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PAPER

The stereocontrolled total synthesis of spirastrellolide A methyl ester. Expedient construction of the key fragments†‡§

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Due to a combination of their promising anticancer properties, limited supply from the marine sponge source and their unprecedented molecular architecture, spirastrellolides represent attractive and challenging synthetic targets. A modular strategy for the synthesis of spirastrellolide A methyl ester, which allowed for the initial stereochemical uncertainties in the assigned structure was adopted, based on the envisaged sequential coupling of a series of suitably functionalised fragments; in this first paper, full details of the synthesis of these fragments are described. The pivotal C26–C40 DEF bis-spiroacetal was assembled by a double Sharpless asymmetric dihydroxylation/acetalisation cascade process on a linear diene intermediate, configuring the C31 and C35 acetal centres under suitably mild acidic conditions. A C1–C16 alkyne fragment was constructed by application of an oxy-Michael reaction to introduce the A-ring tetrahydropyran, a Sakurai allylation to install the C9 hydroxyl, and a 1,4-*syn* boron aldol/directed reduction sequence to establish the C11 and C13 stereocentres. Two different coupling strategies were investigated to elaborate the C26–C40 DEF fragment, involving either a C17–C25 sulfone or a C17–C24 vinyl iodide, each of which was prepared using an Evans glycolate aldol reaction. The remaining C43–C47 vinyl stannane fragment required for introduction of the unsaturated side chain was prepared from (*R*)-malic acid.

Introduction

Marine organisms, particularly sponge invertebrates and their associated bacteria, continue to be an important source of novel biologically active compounds, both in terms of their significant therapeutic potential and as novel molecular probes for chemical biology studies.[1,2] In particular, marine macrolides that exhibit exceptional levels of antimitotic activity, combined with unique modes of action, represent valuable lead structures for the development of new generation anticancer drugs. Furthermore, as the promising biological activity exhibited by many complex marine macrolides is often mirrored by their scarce natural supply, and complicated by the challenge of full stereochemical determination, chemical synthesis represents a critically important exercise. In this regard, the successful development of Halaven by Eisai, as a fully synthetic analogue of the halichondrin marine macrolides for the treatment of metastatic breast cancer, constitutes a compelling proof-of-concept.[3] The Novartis large-scale synthesis of discodermolide, a rare polyketide of marine sponge origin, also represents an impressive example of what can be achieved towards the development of complex marine natural products as anticancer drugs in a pharmaceutical setting.[4]

The spirastrellolides constitute a structurally unprecedented family of antimitotic macrolides, initially isolated by bioassay-guided fractionation from extracts of the Caribbean sponge *Spirastrella coccinea* collected off reef walls near Capucin, Dominica.[5] The most abundant member of this family is spirastrellolide A (**1**), which was first reported by the Andersen group in 2003,[5a] followed by six structurally related congeners (spirastrellolides B–G, **2–7**).[6] As shown in Fig. 1, the spirastrellolide scaffold with its signature 38-membered macrolactone and embedded spiroacetal motifs displays considerable architectural complexity, with variation in the degree of chlorination at C4 and C28, olefination at $\Delta^{15,16}$, methylation at the C46-OH in the unsaturated side-chain and hydroxylation at C8. While the spirastrellolides are C47 carboxylic acids, conversion to the corresponding methyl esters **8–14** proved necessary to enable the complete separation of the congeners and final purification, and the majority of the physical and biological data for the spirastrellolides has been collected for these purified methyl esters and their derivatives. More recently, the Matsunaga group[7] have isolated

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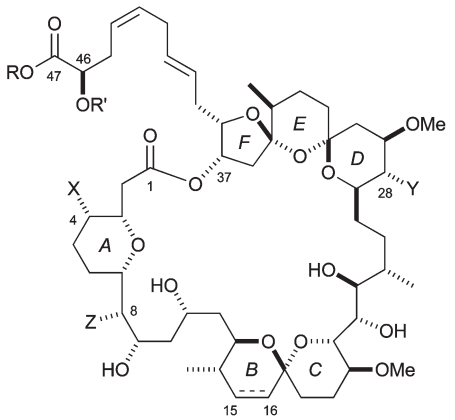
‡ Electronic supplementary information (ESI) available: this provides the entire Experimental section for this paper. See DOI: 10.1039/c2ob25100k

§ Dedicated to Professor Ian Fleming.



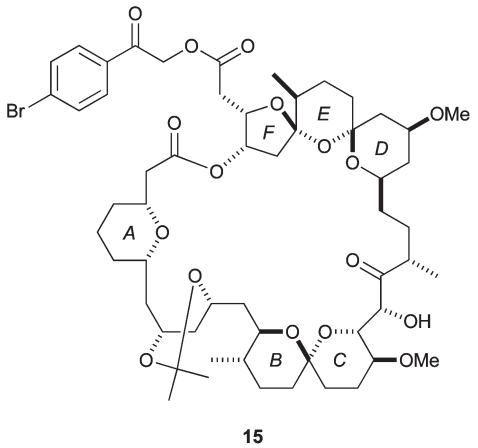
1: R = R' = X = Z = H, Y = Cl, $\Delta^{15,16}$, Spirastrellolide A
2: R = R' = X = Y = Z = H, Spirastrellolide B
3: R = R' = X = Y = H, Z = OH, Spirastrellolide C
4: R = R' = Z = H, X = Y = Cl, $\Delta^{15,16}$, Spirastrellolide D
5: R = R' = X = Y = Z = H, $\Delta^{15,16}$, Spirastrellolide E
6: R = R' = X = Z = H, Y = Cl, Spirastrellolide F
7: R = X = Z = H, Y = Cl, R' = Me, $\Delta^{15,16}$, Spirastrellolide G
8: R = Me, R' = X = Z = H, Y = Cl, $\Delta^{15,16}$
9: R = Me, R' = X = Y = Z = H
10: R = Me, R' = X = Y = H, Z = OH
11: R = Me, R' = Z = H, X = Y = Cl, $\Delta^{15,16}$
12: R = Me, R' = X = Y = Z = H, $\Delta^{15,16}$
13: R = Me, R' = X = Z = H, Y = Cl
14: R = R' = Me, X = Z = H, Y = Cl, $\Delta^{15,16}$

Fig. 1 Structures of spirastrellolides A–G and their corresponding methyl esters.

spirastrellolide A from a different sponge collected off the coast of Nagannu Island, Okinawa, suggesting that the spirastrellolides may be secondary metabolites produced by symbiotic bacteria.

Spirastrellolide A (**1**) was found to accelerate cell entry into mitosis from S-phase, prior to initiating cell-cycle arrest during M-phase, which is thought to be mediated through potent and selective inhibition of protein phosphatase 2A (IC_{50} = 1 nM).[5] Drugs that target the inhibition of either protein kinases (PKs, mediating phosphorylation of proteins) or protein phosphatases (PPs, governing dephosphorylation of proteins) have shown considerable therapeutic potential in fields tackling cancer, obesity, organ transplant rejection and the formation of Alzheimer's plaques.[8] The methyl ester **8** also exhibited potent antiproliferative activity against a panel of cancer cell lines. This promising biological profile marks out the spirastrellolides as exciting lead structures for drug discovery,[9] and combined with the scarcity of the natural supply and the initial uncertainties over the full stereochemistry, has stimulated considerable synthetic interest, with numerous studies towards fragments reported.[10–12]

The continuing efforts of the Andersen group to elucidate the full stereostructure finally led in 2007 to a definitive assignment of the configuration of the macrolide core of spirastrellolide B through single crystal X-ray diffraction studies on the *p*-bromophenacyl derivative **15** (Fig. 2).[6a] This was followed by the assignment of the remote C46 stereocentre within the side chain



15

Fig. 2 Derivative **15** of spirastrellolide B prepared by the Andersen group for structure elucidation by single crystal X-ray diffraction.

by degradation studies on spirastrellolide D and correlation with dimethyl (*R*)-malate.[6b] In the meantime, we and other groups had initiated synthetic studies based on the 2004 spirastrellolide A structure of Andersen,[5b] which had 16 possible stereochemical permutations. Soon after the disclosure of the full stereostructure by the Andersen group,[6b] we communicated our first total synthesis of spirastrellolide A methyl ester (**8**) which validated the configurational assignment.[13] This was followed by the Fürstner group's two total syntheses of spirastrellolide F methyl ester (the 15,16-dihydro congener **13**, Fig. 1).[14] In this and the accompanying paper,[15] we now provide full details and discussion of our total synthesis, concentrating on the ongoing stereochemical issues and the evolution of efficient fragment assembly strategies that ultimately proved successful in preparing spirastrellolide A methyl ester. In this first paper, we provide a full account of the development and optimisation of scaleable and highly stereocontrolled routes to the key spirastrellolide fragments.

Initial synthetic efforts and strategy evolution

The spirastrellolides clearly present a significant synthetic challenge due to the array of functional groups and the high level of oxygenation, which necessitates careful attention to chemoselectivity issues and the selection of a robust but flexible protecting group strategy. However, of arguably greater significance for the synthetic chemist is the issue of stereochemistry which must be addressed.

