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PAPER

The stereocontrolled total synthesis of spirastrellolide A methyl ester. Fragment coupling studies and completion of the synthesis†‡§

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The spirastrellolides are a novel family of structurally unprecedented marine macrolides which show promising anticancer properties due to their potent inhibition of protein phosphatase 2A. In the preceding paper, a modular strategy for the synthesis of spirastellolide A methyl ester which allowed for the initial stereochemical uncertainties was outlined, together with the synthesis of a series of suitably functionalised fragments. In this paper, the realisation of this synthesis is described. Two alternative coupling strategies were explored for elaborating the C26–C40 DEF bis-spiroacetal fragment: a modified Julia olefination of a C26 aldehyde with a C17–C25 sulfone, and a Suzuki coupling of a C25 trialkylborane with a C17–C24 vinyl iodide, which also required the development of a double hydroboration reaction to install the C23/C24 stereocentres. The latter proved a significantly superior strategy, and was fully optimised to provide a C17 aldehyde which was coupled with a C1–C16 alkyne fragment to afford the C1–C40 carbon framework. The BC spiroacetal was then installed within this advanced intermediate by oxidative cleavage of two PMB ethers with spontaneous spiroacetalisation, which also led to unanticipated deprotection of the C23 TES ether. The ensuing truncated seco-acid was cyclised in high yield to construct the 38-membered macrolactone under Yamaguchi macrolactonisation conditions, suggesting favourable conformational pre-organisation. Exhaustive desilylation provided a crystalline macrocyclic pentaol, revealing much about the likely conformation of the macrolactone in solution. Attachment of the remainder of the side chain proved challenging, potentially due to steric hindrance by this macrocycle; an olefin cross-metathesis to install an electrophilic allylic carbonate and subsequent π-allyl Stille coupling with a C43–C47 stannane achieved this goal. Global deprotection completed the first total synthesis of (+)-spirastrellolide A methyl ester which, following detailed NMR correlation with an authentic sample, validated the full configurational assignment. A series of simplified analogues of spirastrellolide incorporating the C26–C47 region were also prepared by π-allyl Stille coupling reactions.

Introduction

Spirastrellolide A (**1**, Scheme 1) was first isolated by Andersen and co-workers from the Caribbean sponge *Spirastrella coccinea* in 2003, and characterised as its methyl ester derivative **2**.[1] This was followed by the isolation of six minor congeners, spirastrellolides B–G, also characterised as their corresponding methyl esters.[2] The intense synthetic interest,[3–5] that the spirastrellolides have generated derives not only from their unique molecular architecture but also from their potential for development as lead structures for novel anticancer agents due to the significant antimitotic behaviour displayed in cell-based assays. Moreover, their identification as potent and selective inhibitors of protein phosphatases may afford valuable molecular probes for cell biology, as well as unique scaffolds for therapeutic development.[6] As with other promising antimitotic macrolides of marine sponge origin however, there is a supply issue requiring the development of a practical chemical synthesis to afford a more sustainable source.[7] In addition, the initial uncertainties reported by the Andersen group[1] over the full stereochemical assignment of the spirastrellolides might be progressively resolved by synthetic means.

In the preceding paper,[8,9] we outlined a modular strategy for the synthesis of spirastrellolide A methyl ester (**2**), allowing for

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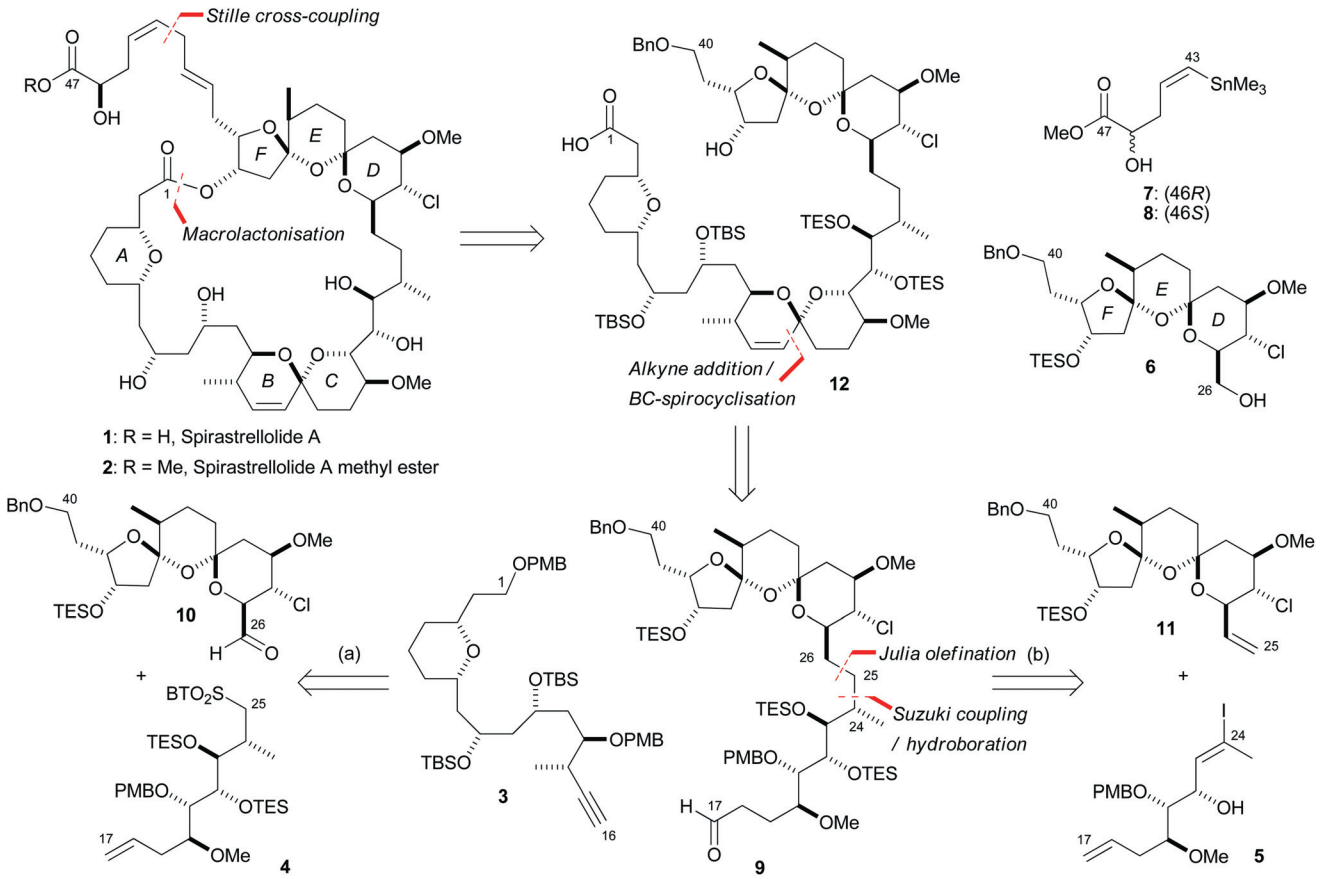
‡ Electronic supplementary information (ESI) available: this provides the entire Experimental Section for this paper. CCDC reference number 669312. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25101a

§ Dedicated to Professor Ian Fleming.



