 1H, d, *J* 6.5, OHCHO), 4.68 (1H, br s, 17-H), 4.99 (1H, t, *J* 9.5, 2-H), 5.20 (1H, dd, *J* 16, 9, 6-H), 5.22 (1H, d, *J* 9.5, 3-H), 5.35 (1H, t, *J* 7.5, 9-H), 5.58 (1H, dd, *J* 15.5, 8.5, 12-H), 5.89 (1H, d, *J* 15.5, 11-H) and 5.81 (1H, d, *J* 16, 5-H); *m*/*z* (FAB) 832 (M^++23, 85%), 562 (75), 430 (75), 370 (79), 352 (71) and 334 (100).

*4.1.22. (3S,4R)-3-[(1S,2S,3R,5S,11S,6E,8E,12E)-1-Acetoxy-3,11-di-tert-butyldimethylsilyloxy-2,8-dimethyl-13-tributylstannyl-5-(2-trimethylsilylethoxy)methoxytrideca-6,8,12-trienyl]-4-((E)-2-iodoprop-1-enyl)-3-methyl-1-[(2S)-2-(4-methoxy)benzyloxy]propanoylazetidin-2-one **94**.* Potassium hexamethyldisilazide (140 μl; 1 M in THF, 140 μmol) was added to the *N*H-azetidinone **87** (113 mg, 93 μmol) in THF (3 ml) at −78 °C and the pale yellow solution stirred for 15 min. A freshly prepared solution of the (2*S*)-2-(4-methoxy)benzyloxypropanoyl chloride (28 mg, 0.121 mmol) in THF (0.2 ml) was added at −78 °C and the mixture stirred for 4 h. Saturated aqueous sodium hydrogen carbonate (50 mg) and ether (10 ml) were added and the mixture was allowed to warm to ambient temperature. The aqueous layer was extracted with ether (3×10 ml) and the organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography of the residue eluting with light petroleum–ether (5:1) gave the *title compound* **94** (91 mg, 70%) as a colourless oil, $[\alpha]_D^{22}$ −54 (*c* 1.7 in CH_2C1_2); ν_{max} 1812, 1729, 1639, 1502, 1325, 1024 and 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [9H, s, $Si(CH_3)_3$], 0.05 and 0.06 [each 6H, s, 2×$Si(CH_3)_2$], 0.75–0.92 [35H, m, $SiCH_2$, 2×$SiC(CH_3)_3$ and $Sn(CH_2CH_2CH_2CH_3)_3$], 1.06 (3H, d, *J* 7, 2″-CH_3), 1.24 (3H, s, 3-CH_3), 1.26 (6H, hex, *J* 7.5, $Sn(CH_2CH_2CH_2CH_3)_3$), 1.41 (3H, d, *J* 6.5, 3′-H_3), 1.47 [6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.62–1.88 (1H, m, 4″-H), 1.72 (3H, s, 8″-CH_3), 1.96 (1H, m, 4″-H′), 2.00 (3H, s, CH_3CO), 2.02 (1H, m, 2″-H), 2.31 (2H, m, 10″-H_2), 2.52 (3H, d, *J* 1.5, 3‴-H_3), 3.45 (1H, m, $OHCHCH_2Si$), 3.62–3.75 (2H, m, $OHCHCH_2Si$ and 3″-H), 3.77 (3H, s, OCH_3), 4.02–4.15 (2H, m, 5″-H and 11″-H), 4.31 (1H, d, *J* 10.5, 4-H), 4.49–4.63 (5H, m, OCH_2O, $ArCH_2O$, and 2′-H), 5.26 (1H, dd, *J* 15.5, 8.5, 6″-H), 5.34 (1H, s, 1″-H), 5.51 (1H, t, *J* 7, 9″-H), 5.94 (1H, dd, *J* 19, 5.5, 12″-H), 5.99 (1H, dq, *J* 10.5, 1.5, 1‴-H), 6.06 (1H, d, *J* 19, 13″-H), 6.15 (1H, d, *J* 15.5, 7″-H) and 6.84 and 7.26 (each 2H, d, *J* 8.5, ArH); *m*/*z* (FAB) 1425 (M^++23, 28%), 259 (32), 227 (100) and 171 (72).

*4.1.23. Methyl (2S,3S,4S,5R,7S,13S,8E,10E,14E)-3-acetoxy-5,13-di-tert-butyldimethylsilyloxy-2-{(1R,2E)-3-iodo-1-[(S)-2-(4-methoxy)benzyloxypropanoylamino]-but-2-enyl}-7-(2-trimethylsilylethoxy)methoxy-15-tributylstannyl-2,4,10-trimethylpentadeca-8,10,14-trienoate **95**.* Anhydrous methanol (52 μl, 1.29 mmol) and potassium cyanide (84 mg, 1.29 mmol) were added to the *N*-acylazetidinone **94** (81 mg, 54.62 μmol) in DMF (2 ml) and the mixture stirred at room temperature for 5 h. Saturated aqueous ammonium chloride (2 ml) and ether (5 ml) were added and the aqueous phase was extracted with ether (3×10 ml). The organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography of the residue eluting with light petroleum–ether (5:1) gave the *title compound* **95** (71 mg, 87%) as a colourless oil, $[\alpha]_D^{22}$ −32 (*c* 0.9 in CH_2C1_2); ν_{max} 3405, 1748, 1682, 1613, 1513, 1463, 1376, 1249, 1100, 1027, 836 and 776 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [9H, s, $Si(CH_3)_3$], 0.02 (6H, s, 2×$SiCH_3$), 0.04 and 0.11 (each 3H, s, $SiCH_3$), 0.81–0.96 [38H, m, 4-CH_3, $SiCH_2$, 2×SiC