Spirastrellolide A (**1**, Fig. 3) bears 20 stereogenic centres distributed around the 38-membered macrocycle, which also incorporates three cyclic subunits: a *cis*-fused tetrahydropyran (A-ring), a [6,6]-spiroacetal (BC-rings) and a [5,6,6]-bis-spiroacetal (DEF-rings), with the latter two benefiting from double anomeric effect stabilisation. From the outset, we reasoned that these well-defined spiroacetal ring systems might be obtained *via* acid-catalysed acetalisation under thermodynamic control from suitable linear precursors. In addition, there is a remote stereocentre at C46 within the unsaturated side-chain. Initially, the configurational relationship between the C3–C7 tetrahydropyran A-ring (red), C9–C24 BC-spiroacetal (green),

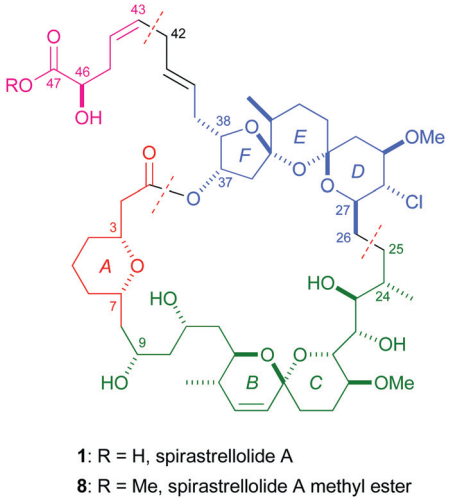
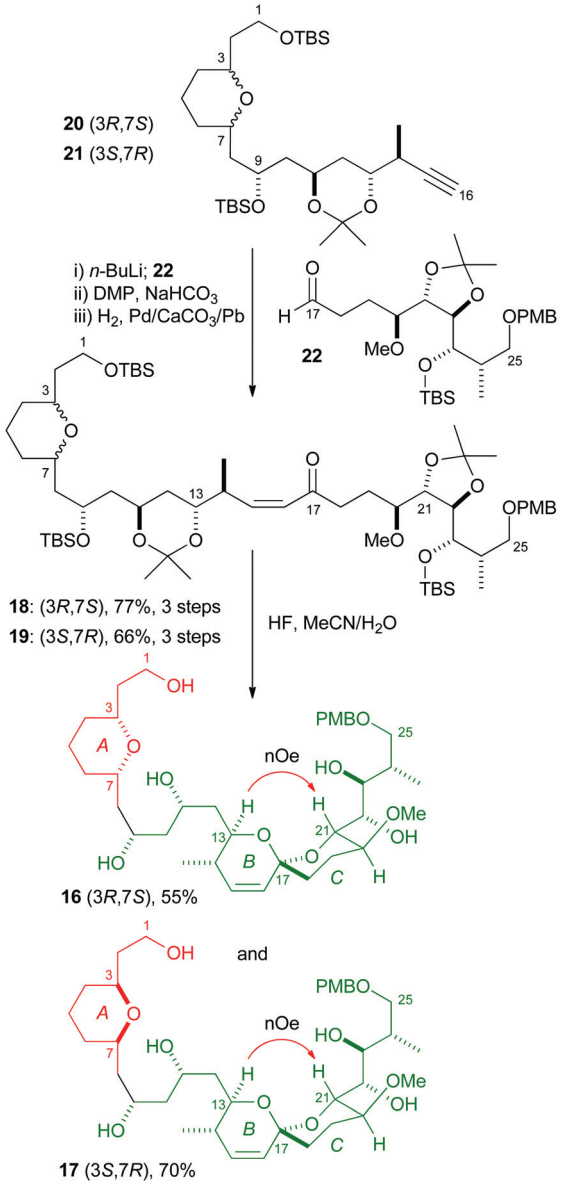


Fig. 3 Initial target structure with key bond disconnections at C42–C43, C25–C26 and C1–OC37; where the configurational relationship between the four coloured stereoclusters was not defined.

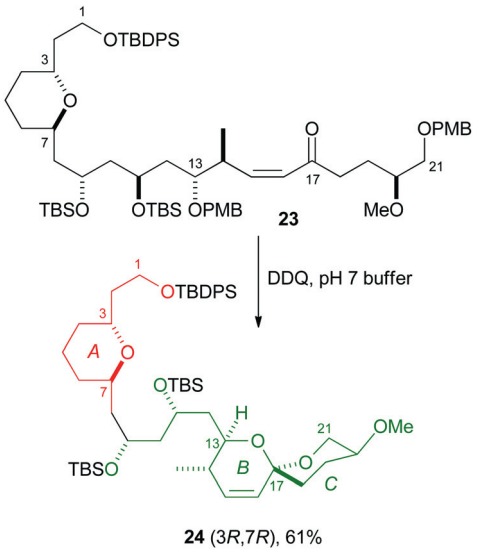
DEF-bis-spiroacetal (blue) and C46 hydroxyl stereocentre (purple) was not confidently assigned by the Andersen group, such that there were 16 possible stereoisomers to be considered. Our synthetic plan therefore needed to be highly flexible due to this configurational uncertainty, and should also allow for access to novel structural analogues for SAR studies. Hence, the adoption of a modular approach, combining the different stereoclusters in suitably functionalised fragments to progressively assemble the northern and southern spiroacetal-containing regions and the macrolide core, lay at the heart of our synthesis plan. Taking the above factors into consideration, our initial studies[12a–d] targeted the construction of fully elaborated northern and southern hemispheres with the objective of narrowing down the number of stereochemical permutations by NMR comparisons with the available data for the natural product. Disconnection of the side-chain at C42–C43, allowing for the undefined C46 stereocentre, would be used to reduce the stereoconundrum to the three highlighted macrocyclic domains (C3–C7, C9–C24, C27–C38) in Fig. 3. Following disconnection across the macrolactone bridge, a C25–C26 bond scission would then isolate the DEF-spiroacetal as a single region of known stereochemistry together with the C1–C25 ABC-region.

Before discussing the details of the synthetic strategy which ultimately proved successful, it is helpful to first summarise some of the key results from intelligence gathering exercises directed towards the construction of the northern and southern hemisphere regions, where the selection of suitable protecting groups was found to be a critical issue. In early exploratory work, we targeted the synthesis of both possible diastereomers of the C1–C25 southern hemisphere in **16** and **17** (Scheme 1).[12b] The precursor C1–C25 enones **18** and **19** were constructed incorporating either the (3*R*,7*S*)- or (3*S*,7*R*)-configuration of the A-ring tetrahydropyran from the diastereomeric alkynes **20** and **21**, combined with the same aldehyde **22**. In order to achieve the removal of the two acetonides and induce controlled spirocyclisation, rather forcing conditions were found to be required (aq. HF, MeCN), leading to complete desilylation and generation of

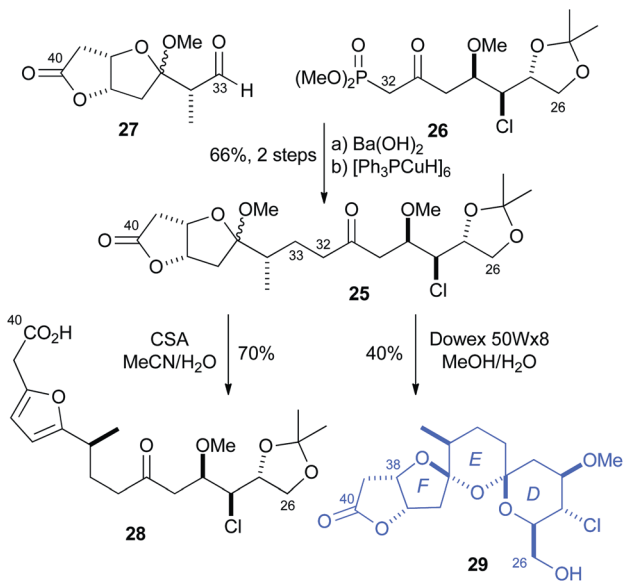


Scheme 1 Initial synthesis of two diastereomers **16** and **17** of southern hemisphere C1–C25 region.

pentaol spiroacetals **16** and **17**. Both these pentaols showed excellent spectroscopic correlation with the natural product, where on balance the (3*R*,7*S*) diastereomer **16** appeared to correlate more closely to the spirastrellolide NMR data than counterpart **17**. However, an unequivocal conclusion could not be reached at this stage. This result was not entirely unexpected as the macrocycle and the appended side-chain are likely to strongly affect the molecular conformation and resultant NMR spectra compared to these simpler fragments, particularly in the C7–C9 region. Nevertheless, this work provided a preliminary indication that **16** was the better match, which was pursued and ultimately proved to be correct. As discussed later, whilst some aspects of the synthesis of spiroacetal **16** would be retained, the conditions required for acetonide deprotection were somewhat harsh and capricious. Consequently, our preferred longer term strategy for BC-spiroacetalisation would incorporate PMB ethers



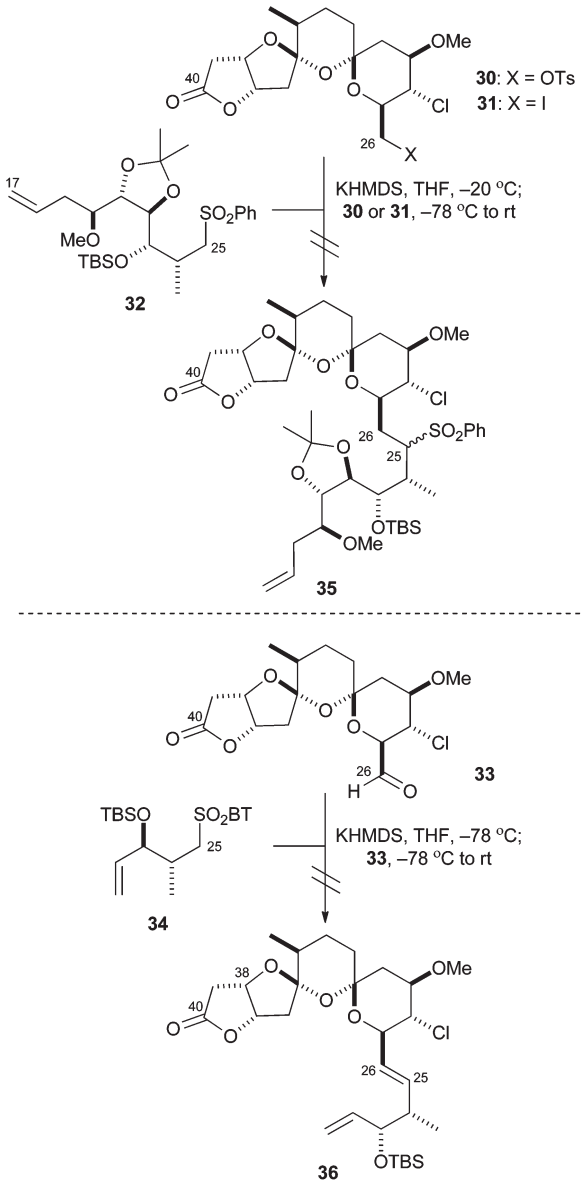
Scheme 2 Initial synthesis of southern hemisphere C1–C21 region **24**.