Scheme 1 Evolved synthetic strategy for spirastrellolide A based on either (a) Julia olefination to form C25–C26 bond or (b) Suzuki coupling and hydroboration to form C24–C25 bond in aldehyde **9**.

the initial stereochemical uncertainties, and described the efficient synthesis of a series of suitably functionalised fragments (C1–C16 alkyne **3**, C17–C25 sulfone **4**, C17–C24 vinyl iodide **5** and C26–C40 bis-spiroacetal **6**, Scheme 1). Notably, the absolute configuration of these fragments was selected on the basis of the stereostructure shown in Andersen's 2004 paper,[1b] with the flexibility that the other enantiomeric form of each could be readily accessed if required. As it turned out, we were fortunate that these four fragments all had the absolute configuration required for elaboration into the macrocyclic core of the spirastrellolides, as revealed in late 2007 by the publication of the X-ray structure of a derivative of spirastrellolide B.[2a] This meant that the only remaining stereochemical ambiguity was the configuration at C46 in the side-chain,[2b] and in recognition of this we had prepared the two enantiomeric forms of the C43–C47 stannane fragment **7** and **8**.

Evolved synthesis plan

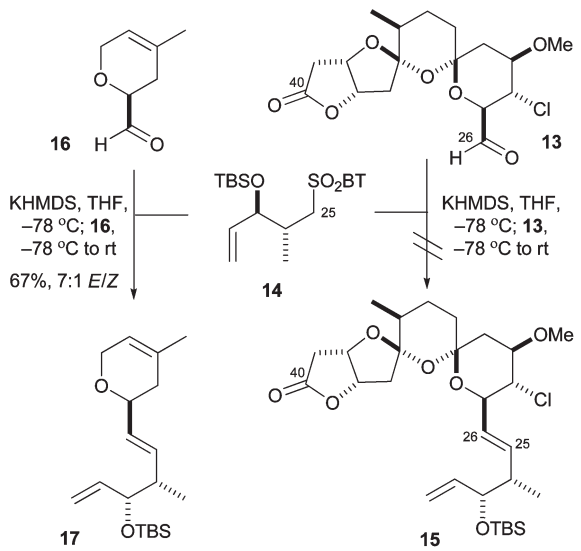
With this groundwork in place, we now needed to identify a suitable coupling strategy to assemble the available fragments and subsequently close the signature 38-membered macrocycle *en route* to spirastrellolide A methyl ester (Scheme 1). As discussed previously,[8] our strategy evolved to consider two complementary approaches to assembling the advanced C17–C40 aldehyde **9**. The first of these (a) was based on a planned Julia-type olefination between sulfone **4** and DEF-bis-spiroacetal aldehyde **10**, followed by selective hydroboration of the terminal alkene and reduction of the internal $\Delta^{25,26}$ alkene so formed. The second, more adventurous approach (b), involved an sp^2–sp^3 *B*-alkyl Suzuki coupling[10] between vinyl iodide **5** and a trialkylborane derived by hydroboration of the homologated DEF-bis-spiroacetal alkene **11**. While the latter route has a clear advantage in that vinyl iodide **5** is more readily available than the corresponding sulfone **4**, there was significant uncertainty in the sense and degree of π-facial selectivity that would arise from hydroboration of the resulting $\Delta^{23,24}$ alkene to install the C23/C24 stereocentres. Assuming that one of these strategies could reliably afford the advanced C17–C40 aldehyde **9**, then an alkyne addition which had proved robust in earlier work[9b,c,d] would be used to couple the C1–C16 fragment **3**, leading to a suitable precursor for the planned BC-spiroacetalisation step which, based on our earlier exploratory findings, would rely on DDQ-mediated PMB ether cleavage.[9c,d] We would then plan to access the truncated seco-acid **12** and explore its macrolactonisation to assemble the 38-membered macrolide core of the spirastrellolides. At this point, we could diverge to install either the (46*R*)-stannane **7** or its enantiomer (**8**) by a planned π-allyl Stille coupling[11] with a suitable appended allylic electrophile. Despite the apparent feasibility of this synthesis plan, we fully expected that it would need to be modified to circumvent unanticipated experimental

bottlenecks and possible roadblocks we might encounter on the uncharted way to spirastrellolide A.

Results and discussion

The Julia coupling route

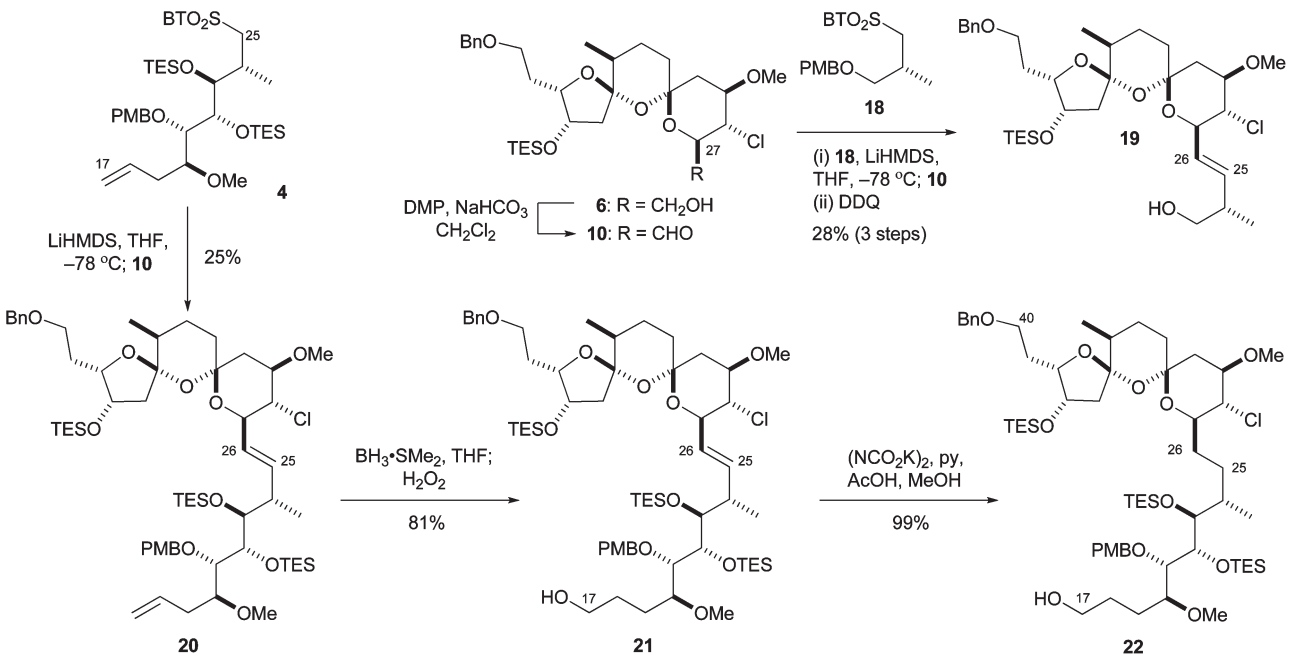
In previous studies,[12] the first-generation tetracyclic DEF-bis-spiroacetal aldehyde **13** had failed to undergo a Julia olefination[13] with model sulfone **14** to give **15** (Scheme 2) using conditions (KHMDS, THF, −78 °C) that had proven successful for a simplified dihydropyran aldehyde (**16** → **17**). Unfortunately, the labile DEF aldehyde **13** could not be recovered, suggesting that it underwent decomposition under these strongly basic reaction conditions.