$(CH_3)_3$ and $Sn(CH_2CH_2CH_2CH_3)_3$], 1.16 (3H, s, 2-CH_3), 1.30 (3H, d, *J* 6.5, 3″-H_3), 1.31 [6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.49 [6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.5–1.8 (2H, m, 6-H_2), 1.74 (3H, s, 10-CH_3), 2.03 (3H, s, CH_3CO), 2.08 (1H, m, 4-H), 2.21–2.43 (2H, m, 12-H_2), 2.54 (3H, d, *J* 1.5, 4′-H_3) 3.46 (2H, m, OHC*H*CH_2Si and 5-H), 3.55 (3H, s, CH_3O), 3.66 (1H, m, OHC*H*CH_2Si), 3.82 (3H, s, OCH_3), 3.86 (1H, q, *J* 6.5, 2″-H), 4.06 (1H, m, 13-H), 4.16 (1H, m, 7-H), 4.38 and 4.50 (each 1H, d, *J* 11, OHC*H*Ar), 453 and 4.65 (each 1H, d, *J* 6.5, OHC*H*O), 4.87 (1H, t, *J* 10, 1′-H), 5.11 (1H, br s, 3-H), 5.28 (1H, dd, *J* 15.5, 8.5, 8-H), 5.51 (1H, t, *J* 7, 11-H), 5.88 (1H, dq, *J* 10, 1.5, 2'-H), 5.95 (1H, dd, *J* 19, 5.5, 14-H), 6.07 (1H, d, *J* 19, 15-H), 6.19 (1H, d, *J* 15.5, 9-H), 6.90 and 7.27 (each 2H, d, *J* 8, ArH) and 7.74 (1H, d, *J* 10, NH); *m*/*z* (FAB) 1455 (M^++23, 4%), 227 (100) and 171 (61).

4.1.24. Methyl (2S,3S,4S,5R,7S,13S,8E,10E,14E)-3-acetoxy-5-tert-butyldimethylsilyloxy-13-hydroxy-2-{(1S,2E)-3-iodo-1-[(S)-2-(4-methoxy)benzyloxypropanoylamino]but-2-enyl}-7-(2-trimethylsilylethoxy)-methoxy-15-tributylstannyl-2,4,10-trimethylpentadeca-8,10,14-trienoate ***96****.* TBAF (68 μl; 1 M in THF, 68 μmol) was added to the bis-silyl ether **95** (33 mg, 22.68 mmol) in THF (0.5 ml) at room temperature and the mixture stirred for 4 h. Water (0.2 ml) was added and the mixture concentrated under reduced pressure. Column chromatography eluting with light petroleum–ether (3:1) gave the *title compound* **96** (24 mg, 81%) as a colourless oil, $[\alpha]_D^{22}$ −40 (*c* 1.4 in CH_2C1_2); ν_{max} 3407, 1748, 1680, 1613, 1514, 1463, 1377, 1249, 1102, 1027 and 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [9H, s, Si$(CH_3)_3$], 0.05 and 0.11 (each 3H, s, $SiCH_3$), 0.85–0.93 [29H, m, 4-CH_3, Si*C*H_2, $SiC(CH_3)_3$ and $Sn(CH_2CH_2CH_2CH_3)_3$], 1.16 (3H, s, 2-CH_3), 1.31 [6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.31 (3H, d, *J* 6.5, 3″-H_3), 1.44–1.53 [6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.69 (2H, m, 6-H_2), 1.77 (3H, s, 10-CH_3), 2.03 (3H, s, CH_3CO), 2.08 (1H, m, 4-H), 2.39 (2H, m, 12-H_2), 2.54 (3H, d, *J* 1.5, 4′-H_3), 3.47 (2H, m, OHC*H*CH_2Si and 5-H), 3.55 (3H, s, CH_3O), 3.65 (1H, m, OHC*H*CH_2Si), 3.81 (3H, s, CH_3O), 3.86 (1H, q, *J* 6.5, 2″-H), 4.15 (3H, m, 7-H, 13-H and OH), 4.38 and 4.50 (each 1H, d, *J* 11, ArHC*H*), 4.54 and 4.66 (each 1H, d, *J* 7, OHC*H*O), 4.87 (1H, t, *J* 10, 1′-H), 5.10 (1H, br s, 3-H), 5.35 (1H, dd, *J* 15.5, 8.5, 8-H), 5.52 (1H, t, *J* 7, 11-H), 5.88 (1H, dq, *J* 10, 1.5, 2′-H), 6.04 (1H, dd, *J* 19, 5.5, 14-H), 6.19 (1H, d, 19, 15-H), 6.22 (1H, d, *J* 15.5, 9-H), 6.90 and 7.27 (each 2H, d, *J* 8, ArH) and 7.73 (1H, d, *J* 10, NH); *m*/*z* (FAB) 1343 (M^++23, 19%), 1262 (27), 694 (90), 634 (30), 388 (37), 267 (100) and 176 (83).

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Supplementary data

Full experimental procedures and spectroscopic data for all steps and new compounds not included here are available as supplementary data. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.129.

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