Scheme 3 Initial synthesis of tetracyclic C26–C40 DEF-bis-spiroacetal **29**.

at C13 and C21, following the success of a DDQ-mediated deprotection and spirocyclisation of **23** in constructing the related C1–C21 spiroacetal **24** (Scheme 2).[12c]

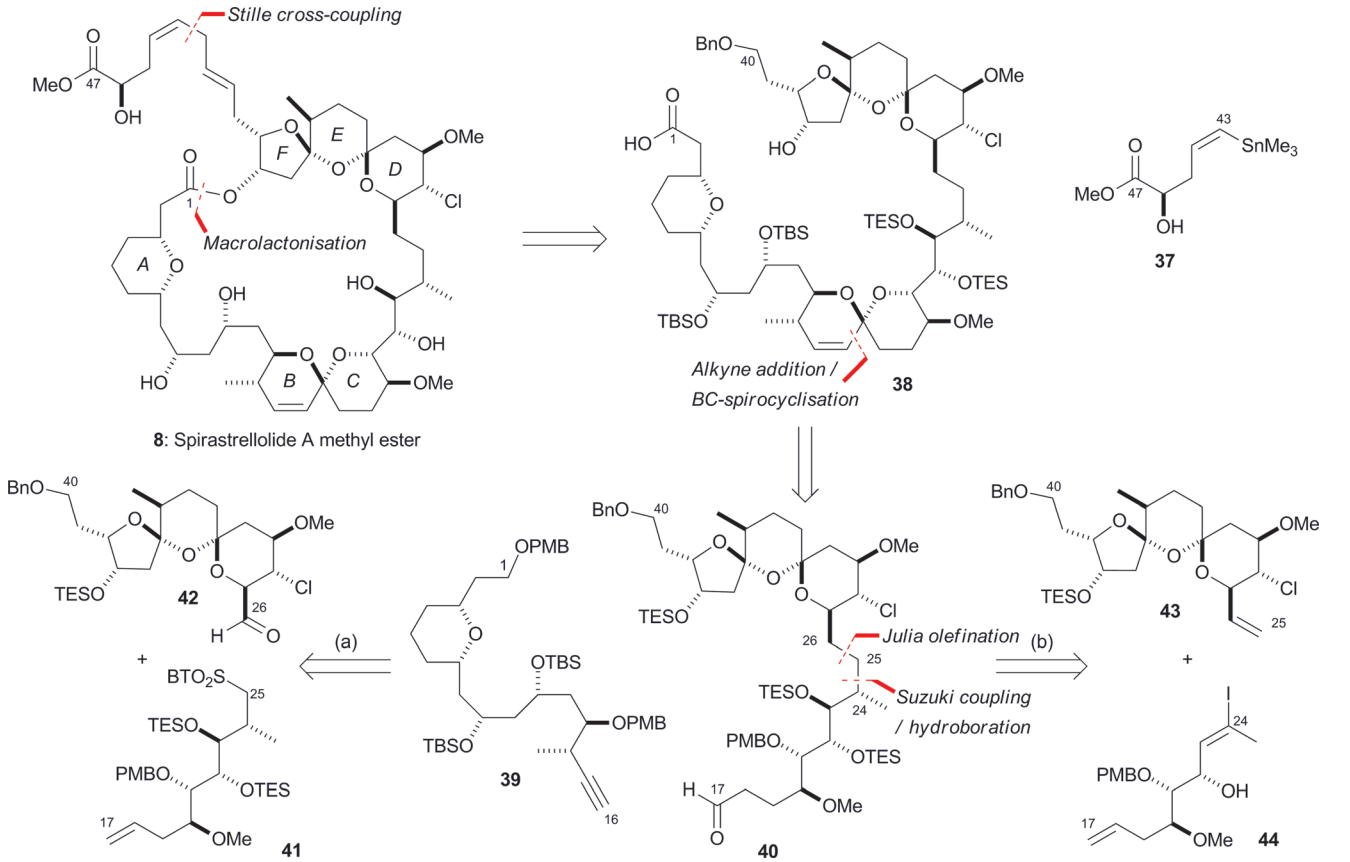
In our early studies on the assembly of the northern hemisphere region, incorporating the characteristic DEF-bis-spiroacetal of spirastrellolide A, the C26–C40 ketone **25**, which we envisaged to be a precursor to this spiroacetal was prepared by HWE coupling between acetonide-containing phosphonate **26** and aldehyde **27** (Scheme 3).[12a] Deprotection again proved problematic, with the strongly acidic conditions required for cleavage (*e.g.* HCl or CSA) leading to competitive elimination of the F-ring to furan **28**. Even under optimised conditions (Dowex 50Wx8, MeOH–H_2O, 70 °C), at best only a 40% yield of the required tetracyclic C26–C40 DEF subunit **29** could be obtained.



Scheme 4 Examples of unsuccessful attempts at C25–C26 bond formation with tetracyclic DEF components.

Nevertheless, detailed ^1H and ^{13}C NMR comparison of **29** with the analogous data reported for spirastrellolide A methyl ester revealed excellent homology, confirming the structural and stereochemical assignment for this key region. While the subsequent examination of alternative routes to the DEF-bis-spiroacetal led to some improvements,[12d,f] it became clear that a complete revision of our synthetic strategy for the northern hemisphere region was required to enable access to adequate stocks of material to advance the total synthesis.

In addition to issues associated with accessing C26–C40 DEF-bis-spiroacetal **29** in useful quantities, preliminary exploratory investigations into the formation of the C25–C26 bond to connect the northern and southern hemisphere regions were carried out (Scheme 4). For this challenging union, two strategies were pursued using substrates which could be readily derived from tetracycle **29**: an alkylation of tosylate **30** or iodide



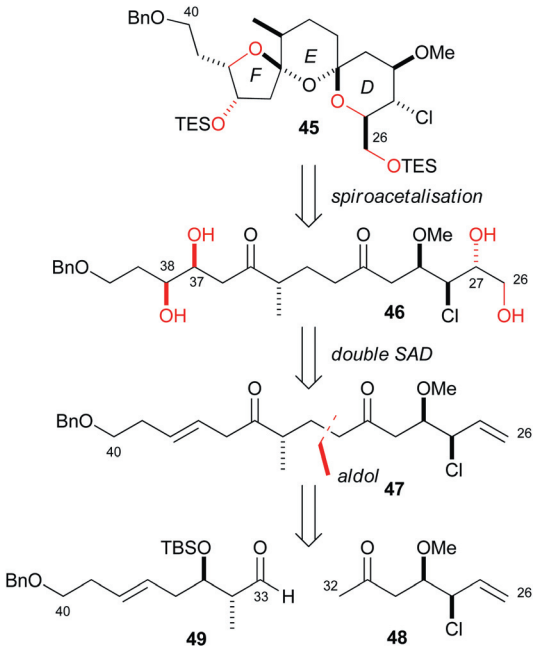
Scheme 5 Revised synthesis plan for spirastrellolide A methyl ester based on either (a) Julia olefination to form C25–C26 bond or (b) Suzuki coupling and hydroboration to form C24–C25 bond in aldehyde **40**.

31 with sulfone **32**, and a Julia olefination of aldehyde **33** with model sulfone **34**.[16] Unfortunately, neither of these approaches proved successful, and in all cases complete degradation of the DEF-component was observed without isolation of any required coupled products **35** or **36**, thought to be due to the sensitive nature of the C40 δ-lactone functionality. Overall, these frustrating setbacks prompted a reconsideration of our approach to not only constructing the DEF-region but the macrocycle as a whole, leading to the following strategy evolution and identification of more suitable fragments and protecting groups.

Revised synthesis plan

The presence of the $\Delta^{15,16}$ alkene in the B-ring of spirastrellolide A meant that our original fragment coupling strategy,[12a,b] involving the union of preformed ABC- and DEF-subunits, was rather inflexible, with chemoselectivity issues arising from any coupling methods that would introduce additional unsaturation. It was recognised that the convergency of the original strategy would have to be sacrificed for an alternative approach, whereby the $\Delta^{15,16}$ alkene could be introduced subsequent to elaboration at the C26 position of the DEF-subunit, which might now be achieved under suitably mild conditions.

As shown in our revised synthesis plan outlined in Scheme 5, spirastrellolide A methyl ester (**8**) would arise from the late-stage Stille coupling of side-chain stannane **37** to a preformed macrocycle, which would be closed by macrolactonisation between the C1 carboxylic acid and C37 hydroxyl group in truncated *seco*-acid **38**. Now however, the C1–C16 alkyne **39** containing the $\Delta^{15,16}$ unsaturation was excised, revealing fully elaborated C17–C40 aldehyde **40**. Coupling of alkyne **39** with aldehyde **40** and formation of the BC-spiroacetal would now use the successful approach developed earlier for spiroacetal **24** (Scheme 2), which relies on the selective and mild removal of PMB ethers at C13 and C21 with *in situ* spiroacetalisation.[12c,e] A modified Julia olefination[17] was initially considered for C25–C26 bond formation, utilising the sulfone fragment **41** which incorporates all five contiguous stereocentres spanning C20–C24 for coupling to the DEF-aldehyde fragment **42**. Hydroboration of the resulting terminal alkene to afford a C17 alcohol would then be followed by reduction of the internal alkene. Alternatively, a *B*-alkyl Suzuki coupling reaction[18] of DEF-alkene **43** with the simpler C17–C24 vinyl iodide **44** would provide a C17–C40 diene, upon which it was proposed that the C23/C24 stereocentres and C17 oxygenation in aldehyde **40** might be installed through an adventurous substrate-controlled double hydroboration reaction. The relative merits of these two complementary coupling strategies would be determined by experiment, as discussed in the accompanying paper.[15] Notably, it was only during the latter stages of this work that the stereochemical uncertainties within the macrocycle were resolved by the Andersen group,[6a] which



Scheme 6 Retrosynthetic analysis of DEF-bis-spiroacetal **45** based on a double asymmetric dihydroxylation/acetalisation cascade from diene **47**.