Scheme 2 Exploratory studies for fragment coupling by Julia olefination using sulfone **14**.

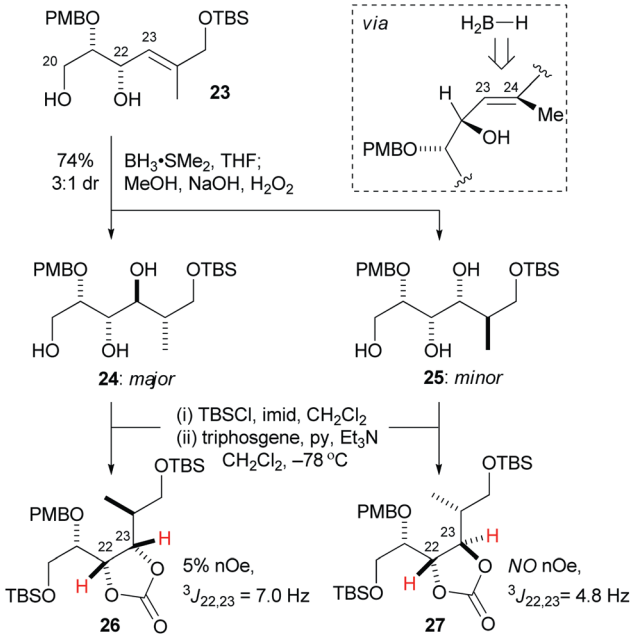
We reasoned that replacement of the appended δ-lactone by a suitably protected 1,4-diol in aldehyde **10** (Scheme 3) might be more rewarding. This entailed a buffered Dess–Martin[14] or Swern[15] oxidation of **6** to afford desired aldehyde **10**, which proved unstable to purification by chromatography and so was routinely used directly in subsequent reactions. With aldehyde **10** in hand, we first explored the Julia coupling option using model sulfone **18**.[16] Aldehyde **10** was added to a pre-mixed solution of sulfone **18** and LiHMDS at −78 °C, followed by warming to room temperature. To facilitate product isolation, the PMB ether was cleaved prior to purification by treatment with DDQ. This afforded coupled alcohol **19** as solely the *E*-alkene (28% over 3 steps from **6**). Encouraged by this promising outcome, we moved to examine the one-pot Julia olefination between the fully-functionalised C17–C25 sulfone **4**[8] and the same aldehyde **10**. Following the same procedure, aldehyde **10** was added to a pre-mixed solution of sulfone **4** and LiHMDS in THF at −78 °C. After slow warming to room temperature, the desired coupled product **20** was obtained, albeit in a modest 25% yield. It is likely that the considerable steric demands of aldehyde **10** inhibit C25–C26 bond formation with the lithiated sulfone, allowing competing degradation pathways to occur. Although the yield for this Julia coupling was disappointing, the planned synthesis of a fully elaborated C17–C40 fragment was still pursued.

Site-selective hydroboration of the terminal alkene in **20** was initially attempted using 9-BBN, although repeated trials gave only low conversion or unidentified by-products. Similarly disappointing results were obtained using disiamylborane with or without Wilkinson's catalyst ($ClRh(PPh_3)_3$).[17] Finally, treatment of **20** with $BH_3{\cdot}SMe_2$ at 0 °C gave the desired primary alcohol



Scheme 3 Synthesis of C1–C20 fragment **22** by Julia coupling route.

21 in 81% yield without disruption of the internal $\Delta^{25,26}$ alkene. Hydrogenation of the latter was now required to complete the fragment synthesis. Due to the presence of the benzyl and PMB ethers in alcohol **21**, care was taken to find a procedure that would saturate only the internal double bond. Hydrogenation in benzene using Wilkinson's catalyst was attempted on the model compound **19**, but led only to several unidentifiable by-products. However, when diimide reduction with $(NCO_2K)_2$ was tested,[18] ^{1}H NMR spectroscopic analysis indicated the clean formation of the desired saturated product. With a suitable reduction protocol in hand, alcohol **21** was now submitted to $(NCO_2K)_2$ in pyridine and acetic acid in methanol (which generates diimide *in situ*). In contrast to **19**, diimide reduction of **21** was slow and required a greater excess of reagent. Although the steric effects around the internal double bond were probably responsible for the reduced reactivity, it was with great relief that the completed C17–C40 fragment **22** could be isolated in essentially quantitative yield after 5 days. This advanced material, although prepared in modest yield due to the inefficient Julia olefination step, proved invaluable in establishing the stereochemistry of the coupled product from the alternative Suzuki coupling/double hydroboration option.



Scheme 4 Model studies for hydroboration of allylic alcohol.