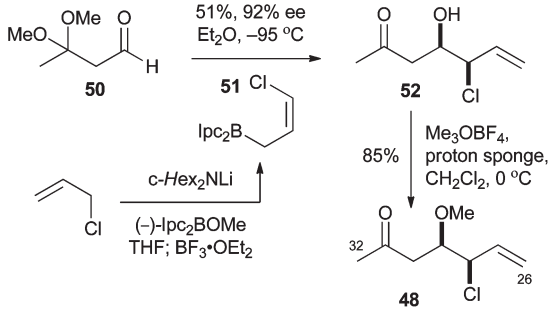
fortuitously validated the decision to pursue stereoisomer **8**, as originally depicted for spirastrellolide A methyl ester.[5b]

Results and discussion

The C26–C40 DEF-bis-spiroacetal 45

Due to the limitations of our originally reported[12a] route to C26–C40 fragment **29** (Scheme 3), an improved synthesis of a new DEF-bis-spiroacetal fragment **45** was devised as shown in Scheme 6, with the principle aim of reducing the susceptibility of the F-ring to furan formation by removing the appended γ-lactone. Importantly, we also recognised that the sense of asymmetric induction in the Sharpless dihydroxylation reactions[19] that would be used to install the C37/C38 and C26/C27 diols in the acyclic precursor **46** was the same.[12e] This would enable us to install all four hydroxyl groups in **46** from the C26–C40 diene **47** with a total avoidance of protecting groups, and subsequent spiroacetalisation might therefore be induced under particularly mild acidic conditions. In turn, diene **47** would be accessed through aldol coupling of C26–C32 methyl ketone **48** and C33–C40 aldehyde **49** (prepared using our lactate aldol methodology[20] to set the C34/C35 *anti*-relationship) in preference to the HWE coupling protocol used previously. In practice, the implementation of these measures greatly streamlined the synthesis and improved the scalability of the preparation of the pivotal DEF-subunit of spirastrellolide A.

Following our earlier studies,[12a] the Oehlschlager–Brown asymmetric chloroallylation reaction[21] was selected to configure a *syn*-α-vinylchlorohydrin and hence provide a route to the chlorinated D-ring of spirastrellolide A. Accordingly, treatment of readily available aldehyde **50** (Scheme 7) with

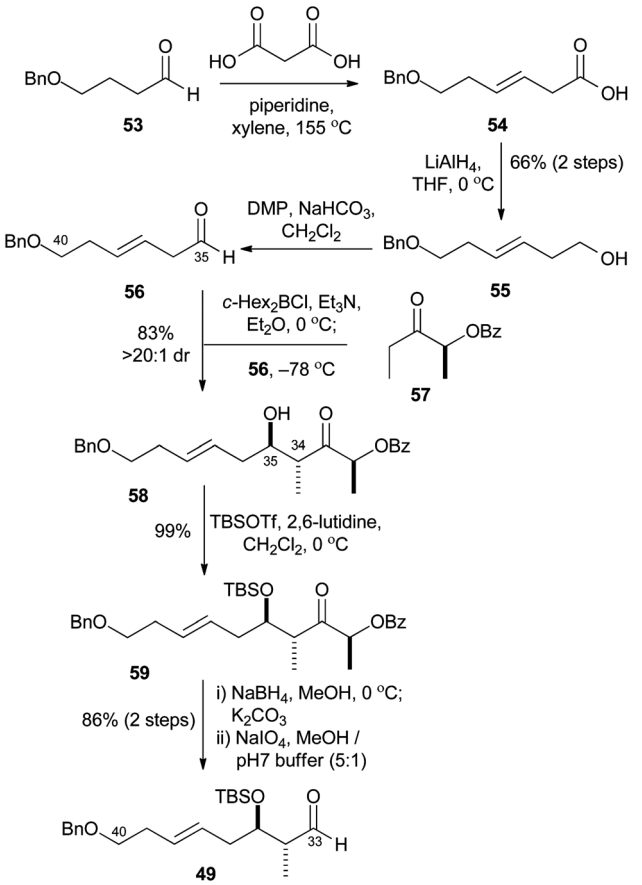


Scheme 7 Synthesis of methyl ketone **48** by asymmetric chloroallylation.

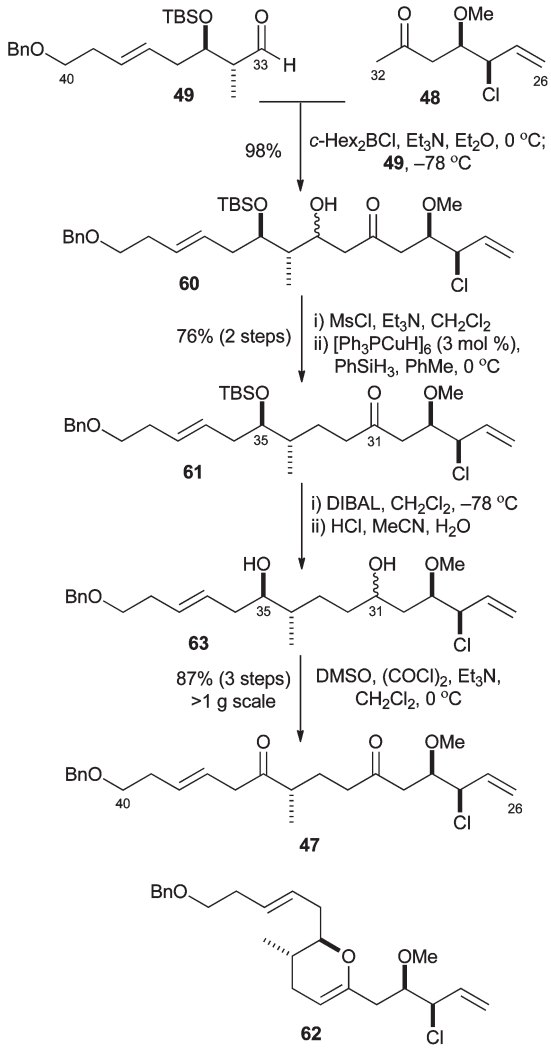
(*Z*)-(γ-chloroallyl)borane **51**, derived *in situ* from allyl chloride and (−)-Ipc$_2$BOMe, afforded *syn*-chlorohydrin **52** (>20 : 1 dr) in 51% yield and 92% ee (^{1}H NMR analysis of the corresponding Mosher esters).[22] The dimethyl acetal of **50** is conveniently unmasked during this process, and subsequent methyl ether formation from **52** with Meerwein's salt delivered methyl ketone **48**. Although operationally demanding, this process could be performed on a reasonably large scale, providing access to multigram quantities of this C26–C32 building block.

A suitable C33–C40 component **49** was now required for aldol coupling with **48**. For this purpose, aldehyde **53** was submitted to a modified Knoevenagel reaction[23] with malonic acid to access β,γ-unsaturated carboxylic acid **54** (Scheme 8). Oxidation state adjustment provided aldehyde **56**, which could not be purified by column chromatography on SiO$_2$ due to the propensity for isomerisation to the conjugated enal. Under our standard conditions,[20c] reaction of the (*E*)-boron enolate of ethyl ketone **57**[24] with crude aldehyde **56** provided the anti-aldol adduct **58**, which following oxidative work-up, was isolated cleanly and in high yield (83%, >20 : 1 dr). Silyl protection of aldol adduct **58** (TBSOTf) to give **59**, followed by cleavage of the lactate auxiliary under standard conditions,[20c] afforded aldehyde **49** in 85% overall yield.

With scaleable routes to both ketone **48** and aldehyde **49** established, their coupling to form C26–C40 diene **47** could now be pursued (Scheme 9). Again a boron aldol reaction was conveniently employed for this purpose, which provided an inconsequential mixture of epimeric alcohols **60** in excellent yield (98%). Treatment of **60** with MsCl and Et$_3$N induced an E1$_{cb}$ elimination to give the corresponding (*E*)-enone. Conjugate reduction[25] under the catalytic conditions reported by Lipshutz,[26] requiring only 3 mol% of Stryker's reagent ([Ph$_3$PCuH]$_6$), provided diene **61** in excellent yield (94%). Acid-mediated desilylation of **61** and Dess–Martin oxidation of the ensuing C35 alcohol then provided **47** in 66% yield on small scale (*ca.* 50 mg), however repetition of this two-step process on larger scales delivered the desired diketone **47** in much lower yields, with predominant formation of dihydropyran **62** instead being observed. To circumvent this side-reaction, a three-step procedure was developed in which the C31 ketone in **61** was reduced prior to desilylation at C35, thus preventing cyclisation. The resulting diol **63** could then be converted cleanly to diketone **47** using a double Swern oxidation, in a reliable 87% yield.



Scheme 8 Synthesis of aldehyde **49** using an asymmetric boron aldol reaction.

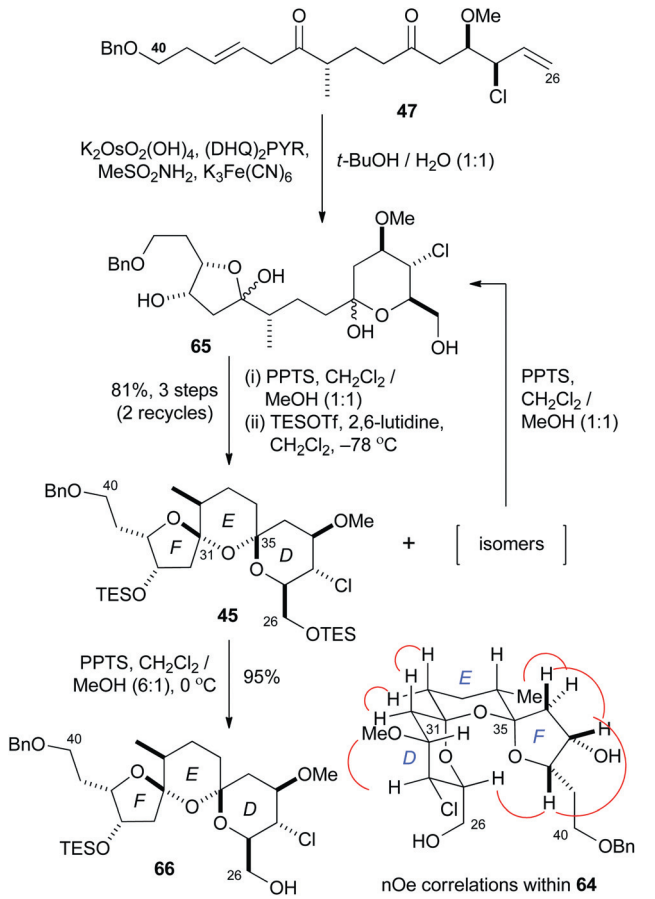


Scheme 9 Synthesis of linear diene **47**, the substrate for double asymmetric dihydroxylation.

With C26–C40 diene **47** in hand, the key tandem double asymmetric dihydroxylation and bis-spiroacetalisation sequence was addressed. Submission of diene **47** to Sharpless conditions,[19] utilising $(DHQ)_2PYR$ as ligand, effected a stereoselective double dihydroxylation but did not lead directly to C26–C40 DEF-bis-spiracetal **64** (Scheme 10). Instead, a complex mixture of products was isolated, considered to be the C26–C40 hemi-acetals **65**, which were fully cyclised under mildly acidic conditions (PPTS, CH_2Cl_2–MeOH). Per-silylation of the crude diol product facilitated purification, giving access to targeted DEF-bis-spiroacetal **45** in 43% yield (chromatographically separable from other spirocyclic isomers). Clear nOe enhancements between key protons in bis-spiroacetal diol **64**[27] confirmed the major product of the double dihydroxylation/bis-spirocyclisation sequence to contain the desired double anomerically stabilised configurations at C31 and C35.

In our earlier work, in which these asymmetric dihydroxylations were performed on the individual alkenes in separate fragments, the diastereoselectivity of each dihydroxylation was found to be around 20 : 1 dr in each case.[12b] Notably, the dihydroxylation of the terminal $\Delta^{26,27}$ alkene corresponds to a reinforcing situation based on the inherent 1,2-*anti* stereoinduction from the allylic chloride (which acts in a manner comparable to an allylic alcohol).[28] Therefore, the minor isomers obtained in the double asymmetric dihydroxylation of **47** were assigned as epimers at the C31 and C35 acetal centres. Although the major product, desired bis-spiroacetal **64**, adopts the expected anomeric effect-stabilised configuration, the resulting cage-like structure shown may suffer from destabilising steric interactions. By contrast, other C31/C35 configurations, although less favourable stereoelectronically, may result in reduced steric crowding. Importantly, it was found that these minor DEF isomers could be resubmitted to the spiroacetalisation conditions (PPTS, CH_2Cl_2–MeOH), leading to desilylation and epimerisation at the spirocyclic centres (C31 and C35) which, upon TES reprotection, generated further quantities of **45**. In this fashion, the required C26–C40 bis-spiroacetal **45** could be accessed in a reliable 81% yield after two equilibrations of the mixed isomer by-products. The success of this approach owes much to the increased stability of DEF-spiroacetal **64** with respect to furan formation, allowing access to the thermodynamic equilibrium mixture of products rather than the kinetic outcome.

The development of this expedient double asymmetric dihydroxylation/acetalisation cascade process ensured that we could now prepare multi-gram quantities of DEF-bis-spiroacetal **45** to go forward with the total synthesis effort. Importantly, selective

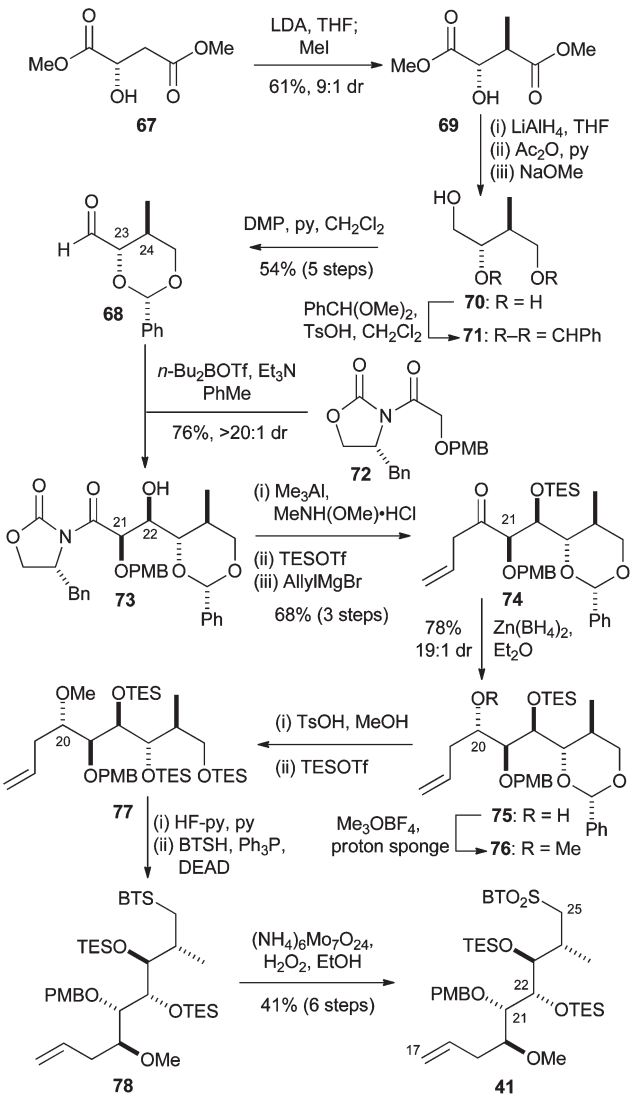


Scheme 10 Double asymmetric dihydroxylation/spiroacetalisation cascade sequence to give C26–C40 DEF-bis-spiroacetal **45**.

deprotection of the primary TES ether provided C26 alcohol **66** for further elaboration to aldehyde **42** and alkene **43** for fragment coupling (described in the following paper[15]). Based on the two alternative strategies proposed in Scheme 5, we now required access to both the C17–C25 sulfone fragment **41** for the planned Julia olefination approach, and the simpler C17–C24 vinyl iodide **44** for exploration of the Suzuki cross-coupling approach.

The C17–C25 sulfone 41

The polyoxygenated C20–C24 region in spirastrellolide A contains five contiguous stereocentres. The construction of this stereopentad commenced with dimethyl (*S*)-malate (**67**), which was converted into aldehyde **68** by adaptation of a literature procedure.[29] Thus, a Fráter–Seebach-type enolate alkylation with methyl iodide afforded the expected *anti*-isomer **69** (61%, 9 : 1 dr). Reduction of **69** with $LiAlH_4$ then gave triol **70**, which proved too water soluble to be isolated from the aqueous phase during work up. To circumvent this, addition of anhydrous acetic acid in place of an aqueous work up, followed by *in situ* acetylation, enabled efficient isolation of the tris-acetate of **70**.[30] Without exposure to water, triol **70** was then easily obtained by methanolysis (NaOMe, MeOH). Regioselective acetalisation then produced the thermodynamically preferred six-membered benzylidene acetal **71** (77%, 4 steps), which was converted to



Scheme 11 Synthesis of C17–C25 sulfone fragment **41**.

aldehyde **68** *via* Dess–Martin oxidation buffered by pyridine. For the purpose of establishing the *syn*-diol relationship between C21 and C22 in the targeted C17–C25 sulfone **41** (Scheme 11), whilst simultaneously installing a PMB ether at C21 for the planned BC-spiroacetalisation, an Evans glycolate aldol reaction was selected.[31] This strategy would also allow the requisite C20 methoxy-bearing stereocentre to be installed by reduction of an ensuing ketone, utilising this PMB ether for chelation control.

In the event, glycolate imide **72** was accessed using a convenient three-step process from (*R*)-benzyloxazolidinone.[32] Enolisation of **72** (*n*-Bu_2BOTf, Et_3N, PhMe), followed by addition of aldehyde **68** then gave *syn*-aldol adduct **73** (76%, >20 : 1 dr). Transamination with *N*,*O*-dimethylhydroxylamine hydrochloride and subsequent TES ether formation followed by addition of allylmagnesium bromide produced ketone **74** (68%, 3 steps). Chelation-controlled reduction[33] of **74** was best achieved using $Zn(BH_4)_2$, which gave alcohol **75** (78%, 19 : 1 dr).

With all of the necessary stereocentres now installed, the secondary alcohol in **75** was converted into its methyl ether **76** by

reaction with Me_3OBF_4 in the presence of proton sponge.[34] For the purpose of obtaining a suitable substrate for introduction of the required sulfone group by a Mitsunobu reaction, a selective three step protecting group manipulation of **76** was performed. This involved acidic cleavage of the acetal and silyl ether of **76**, followed by tris-TES protection and cleavage of the primary silyl ether of **77**. This latter step proved challenging, but following a screen of various conditions, treatment with HF·py/py in THF was found to selectively liberate the primary alcohol, and a Mitsunobu reaction with 2-mercaptobenzothiazole (BTSH) gave sulfide **78** (99%). Finally, the synthesis of the Julia coupling partner was completed by oxidation of sulfide **78** using H_2O_2 in the presence of an ammonium molybdate catalyst, affording the desired C17–C25 sulfone **41** (70%).