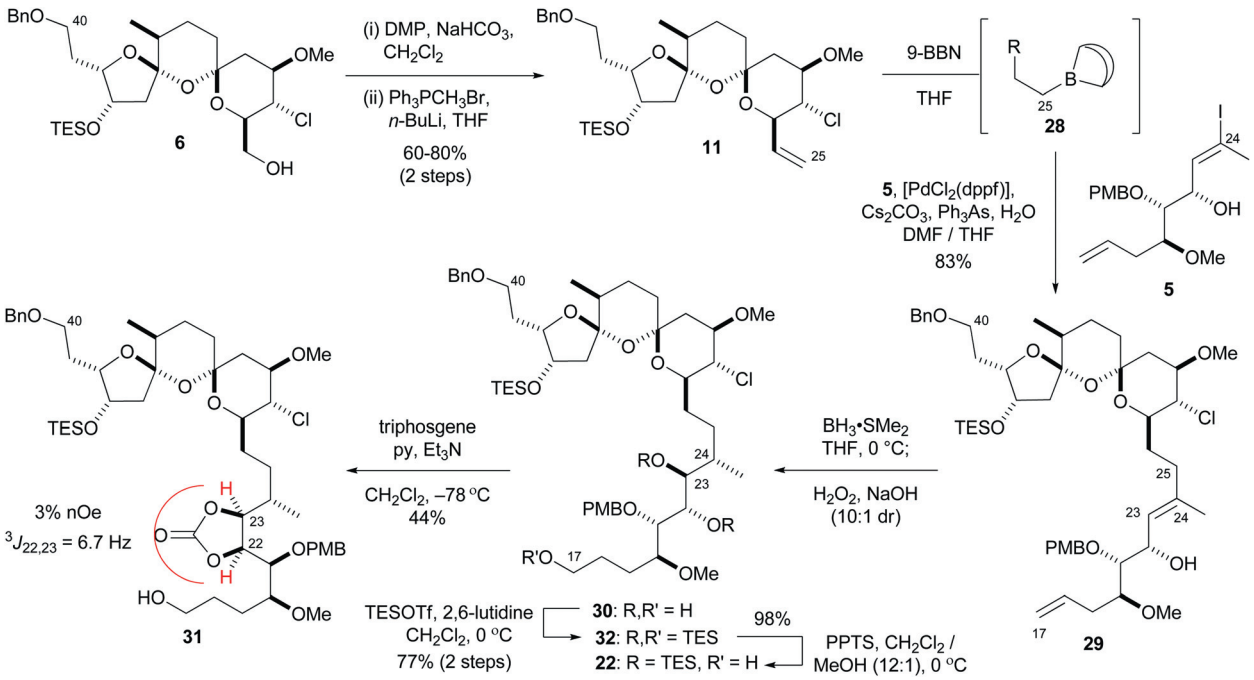
The Suzuki coupling route

Our concerns over the limited success of the Julia olefination strategy led us to reevaluate the original C25–C26 disconnection altogether (disconnection (a), Scheme 1), and seek one that might allow for a milder, more reliable mode of fragment coupling, compatible with both the steric demands of the DEF-ring system and the base sensitivity of the associated C26 aldehyde **10**. A Suzuki-type fragment coupling at C24–C25 (disconnection (b)) was considered attractive due to the mild and chemoselective conditions under which it might be achieved,[10] whilst also potentially relieving the steric factors imposed by the DEF-ring system through the insertion of an additional carbon in the connecting chain. However, the planned introduction of the C23/C24 stereocentres by subsequent hydroboration of the resulting trisubstituted $\Delta^{23,24}$ alkene was an unknown factor.[19] Somewhat surprisingly, the hydroboration of internal allylic alcohols with the alkene substitution pattern we required for this campaign has not previously been investigated. Nevertheless, we conjectured that, following Kishi's empirical rule[20] and the Stork/Houk–Jäger model,[21] hydroboration might occur preferentially on the desired π-face as dictated by the 'inside-alkoxy' effect (see insert, Scheme 4). Preliminary intelligence-gathering commenced by way of some initial model studies. With diol **23**,[22] hydroboration with $BH_3{\cdot}SMe_2$ in THF, followed by standard oxidative workup, provided a mixture of triols **24** and **25** with 3 : 1 dr, gratifyingly in favour of the desired isomer **24**. Stereochemical determination was achieved by conversion into the corresponding cyclic carbonates and ^{1}H NMR nOe analysis. Further model studies also identified the requirement for a free hydroxyl at C22 for successful reaction.

Encouraged by this preliminary success, we turned to examination of the real system (Scheme 5), which required access to DEF-bis-spiroacetal alkene **11** for the planned Suzuki coupling with vinyl iodide **5**. Initially, the mild, rhodium-catalysed methylenation method of Lebel[23] was selected based on the sensitivity of the DEF aldehyde substrate. This involved treatment of freshly prepared aldehyde (from DMP oxidation of alcohol **6**) with a mixture of Wilkinson's catalyst, PPh_3, ethanol and $TMSCHN_2$. The targeted DEF-alkene **11** was isolated in 60–80% yield from **6**, where the variability in yield was due more to the rather capricious oxidation than to the methylenation step. In reality, this reaction is a modification of the Wittig olefination, which proved a similarly effective method for the preparation of **11** (60–80% from **6**) and was ultimately the method of choice due to its greater operational simplicity.

With both DEF-alkene **11** and vinyl iodide **5** in hand, their union and the construction of the C17–C40 carbon skeleton of spirastrellolide A could be investigated. Following a procedure developed in model systems,[12] DEF-alkene **11** was treated with 9-BBN to generate the corresponding trialkylborane **28**. The quality of this reagent proved critical to the reaction and the success of the Pd-catalysed cross-coupling as a whole.[24] Following slow addition of the intermediate trialkylborane to vinyl iodide **5** under optimised Suzuki coupling conditions ($Pd(dppf)Cl_2$, Cs_2CO_3, Ph_3As, aq DMF),[25] the desired C17–C40 diene **29** was isolated in an excellent 83% yield. With a more successful fragment coupling achieved, the crucial double hydroboration reaction was now needed to complete the C20–C24 stereopentad and reveal the required C17 oxygenation.

In the event (Scheme 5), treatment of diene **29** with an excess (10 equiv.) of $BH_3{\cdot}SMe_2$ in THF for 2 h, followed by an oxidative workup provided the triol **30** as a 3 : 1 mixture of diastereomers by ^{1}H NMR analysis. Chromatographic purification enabled clean isolation of the major isomer. Determination of the stereochemical outcome was achieved by derivatisation of this triol as the corresponding cyclic carbonate **31**. A diagnostic nOe between H22 and H23 suggested the *cis*-configured carbonate, corresponding to the required spirastrellolide stereochemistry in



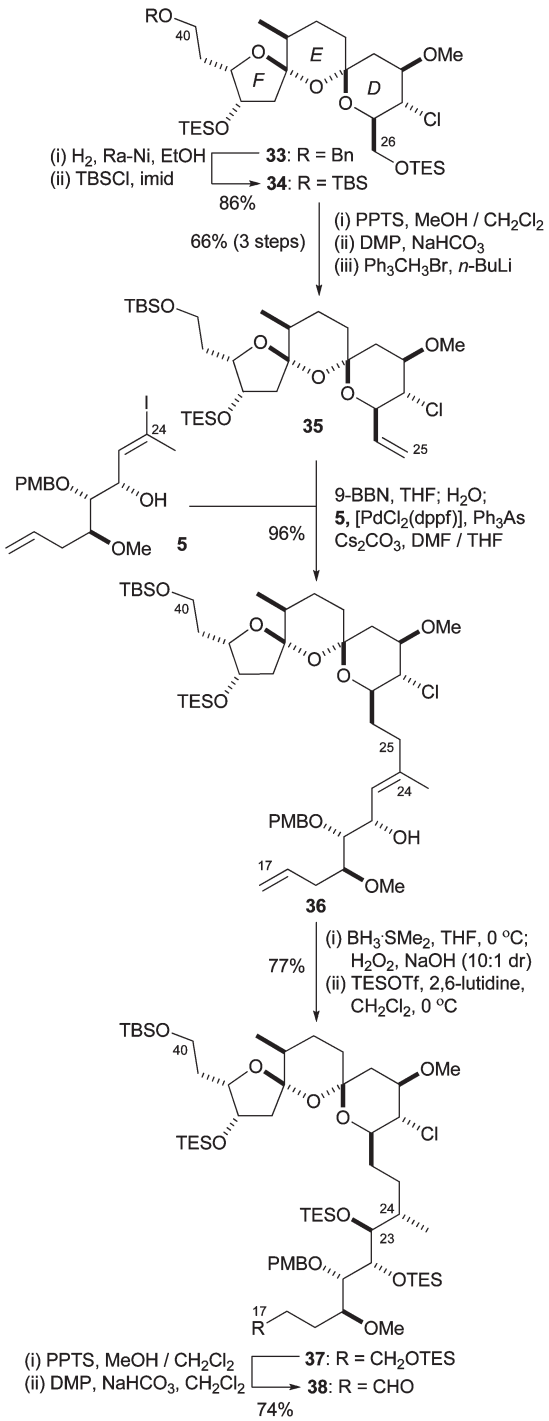
Scheme 5 Suzuki coupling and double hydroboration to assemble C17–C40 fragment **32**.

this region. Ultimately, rigorous proof of stereochemistry was achieved by conversion of **32** into alcohol **22** (PPTS, CH_2Cl_2–MeOH), and comparison with authentic material prepared by the earlier Julia olefination route (Scheme 3). ^{1}H NMR data for this latter compound was in *complete agreement* with that for the major isomer of the double hydroboration reaction, and substantially different from the minor isomer, thus confirming the stereochemical assignment at C23 and C24. To our delight, double hydroboration of diene **29** had indeed given predominantly the desired stereochemistry at C23 and C24, which was a major breakthrough in advancing the total synthesis effort.