The C17–C24 vinyl iodide 44

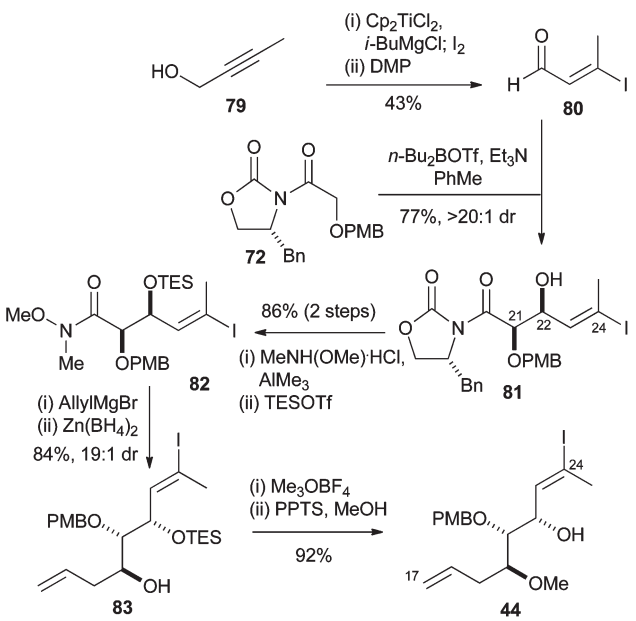
For the alternative Suzuki coupling approach, access to C17–C24 vinyl iodide fragment **44** was required. In practice, this (*E*)-vinyl iodide was installed through hydrotitanation of but-3-ynol (**79**) according to the procedure developed by the Sato group (Scheme 12).[35] Dess–Martin oxidation then afforded aldehyde **80** (89%).[36]

As in the earlier case, an Evans glycolate aldol coupling between imide **72** and aldehyde **80** (*n*-Bu_2BOTf, Et_3N, PhMe) proceeded smoothly to afford *syn*-aldol adduct **81** (77%, >20 : 1 dr). With the C21/C22 stereocentres in place, transamination of **81**, with subsequent silyl protection, gave Weinreb amide **82**. Treatment of **82** with allylmagnesium bromide and chelation-controlled reduction of the resulting ketone with $Zn(BH_4)_2$, then afforded alcohol **83** (90%, 19 : 1 dr). The required C17–C24 vinyl iodide fragment **44** was then completed through methylation of the C20 alcohol (Me_3OBF_4) and desilylation under mildly acidic conditions (PPTS, MeOH).[37] Using the above procedure, vinyl iodide **44** could be efficiently accessed on multi-gram scales, in seven steps and 37% yield from aldehyde **80**. Notably, this expedient sequence proved to be more convenient than the much lengthier route to the corresponding sulfone **41**.

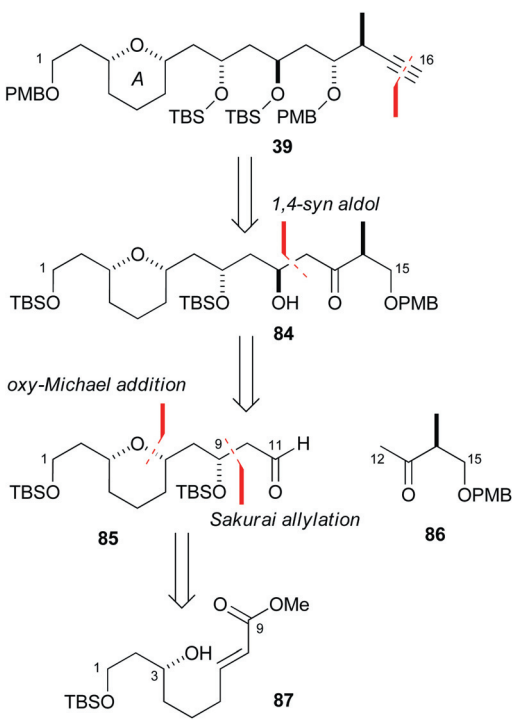
The C1–C16 alkyne 39

The optimised synthetic route to the C1–C16 alkyne **39** (Scheme 13), containing the remaining carbon atoms required for the spirastrellolide A macrocycle, evolved from strategies we had previously developed for construction of a range of related ABC-ring fragments (*e.g.*, **16** and **17** in Scheme 1).[12b,e] Alkyne **39** would now come from β-hydroxy ketone **84**, itself generated from a 1,4-*syn* aldol reaction[38,39] between C1–C11 aldehyde **85** and methyl ketone **86**. In turn, aldehyde **85** would arise from an intramolecular oxy-Michael addition of C1–C9 enoate **87**, with subsequent chelation-controlled allylation to set the C9 stereocentre.

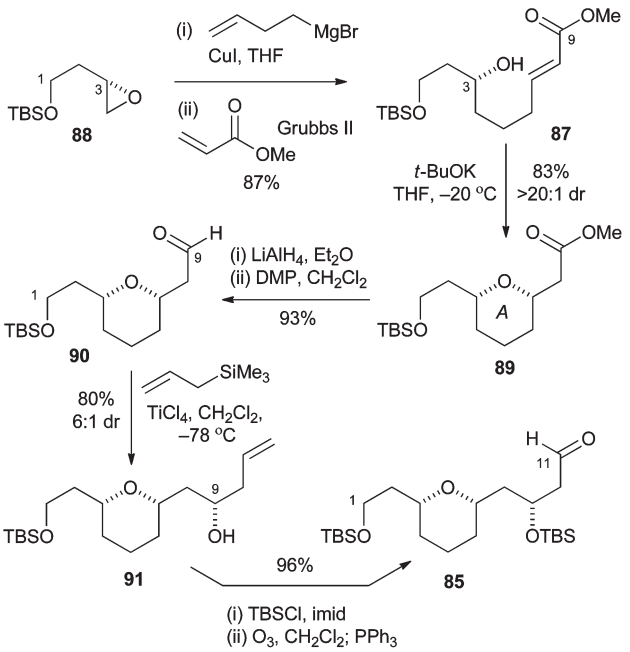
The synthesis of aldehyde **85** commenced with the opening of epoxide **88** (obtained in >95 : 5 er using Jacobsen hydrolytic kinetic resolution)[40] with butenylmagnesium bromide (Scheme 14). Cross metathesis[41] of the ensuing alkene with methyl acrylate (Grubbs II, 0.5 mol%) gave (*E*)-enoate **87**, which then underwent a hetero-Michael reaction on treatment with *t*-BuOK, giving C1–C9 *cis*-tetrahydropyran **89** in good yield and selectivity (83%, >20 : 1 dr). Oxidation state adjustment at C9 afforded C1–C9 aldehyde **90**, which proved a good substrate for allylation under Sakurai-type conditions[42] ($TiCl_4$, 80%, 6 : 1 dr). This last step replaced previous reliance on stoichiometric chiral reagents to set the C9 stereocentre,[12b] with the



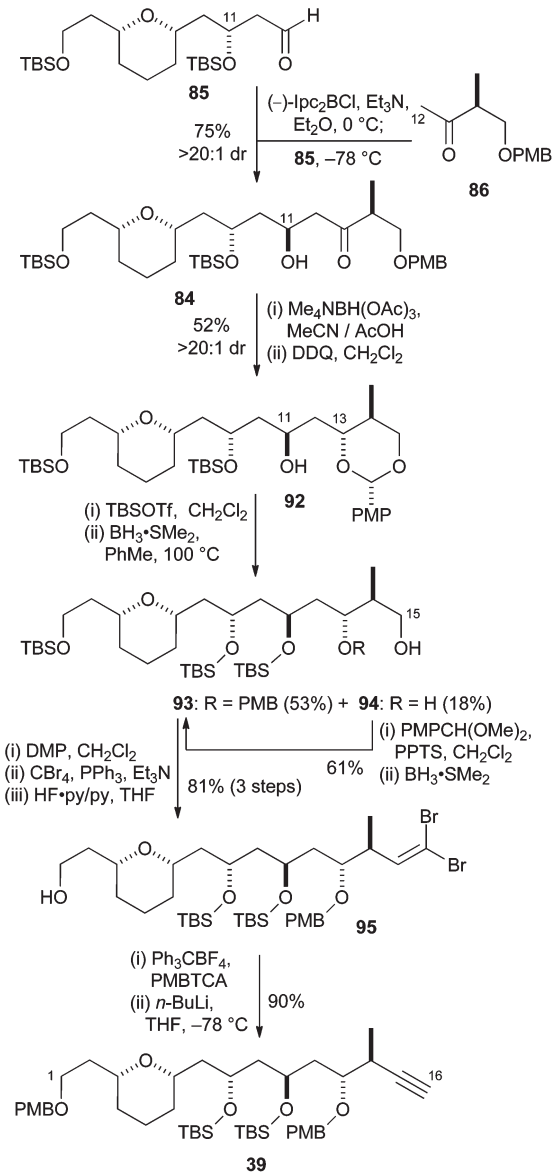
Scheme 12 Synthesis of C17–C24 vinyl iodide fragment **44**.



Scheme 13 Retrosynthetic analysis of C1–C16 alkyne fragment **39**.



Scheme 14 Synthesis of C1–C11 aldehyde **85**.



Scheme 15 Synthesis of C1–C16 alkyne fragment **39**.

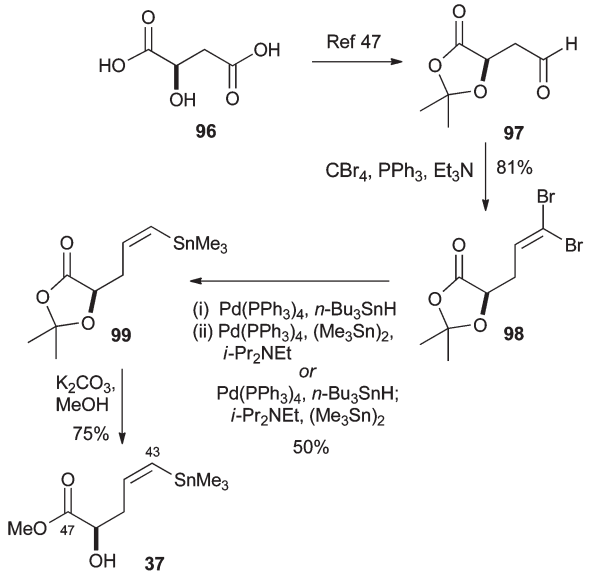
diastereoselectivity attributed to a π-facial bias for pseudo-axial attack of allyltrimethylsilane onto a β-alkoxy-chelated intermediate. Silyl protection of alcohol **91** and ozonolysis completed the C1–C11 aldehyde **85** in 62% overall yield from epoxide **88**.

Using our standard conditions, aldehyde **85** underwent smooth aldol coupling[38] with the diisopinocamphenylboron enolate derived from methyl ketone **86**, to give the expected 1,4-*syn* adduct **84** with good yield and selectivity (75%, >20 : 1 dr) (Scheme 15).[43] Next, an Evans–Saksena reduction[44] of ketone **84** afforded the corresponding 1,3-*anti* diol (92%, >20 : 1 dr). Subsequent formation of the PMP acetal **92** under oxidative conditions (DDQ) and silylation of the residual C11 alcohol then gave the fully protected polyol. Regioselective opening of the PMP acetal to reveal the terminal C15 alcohol in **93** proved difficult, with many conditions (including standard treatment with DIBAL) resulting in over-deprotection to afford 1,3-diol **94**. Under optimised conditions using $BH_3{\cdot}SMe_2$ at 100 °C,[45] the ratio of desired alcohol **93** to diol **94** was at best 3 : 1, although **94** could be easily recycled. While Corey–Fuchs alkynylation[46] could then be used to complete the C1–C16 alkyne fragment in good yield (not shown), the sequence was amended to include a protecting group exchange, in order to mitigate any late-stage selectivity issues with respect to deprotection at C1 in the presence of TBS ethers at C37 and C40. This entailed selectively cleaving the TBS ether at C1 (HF·py, py) to give alcohol **95**, followed by PMB ether formation and conversion of the dibromoalkene to the alkyne **39** (73%, 5 steps). The newly-formed C1 PMB ether should then be cleaved to reveal the primary alcohol during the planned DDQ-mediated BC-spiroacetalisation step. This reaction sequence proved sufficiently robust to be able to afford multi-gram quantities of the C1–C16 alkyne fragment **39**.

The C43–C47 vinyl stannane 37

Either the (*R*)- or (*S*)-configuration of the C46 stereocentre in the side-chain stannane fragment **37** could be obtained by starting from the appropriate enantiomer of malic acid. The synthesis of (46*R*)-**37** from (*R*)-malic acid (**96**) is shown in Scheme 16, where its antipode was prepared in an analogous fashion.

Following a literature procedure,[47] aldehyde **97** was prepared from **96**,[48] and a Corey–Fuchs reaction[46] afforded vinyl dibromide **98**. In order to prepare (*Z*)-vinyl stannane **99**, selective reduction of the *trans*-bromide of **98** with *n*-Bu_3SnH was investigated in the presence of catalytic $Pd(PPh_3)_4$,[49] with the reaction monitored using ^1H NMR spectroscopy. After isolation of the (*Z*)-vinyl bromide product, tin–halogen exchange was carried out with $(Me_3Sn)_2$ and the same Pd(0) catalyst.[50] By following this two-step procedure, the (*Z*)-vinyl stannane **99** could be isolated



Scheme 16 Synthesis of vinyl C43–C47 stannane fragment **37**.

as the only isomer, albeit in low yield. Alternatively, a one-pot procedure allowed selective debromination and sequential tin–halogen exchange to afford **99** in improved yield (50%) and with reduced effort. Using this convenient one-pot procedure, both the (*R*)- and (*S*)-dioxolanones **99** and *ent*-**99** could be prepared in useful quantities. Finally, the corresponding methyl esters **37** and *ent*-**37** were obtained by methanolysis (75%), such that attachment of the side chain would directly generate the spirastrellolide A methyl ester without additional manipulation.

Conclusions

Due to a combination of their promising anticancer properties (as potent and selective PP2A inhibitors), the limited supply from the marine sponge source and their unprecedented molecular architecture, the spirastrellolides represent attractive yet challenging synthetic targets. A modular strategy for the synthesis of spirastrellolide A methyl ester (**8**), allowing for the initial stereochemical uncertainties in the assigned structure, was adopted based on the envisaged sequential coupling of a series of suitably functionalised fragments. An expedient synthesis of the northern hemisphere C26–C40 DEF-bis-spiroacetal fragment **45** by a double asymmetric dihydroxylation/acetalisation cascade sequence enabled the preparation of multi-gram quantities of this key component. The remaining fragments **37**, **39**, **41** and **44** were all prepared by efficient and highly stereocontrolled routes, exploiting both reagent and substrate stereocontrol.[51] The synthetic routes developed for all the key fragments of the spirastrellolides proved sufficiently robust to be scaled up to the extent that gram quantities could usually be produced in a single campaign. This reliable access to these functionalised fragments equipped with suitable protecting groups then set the stage for completion of the first total synthesis of spirastrellolide A methyl ester, as described in the following paper.[15]

Experimental

Full experimental and characterisation details are provided in the ESI.§

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References

1 An annual review is dedicated to marine natural products: J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro and M. R. Prinsep, *Nat. Prod. Rep.*, 2012, **29**, 144.
2 (*a*) A. M. S. Mayer, K. B. Glaser, C. Cuevas, R. S. Jacobs, W. Kem, R. D. Little, J. M. McIntosh, D. J. Newman, B. C. Potts and D. E. Schuster, *Trends Pharmacol. Sci.*, 2010, **31**, 255; (*b*) S. M. Dalby and I. Paterson, *Curr. Opin. Drug Discovery Dev.*, 2010, **13**, 777; (*c*) M. S. Butler, *Nat. Prod. Rep.*, 2008, **25**, 475; (*d*) D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2007, **70**, 461; (*e*) I. Paterson and E. A. Anderson, *Science*, 2005, **310**, 451; (*f*) I. Paterson and K.-S. Yeung, *Chem. Rev.*, 2005, **105**, 4237; (*g*) K.-S. Yeung and I. Paterson, *Angew. Chem., Int. Ed.*, 2002, **41**, 4632.
3 H. Ledford, *Nature*, 2010, **468**, 608.
4 (*a*) G. J. Florence, N. M. Gardner and I. Paterson, *Nat. Prod. Rep.*, 2008, **25**, 342; (*b*) S. J. Mickel, D. Niederer, R. Daeffler, A. Osmani, E. Kuesters, E. Schmid, K. Schaer, R. Gamboni, W. Chen, E. Loeser, F. R. Kinder, K. Konigsberger, K. Prasad, T. M. Ramsey, O. Repic, R.-M. Wang, G. Florence, I. Lyothier and I. Paterson, *Org. Process Res. Dev.*, 2004, **8**, 122.
5 (*a*) D. E. Williams, M. Roberge, R. V. Soest and R. J. Andersen, *J. Am. Chem. Soc.*, 2003, **125**, 5296; (*b*) D. E. Williams, M. Lapawa, X. Feng, T. Tarling, M. Roberge and R. J. Andersen, *Org. Lett.*, 2004, **6**, 2607.
6 (*a*) K. Warabi, D. E. Williams, B. O. Patrick, M. Roberge and R. J. Andersen, *J. Am. Chem. Soc.*, 2007, **129**, 508; (*b*) D. E. Williams, R. A. Keyzers, K. Warabi, K. Desjardine, J. L. Riffell, M. Roberge and R. J. Andersen, *J. Org. Chem.*, 2007, **72**, 9842.
7 S. Matsunaga, personal communication, Laboratory of Aquatic Natural Products Chemistry, University of Tokyo.
8 (*a*) V. V. Vintonyak, A. P. Antonchick, D. Rauh and H. Waldmann, *Curr. Opin. Chem. Biol.*, 2009, **13**, 272; (*b*) J. L. McConnell and B. E. Wadzinski, *Mol. Pharmacol.*, 2009, **75**, 1249; (*c*) R. E. Honkanen and T. Golden, *Curr. Med. Chem.*, 2002, **9**, 2055; (*d*) A. McCluskey, A. T. R. Sim and J. A. Sakoff, *J. Med. Chem.*, 2002, **45**, 1151; (*e*) L. D. Klaman, O. Boss, O. D. Peroni, J. K. Kim, J. L. Martino, J. M. Zabolotny, N. Moghal, M. Lubkin, Y. B. Kim, A. H. Sharpe, A. Stricker-Krongrad, G. I. Shulman, B. G. Neel and B. B. Kahn, *Mol. Cell. Biol.*, 2000, **20**, 5479; (*f*) A. I. Lazarovits, S. Poppema, Z. Zhang, M. Khandaker, C. E. LeFeuvre, S. K. Singhal, B. M. Garcia, N. Ogasa, A. M. Jevnikar, M. J. White, G. Singh, C. R. Stiller and R. Z. Zhong, *Nature*, 1996, **380**, 717.
9 R. Andersen, M. Roberge and D. Williams, *Canada Patent, CA* 2464687, 2005.
10 For reviews of synthetic efforts towards the spirastrellolides, see: (*a*) I. Paterson and S. M. Dalby, *Nat. Prod. Rep.*, 2009, **26**, 865; (*b*) M. V. Perkins, *Angew. Chem., Int. Ed.*, 2008, **47**, 2921.
11 (*a*) J. Liu and R. P. Hsung, *Org. Lett.*, 2005, **7**, 2273; (*b*) Y. Pan and J. K. De Brabander, *Synlett*, 2006, 853; (*c*) C. Wang and C. J. Forsyth, *Org. Lett.*, 2006, **8**, 2997; (*d*) A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem., Int. Ed.*, 2006, **45**, 5506; (*e*) A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem., Int. Ed.*, 2006, **45**, 5510; (*f*) J. Liu, J. H. Yang, C. Ko and R. P. Hsung, *Tetrahedron Lett.*, 2006, **47**, 6121; (*g*) A. B. Smith III and D.-S. Kim, *Org. Lett.*, 2007, **9**, 3311; (*h*) C. Wang

and C. J. Forsyth, *Heterocycles*, 2007, **72**, 621; (*i*) A. Fürstner, B. Fasching, G. W. O'Neil, M. D. B. Fenster, D. Godbout and L. Ceccon, *Chem. Commun.*, 2007, **3045**; (*j*) K. A. Keaton and A. J. Phillips, *Org. Lett.*, 2008, **10**, 1083; (*k*) J. H. Yang, J. Liu and R. P. Hsung, *Org. Lett.*, 2008, **10**, 2525; (*l*) S. Chandrasekhar, C. Rambabu and A. S. Reddy, *Org. Lett.*, 2008, **10**, 4355; (*m*) A. B. Smith III, H. Smits and D.-S. Kim, *Tetrahedron*, 2010, **66**, 6597; (*n*) G. Sabitha, A. S. Rao and J. S. Yadav, *Synthesis*, 2010, **2010**, 505; (*o*) J. L.-Y. Chen and M. Brimble, *Chem. Commun.*, 2010, **46**, 3967.