Following this gratifying result, we concentrated on improving the key double hydroboration step. In practice, the yield could be increased by per-silylation of the crude hydroboration products, which delivered tetra-TES ether **32** (as a 3 : 1 mixture with its chromatographically inseparable minor diastereomer) in 77% yield from diene **29**. Significant enhancement in the diastereoselectivity of this key transformation was then realised by exploiting a marked substrate concentration dependence. Under optimised conditions,[26] diene **29** was added dropwise over 2 h *via* syringe pump to a solution of $BH_3{\cdot}SMe_2$ in THF at 0 °C. Oxidative workup (H_2O_2, NaOH) and per-silylation of the crude triol then provided the tetra-TES ether **32** in excellent yield and diastereoselectivity (85%, 10 : 1 dr). Whilst it is tempting to rationalise this highly stereoselective reaction using the stereochemical model depicted in Scheme 4, the lack of stereoselectivity observed for other model systems[27] suggests that stereoinduction arises principally as a result of the DEF-ring system, presumably through steric blocking of one of the alkene π-faces in the reacting conformation of **29**.

With the material prepared by this route, we explored its elaboration into truncated C1–C40 seco-acid **12** (Scheme 1) but ran into difficulties in the critical macrolactonisation step. For the sake of brevity, this phase of the project is not detailed here,[12] although it gave us confidence to go forward with the preferred Suzuki coupling route with some redesign of the protecting groups. In particular, the controlled late stage removal of the benzyl ether at C40 would likely raise chemoselectivity issues in the presence of the $\Delta^{15,16}$ olefin and the C28 chlorine substituent. In its place, a TBS ether was chosen which should be inert to the conditions used for manipulation of the C1 and C37 oxygenation in preparation for macrolactonisation, yet might be selectively removed after the macrolactone ring had been closed.

For rapid access to the modified DEF-bis-spiroacetal **34** (Scheme 6), the benzyl ether in C26–C40 fragment **33** was best cleaved by hydrogenolysis with W-6 Raney nickel in EtOH to cleanly afford the corresponding C40 alcohol.[28] TBS protection of this alcohol then gave tris-silyl ether **34** in good yield (86% from **33**). With **34** in hand, the same sequence employed previously was adapted to give alkene **35**. Accordingly, selective cleavage of the C26 TES ether was followed by oxidation to the corresponding aldehyde under optimised Dess–Martin conditions (dilute in wet CH_2Cl_2). Wittig methylenation then afforded the revised DEF-alkene **35** in readiness for Suzuki coupling with vinyl iodide **5**. As before, hydroboration of **35** was performed with 9-BBN, the reaction was quenched with water, and the crude trialkylborane was used directly in the Suzuki coupling. As previously, the cross-coupling reaction was performed by slow addition of trialkylborane to vinyl iodide **5** in wet DMF,[25] in the presence of $Pd(dppf)Cl_2$, Cs_2CO_3 and Ph_3As.[29] Due to the oxygen-sensitivity of the palladium catalyst, all reaction solvents had to be carefully degassed before use, under which conditions the desired product **36** was isolated in 83% yield. Using the optimum slow addition procedure developed for the double hydroboration of **29** (Scheme 5), diene **36** was converted into tris-silyl ether **37** in excellent yield and selectivity (95%, 10 : 1 dr). At this juncture, selective cleavage of the C17 TES ether in **37** was achieved by treatment with PPTS



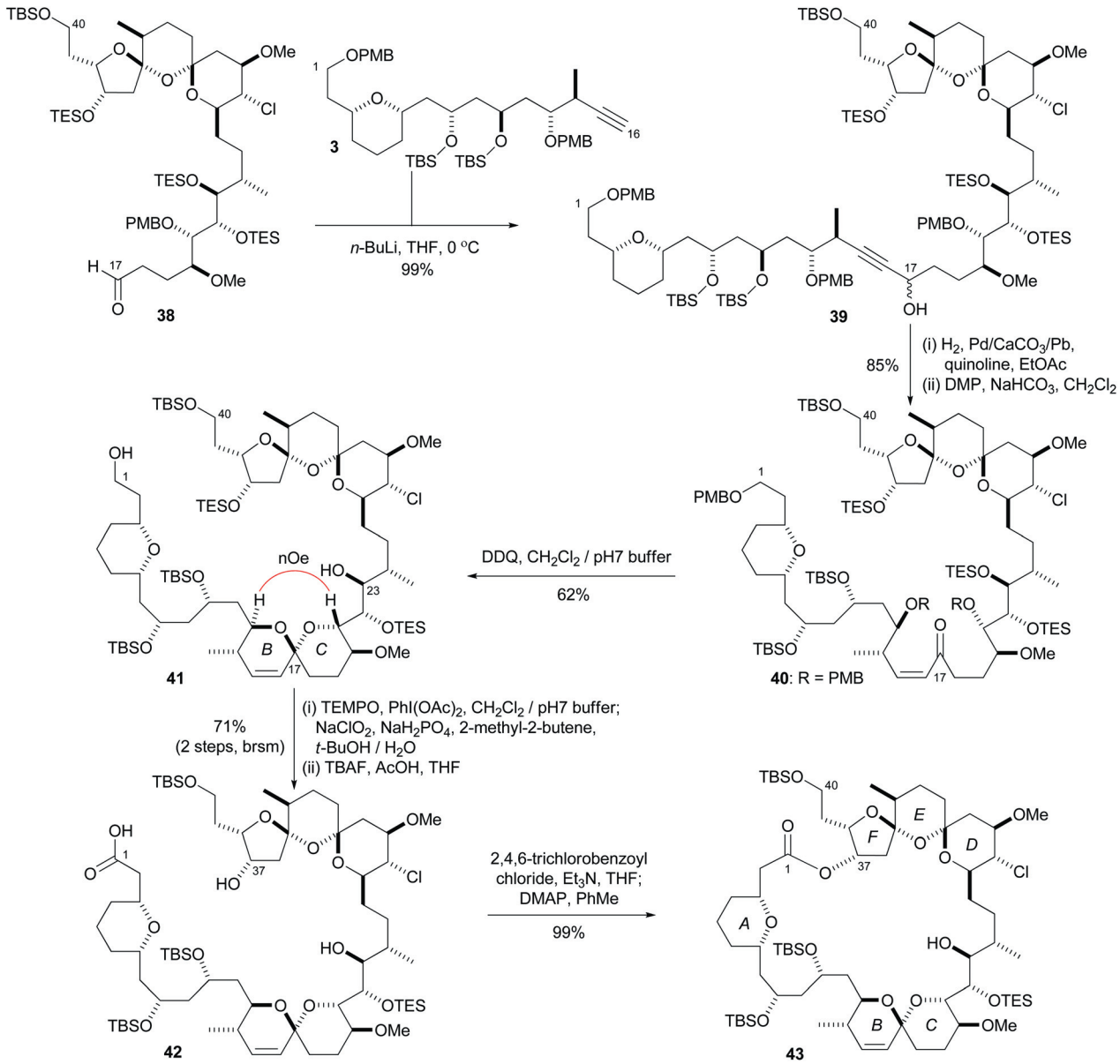
Scheme 6 Suzuki coupling in modified C40 TBS ether series.

(CH_2Cl_2, MeOH, 10 : 1), followed by Dess–Martin oxidation to afford C17–C40 aldehyde **38**, incorporating all of the oxygenation required for spirastrellolide A, with the correct stereochemistry.