12 (*a*) I. Paterson, E. A. Anderson, S. M. Dalby and O. Loiseleur, *Org. Lett.*, 2005, **7**, 4121; (*b*) I. Paterson, E. A. Anderson, S. M. Dalby and O. Loiseleur, *Org. Lett.*, 2005, **7**, 4125; (*c*) I. Paterson, E. A. Anderson and S. M. Dalby, *Synthesis*, 2005, 3225; (*d*) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, P. Maltas and C. Moessner, *Chem. Commun.*, 2006, 4186; (*e*) I. Paterson, E. A. Anderson, S. M. Dalby, J. Genovino, J. H. Lim and C. Moessner, *Chem. Commun.*, 2007, 1852; (*f*) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, O. Loiseleur, P. Maltas and C. Moessner, *Pure Appl. Chem.*, 2007, **79**, 667; (*g*) I. Paterson, S. M. Dalby and P. Maltas, *Isr. J. Chem.*, 2011, **51**, 406.

13 (*a*) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, J. Genovino, P. Maltas and C. Moessner, *Angew. Chem., Int. Ed.*, 2008, **47**, 3016; (*b*) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, J. Genovino, P. Maltas and C. Moessner, *Angew. Chem., Int. Ed.*, 2008, **47**, 3021.

14 (*a*) G. W. O'Neil, J. Ceccon, S. Benson, M.-P. Collin, B. Fasching and A. Fürstner, *Angew. Chem., Int. Ed.*, 2009, **48**, 9940; (*b*) S. Benson, M.-P. Collin, G. W. O'Neil, J. Ceccon, B. Fasching, M. D. B. Fenster, C. Godbout, K. Radkowski, R. Goddard and A. Fürstner, *Angew. Chem., Int. Ed.*, 2009, **48**, 9946; (*c*) S. Benson, M.-P. Collin, A. Arlt, B. Gabor, R. Goddard and A. Fürstner, *Angew. Chem., Int. Ed.*, 2011, **50**, 8739.

15 I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim and P. Maltas, *Org. Biomol. Chem.*, 2012, **10**, DOI: 10.1039/c2ob25101a.

16 S. M. Dalby, PhD Thesis, University of Cambridge, 2007.

17 (*a*) J. B. Baudin, G. Hareau, S. A. Julia and O. Ruel, *Tetrahedron Lett.*, 1991, **32**, 1175; (*b*) P. R. Blakemore, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2563.

18 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*b*) S. R. Chemler, D. Trauner and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2001, **40**, 4544; (*c*) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442.

19 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.

20 (*a*) I. Paterson, D. J. Wallace and S. M. Velazquez, *Tetrahedron Lett.*, 1994, **35**, 9083; (*b*) I. Paterson and D. J. Wallace, *Tetrahedron Lett.*, 1994, **35**, 9087; (*c*) I. Paterson, D. J. Wallace and C. J. Cowden, *Synthesis*, 1998, 639.

21 S. Hu, S. Jayaraman and A. C. Oehlschlager, *J. Org. Chem.*, 1996, **61**, 7513.

22 I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.

23 N. Ragoussis, *Tetrahedron Lett.*, 1987, **28**, 93.

24 For some recent applications of this aldol reaction in other complex polyketide syntheses, see: (*a*) I. Paterson, V. A. Steadman neé Doughty, M. D. McLeod and T. Trieselmann, *Tetrahedron*, 2011, **67**, 10119; (*b*) I. Paterson, G. J. Naylor, N. M. Gardner, E. Guzman and A. E. Wright, *Chem.–Asian J.*, 2011, **6**, 459; (*c*) I. Paterson and P. Rubenbauer, *Synlett*, 2010, 571; (*d*) I. Paterson, G. J. Naylor and A. E. Wright, *Chem. Commun.*, 2008, 4628.

25 W. S. Mahoney, D. M. Brestensky and J. M. Stryker, *J. Am. Chem. Soc.*, 1988, **110**, 291.

26 B. H. Lipschutz, J. Keith, P. Papa and R. Vivian, *Tetrahedron Lett.*, 1998, **39**, 4627.

27 A sample of **64** was purified for the purposes of characterisation.

28 The same sense of π-facial selectivity is induced by a hydroxyl group in the dihydroxylation of secondary allylic alcohols. (*a*) J. K. Cha, W. J. Christ and Y. Kishi, *Tetrahedron*, 1984, **40**, 2247; (*b*) K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Rondan, V. Jäger, R. Schohe and F. R. Fronczek, *J. Am. Chem. Soc.*, 1984, **106**, 3880.

29 R. W. Hoffmann, G. Mas and T. Brandl, *Eur. J. Org. Chem.*, 2002, 3455.

30 T. Motozaki, K. Sawamura, A. Suzuki, K. Yoshida, T. Ueki, A. Ohara, R. Munakata, K. Takao and K. Tadano, *Org. Lett.*, 2005, **7**, 2261.

31 (*a*) T. K. Jones, R. A. Reamer, R. Desmond and S. G. Mills, *J. Am. Chem. Soc.*, 1990, **112**, 2998; (*b*) D. A. Evans, J. R. Gage, J. L. Leighton and A. S. Kim, *J. Org. Chem.*, 1992, **57**, 1961.

32 Imide **72** was prepared through acylation of the lithiated oxazolidinone with $BnOCH_2COCl$, which was then subjected to protecting group exchange to install a PMB ether. This entailed debenzylation through hydrogenation over Pearlman's catalyst and treatment of the resulting alcohol with PMBTCA in the presence of catalytic Ph_3CBF_4 to afford **72**. For experimental details, see the ESI§.

33 T. Nakata, T. Tanaka and T. Oishi, *Tetrahedron Lett.*, 1983, **24**, 2653.

34 D. A. Evans, A. M. Ratz, B. E. Huff and G. S. Sheppard, *Tetrahedron Lett.*, 1994, **35**, 7171.

35 (*a*) F. Sato and Y. Kobayashi, *Org. Synth.*, 1990, **69**, 106; (*b*) Y. Gao and F. Sato, *J. Chem. Soc., Chem. Commun.*, 1995, 659.

36 This sensitive aldehyde was best prepared and used directly for the subsequent Evans aldol addition step, as it was observed to decompose if concentrated or exposed to light.

37 In model studies, it was found to be necessary to cleave the TES ether in the vinyl iodide fragment to achieve the required hydroboration following the C24–C25 Suzuki coupling step.

38 (*a*) I. Paterson, J. M. Goodman and M. Isaka, *Tetrahedron Lett.*, 1989, **30**, 7121; (*b*) I. Paterson and R. M. Oballa, *Tetrahedron Lett.*, 1997, **38**, 8241.

39 For some recent applications of this aldol reaction in other complex polyketide syntheses, see: (*a*) I. Paterson, L. J. Gibson and S. B. J. Kan, *Org. Lett.*, 2010, **12**, 5530; (*b*) I. Paterson and T. Paquet, *Org. Lett.*, 2010, **12**, 2158; (*c*) I. Paterson, K. Ashton, R. Britton, G. Cecere, G. Chouraqui, G. J. Florence, H. Knust and J. Stafford, *Chem.–Asian J.*, 2008, **3**, 367.

40 (*a*) W. Zhang, J. L. Loebach, S. R. Wilson and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1990, **112**, 2801; (*b*) L. E. Martínez, J. L. Leighton, D. H. Carsten and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1995, **117**, 5897.

41 A. K. Chatterjee, J. P. Morgan, M. Scholl and R. H. Grubbs, *J. Am. Chem. Soc.*, 2000, **122**, 3783.

42 A range of other Lewis acids and allyl metals were screened but the Sakurai protocol using $TiCl_4$ was found to be optimum.

43 The origin of the high level of stereocontrol in such boron-mediated aldol reactions has been rationalised by computational studies: where the inherent 1,4-*syn* selectivity arising from a formyl H-bonded boat TS is enhanced by the use of reinforcing Ipc chiral ligands. (*a*) R.S. Paton and J. M. Goodman, *Org. Lett.*, 2006, **8**, 4299; (*b*) J. M. Goodman and R. S. Paton, *Chem. Commun.*, 2007, 2124; (*c*) R. S. Paton and J. M. Goodman, *J. Org. Chem.*, 2008, **73**, 1253.

44 D. A. Evans, K. T. Chapman and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560.

45 I. Shiina, J. Shibata, R. Ibuka, Y. Imai and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 113.

46 E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, **13**, 3769.

47 F. E. Dutton, B. H. Lee, S. S. Johnson, E. M. Coscarelli and P. H. Lee, *J. Med. Chem.*, 2003, **46**, 2057.

48 This preparation required considerable care as the intermediate alcohols have the potential to cyclise and form the undesired α-hydroxy-γ-butyrolactone. Furthermore, the unstable character of aldehyde **96** prevented the use of conventional purification methods, leading to 37% yield obtained over 3 steps.

49 (*a*) J. Uenishi, R. Kawahama, O. Yonemitsu and J. Tsuji, *J. Org. Chem.*, 1996, **61**, 5716; (*b*) J. Uenishi, R. Kawahama, O. Yonemitsu and J. Tsuji, *J. Org. Chem.*, 1998, **63**, 8965.

50 (*a*) W. D. Wulff, G. A. Peterson, W. E. Bauta, K.-S. Chan, K. L. Faron, S. R. Gilbertson, R. W. Kaesler, D. C. Yang and C. K. Murray, *J. Org. Chem.*, 1986, **51**, 277; (*b*) W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, 1986, **108**, 3033; (*c*) C. D. Vanderwal, D. A. Vosburg and E. J. Sorensen, *Org. Lett.*, 2001, **3**, 4307.

51 Yields over longest linear sequences for fragments: alkyne **39**: 11.6% over 18 steps from **88**; DEF spiroacetal **45**: 24.5% over 16 steps from **53**; vinyl iodide **44**: 22% over 9 steps from **79**; sulphone **41**: 5.4% over 17 steps from **67**; stannane **37**: 30.4% over 3 steps from **97**.