Alkyne addition, BC-spiroacetalisation and macrolactonisation

Building on our early work on synthesising the southern hemisphere in isolation,[9b–d] completion of the more elaborate C1–C40 carbon framework of the spirastrellolides could now be realised through a coupling reaction between alkyne fragment **3**[8] and aldehyde **38** (Scheme 7). Lithiation of alkyne **3**, followed by addition of aldehyde **38** afforded the coupled product **39**, isolated as an inconsequential (*ca.* 1 : 1) mixture of epimeric C17 alcohols. Lindlar reduction[30] followed by Dess–Martin oxidation provided (*Z*)-enone **40** in 82% yield over 3 steps. At this stage, the planned tris-PMB deprotection and *in situ* spirocyclisation could be implemented to construct the BC-spiroacetal moiety in spirastrellolide A. On submission of **40** to DDQ in CH_2Cl_2/pH 7 buffer, the fully functionalised ABCDEF-ring system was obtained in 62% yield. Notably, **41** was isolated cleanly, with the minor C23/C24 hydroboration diastereomer now able to be separated chromatographically. Based on the anticipated stabilisation by the anomeric effect, the configuration at C17 of the newly formed BC-spiroacetal in **41** was confirmed through a diagnostic nOe correlation between protons at C13 and C21. It is also noteworthy that the major product **41** was found to have a free hydroxyl group at C23 due to an unexpected silyl deprotection. At this point, it was decided to progress the synthesis with a free hydroxyl at C23 in **41**, a decision we later found to be crucial for successful macrolactonisation.[31]

Having the complete C1–C40 component **41** now in hand, elaboration into the truncated seco-acid was carried out in readiness for macrolactonisation. From **41**, the required seco-acid **42** was prepared *via* a 3-step sequence. For selective oxidation of the primary alcohol at C1, the nitroxyl radical TEMPO was used in the presence of $PhI(OAc)_2$.[32] Through this TEMPO oxidation, the expected aldehyde was formed together with some material which had been further oxidised to carboxylic acid. Notably, no oxidation of the C23 secondary alcohol was observed. Without purification, Lindgren–Pinnick oxidation[33,34] was carried out to convert all of this material to the carboxylic acid in 86% yield over 2 steps. To complete the preparation of *seco*-acid **42**, TES deprotection of the C37 alcohol was carefully performed with a mixture of TBAF–AcOH (1 : 3 molar ratio) in THF. It was necessary to stop this reaction before full conversion of starting material due to the lability of the other silyl ethers. Quenching of the reaction after 45 min produced **42** in 57% yield, while 31% of unreacted starting material could be recovered and reused. Based on our extensive experience in macrolide total synthesis,[35] the tried and tested method of Yamaguchi was selected to close the 38-membered macrolactone of spirastrellolide A.[36,37] Accordingly, a mixed anhydride of **42** was initially formed with 2,4,6-$Cl_3(C_6H_2)COCl$ and Et_3N in THF; this was diluted with PhMe and slowly added by syringe pump to a solution of DMAP. Gratifyingly, clean macrolactonisation to afford **43** was achieved in essentially quantitative yield within 2 h, without the need for heating. The remarkable ease with which this highly functionalised 38-membered macrolactone could be prepared, together with the observation that no cyclisation was observed involving the free alcohol at C23, suggests that the seco-acid **43** may favour a pre-organised pseudo-macrocyclic conformation. We attribute this effect to the nature of the C22–C24 linker region between the BC and DEF-spiroacetal ring systems, which serves to orientate the BC and DEF spiroacetals in a productive manner for closure of the 38-membered macrolactone. This conformational preference may derive from possible hydrogen bonding of the free C23 alcohol with the C11 ether (see Fig. 1)



Scheme 7 Alkyne addition, BC-spiroacetalisation and macrolactonisation to give **43**.

or a subtle steric or stereoelectronic control over the C22/C24 rotamer distribution.[38]

Exploring the side-chain attachment

Delighted with the efficiency of the crucial macrolactonisation step, completion of the synthesis seemed imminently possible from advanced intermediate **43**. The only remaining task appeared to be attachment of the full side chain at the C40 position. However, despite significant experimentation, selective cleavage of the supposedly labile primary TBS ether in **43** to reveal the free C40 hydroxyl could not be achieved. Most attempts led to a mixture of non-selectively deprotected compounds, revealing a variety of alcohols in the macrocycle. Therefore, our preferred course of action became a global deprotection followed by protecting group adjustment. Using HF·py/py (2 : 1 v/v) in THF (Scheme 8), all the silyl ethers were cleaved to afford the remarkable macrocyclic pentaol **44**, which was isolated as colourless needle-shaped crystals (m.p. 174 °C). The excellent quality of these crystals enabled X-ray diffraction analysis, yielding the crystal structure shown in Fig. 1.[39] Interestingly, this revealed a network of both intermolecular and intramolecular hydrogen bonding, which leads to a well-defined conformation within the 38-membered macrocycle. This first solid-state structure[40] of the exact macrocyclic core of spirastrellolide A confirmed that the configuration of all the stereocentres had been installed as planned and corresponded to that within the natural product itself, and furthermore revealed the precise location in space of the various macrocycle substituents – information which is likely to prove invaluable in the design of spirastrellolide analogues.[2a]

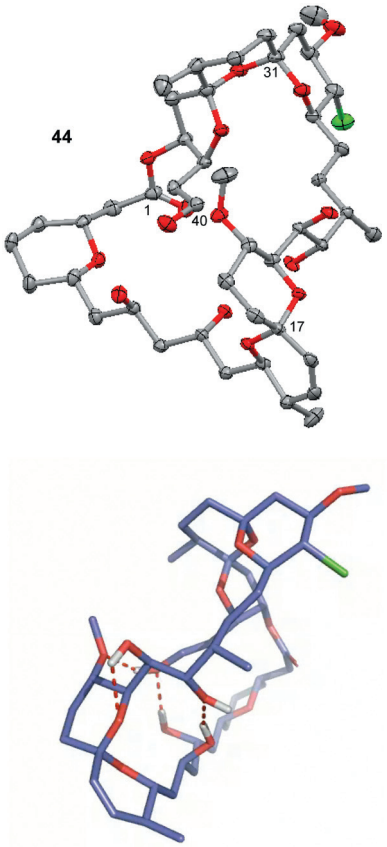
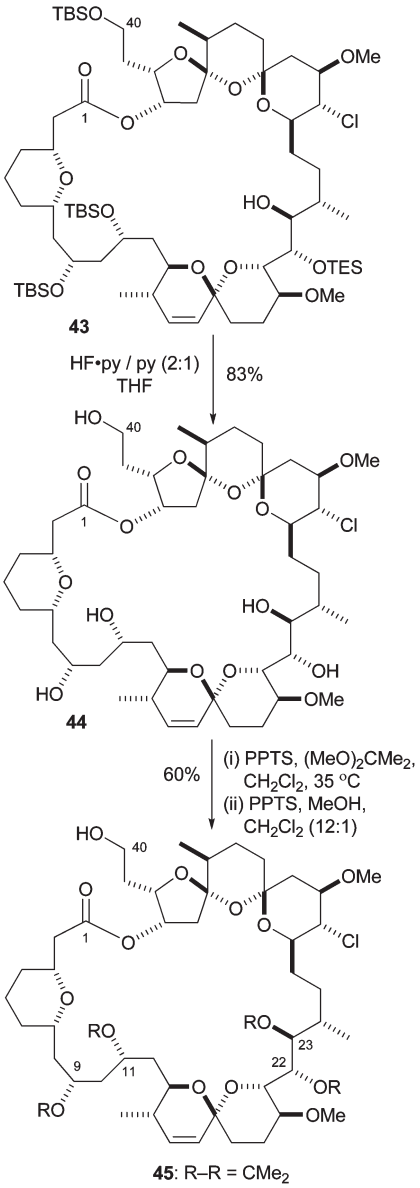


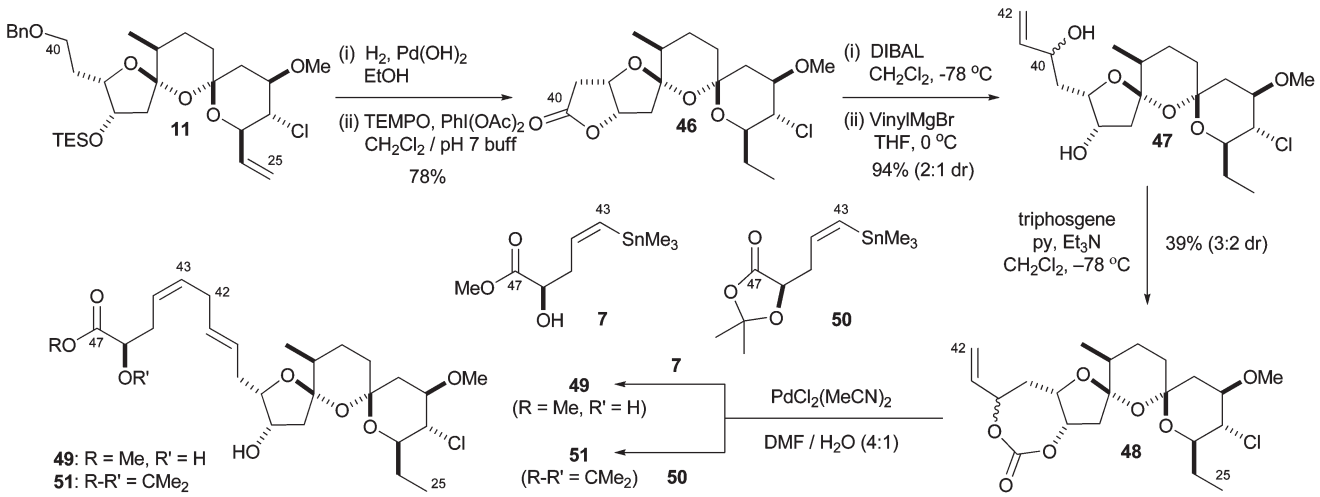
Fig. 1 Crystal structure[39] of macrocyclic pentaol **44** and depiction of internal hydrogen-bond network.



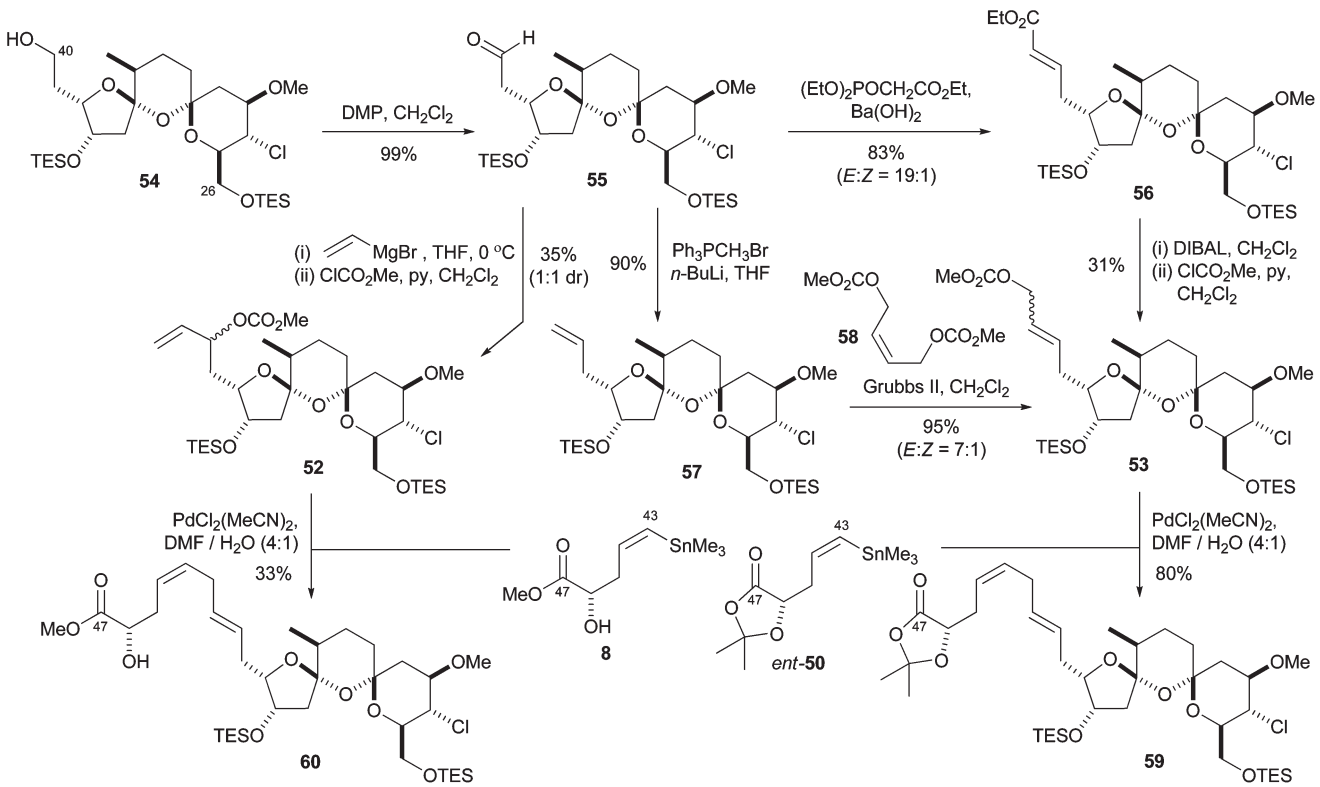
Scheme 8 Preparation of macrocyclic pentaol **44** and bis-acetonide derivative **45**.

Inspired by the preparation of the bis-acetonide of spirastrellolide A methyl ester in the structural elucidation studies of the Andersen group,[1b] acetonide protection of the C22/C23 and C9/C11 diol regions in **44** was proposed in the anticipation that this would lead to an opportunity for NMR correlation. Bis-acetonide **45** having a primary alcohol at C40 was prepared in a two-step sequence. Full protection of **44** with an excess of 2,2-dimethoxypropane in the presence of PPTS, followed by cleavage of the accompanying mixed acetal group at C40, produced the desired alcohol **45** (60%). The latter step also produced some over-deprotected compounds, which could be easily recycled through the same reaction sequence. In general, an overall yield of 78% for **45** was obtained after one recycle. Comparison of the ^{1}H NMR spectroscopic data of bis-acetonide **45** with the reported data for the bis-acetonide of spirastrellolide A methyl ester (see ESI‡) now indicated a close correlation. In this key synthetic intermediate, the conformation of the macrocyclic core in solution appears to correlate closely with the derivatised natural material within comparable regions.

With the fully functionalised macrocycle established, we could now investigate various endgame options. From the outset, our preferred approach called for the late-stage installation of the full side chain of spirastrellolide A, incorporating the 1,4-diene moiety and α-hydroxy methyl ester, as dictated by the initially unknown configuration at C46. By use of C43–C47 stannane fragment **7** (Scheme 1) and a π-allyl Stille coupling,[11] it was anticipated that both configurations could be generated and hence the two possible diastereomers of the natural product could be accessed. In order to establish suitable reaction conditions, while conserving advanced material, this Stille coupling sequence was explored starting out from already prepared C25–C40 DEF-alkene **11** (Scheme 9). Hydrogenation of **11** with Pearlman's catalyst effected C40 debenzylation, alkene reduction together with C37 desilylation, affording the corresponding diol in near quantitative yield. Selective primary oxidation (TEMPO, $PhI(OAc)_2$) then gave γ-lactone **46** as a crystalline solid (m.p. 153 °C). Reduction of γ-lactone **46** to the lactol with DIBAL followed by addition of vinylmagnesium bromide provided allylic alcohol **47** (94%, 2 : 1 dr), which was subjected to cyclic carbonate formation by treatment with triphosgene to provide **48** (39%, 3 : 2 dr).[41] The Stille cross-coupling between **48** and stannane **7**[8] was carried out using catalytic



Scheme 9 Synthesis of northern hemisphere analogues of spirastrellolide by π-allyl Stille coupling with cyclic carbonate **48**.



Scheme 10 Synthesis of additional northern hemisphere analogues of spirastrellolide by π-allyl Stille coupling with acyclic carbonates **52** and **53**.

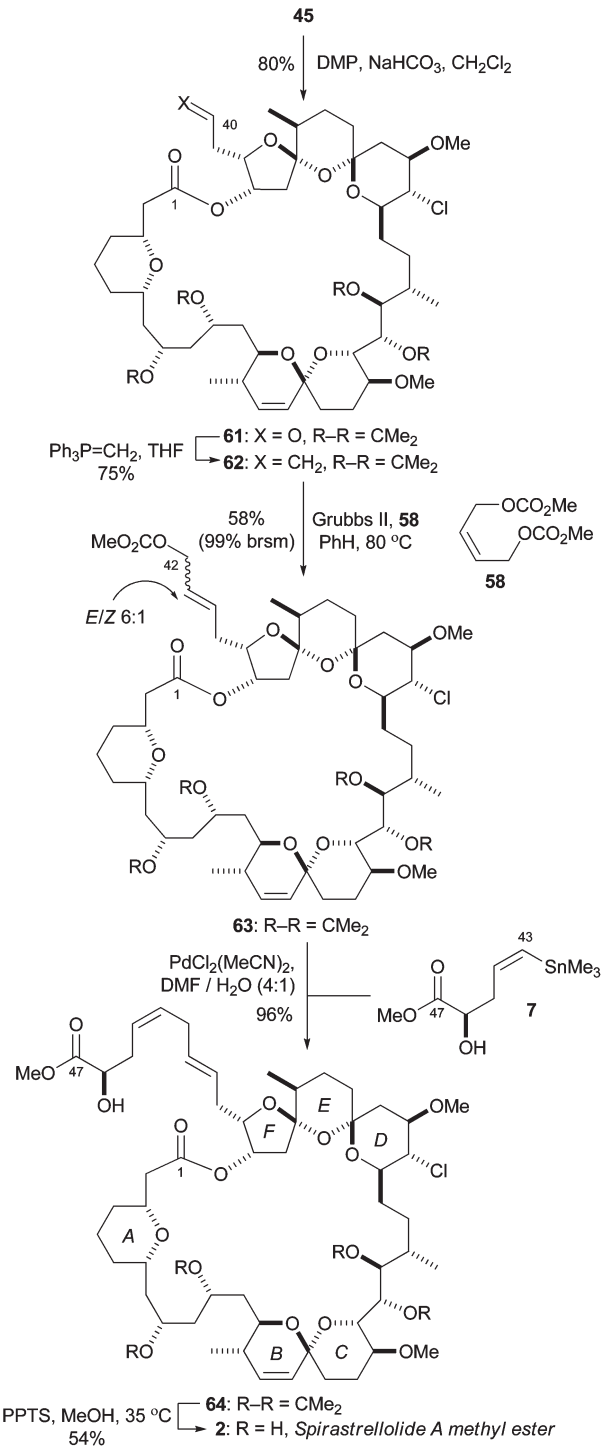
$PdCl_2(MeCN)_2$ in wet DMF, which afforded methyl ester **49** (72%) *via* an intermediate π-allyl palladium species. Pleasingly, this reaction proceeded with the expected conservation of the (43*Z*)-alkene ($^3J_{H43,H44}$ = 10.8 Hz) and installation of the required (40*E*)-alkene ($^3J_{H40,H41}$ = 14.6 Hz). Repeating the reaction with structurally related stannane **50** was also successful, affording the corresponding skipped diene **51** (57%). To increase the flexibility of the synthesis endgame, we also prepared the acyclic regioisomeric allylic carbonates **52** and **53** (incorporating TES ethers at C26 and C37) as substrates for the π-allyl Stille coupling reaction (Scheme 10). Dess–Martin oxidation of alcohol **54** (from debenzylation of **33**, Scheme 6) gave aldehyde **55**. Vinylmagnesium bromide addition to **55** followed by acylation with methyl chloroformate produced a 1 : 1 epimeric mixture of secondary allylic carbonates **52**. As an alternative, an HWE olefination[42] of aldehyde **55** extended the side chain giving (*E*)-enoate **56**. Ester reduction followed by carbonate formation produced coupling substrate **53** containing only the (*E*)-alkene. In order to develop a strategy that might be more applicable to the real system, which contains a potentially sensitive

macrolactone functionality, an alternative route to **53** was also devised to exclude the reduction step. Wittig methylenation of **55** to give **57**, followed by cross-metathesis[43] with bis-allylic carbonate **58**[44] using Grubbs II catalyst (5 mol%, CH_2Cl_2, 40 °C) proceeded smoothly to afford alkene **53** in 95% yield as an inseparable mixture of isomers (*E*/*Z* = 7 : 1). As the cross-coupling is proposed to proceed *via* a π-allyl palladium intermediate, this alkene geometry ought to be irrelevant (*i.e.*, both (*E*)- and (*Z*)-alkenes should give the same product), providing the rate of stereochemical equilibration of the π-allyl complexes to the more stable transoid configuration exceeds that of transmetallation. We were most gratified to find that Stille coupling between stannane *ent*-**50** and **53**, using $PdCl_2(MeCN)_2$ (10 mol %) in wet DMF, indeed gave 1,4-diene **59** as a single diastereomer in 80% yield despite the mixture of *E*/*Z* isomers in **53**. Carbonate **53** underwent coupling with **50** with equal facility (**59a**, 69% brsm). The isomeric carbonate **52** proved a somewhat poorer substrate for cross-coupling however, providing **59** in 59% yield, and the methyl ester **60** on reaction with **8** in 33% yield. The diastereoisomeric dioxolanone **59a** could then be smoothly converted into methyl ester **60a** by methanolysis (K_2CO_3, MeOH).[45]

As well as showing that Stille coupling of an *in situ* generated π-allyl palladium species is a viable approach for elaborating the characteristic C38 side chain of the spirastrellolides, this temporary detour also provided several simplified analogues (**49**, **51**, **59** and **60**) for future structure–activity relationship studies.

Completion of the total synthesis of spirastrellolide A methyl ester

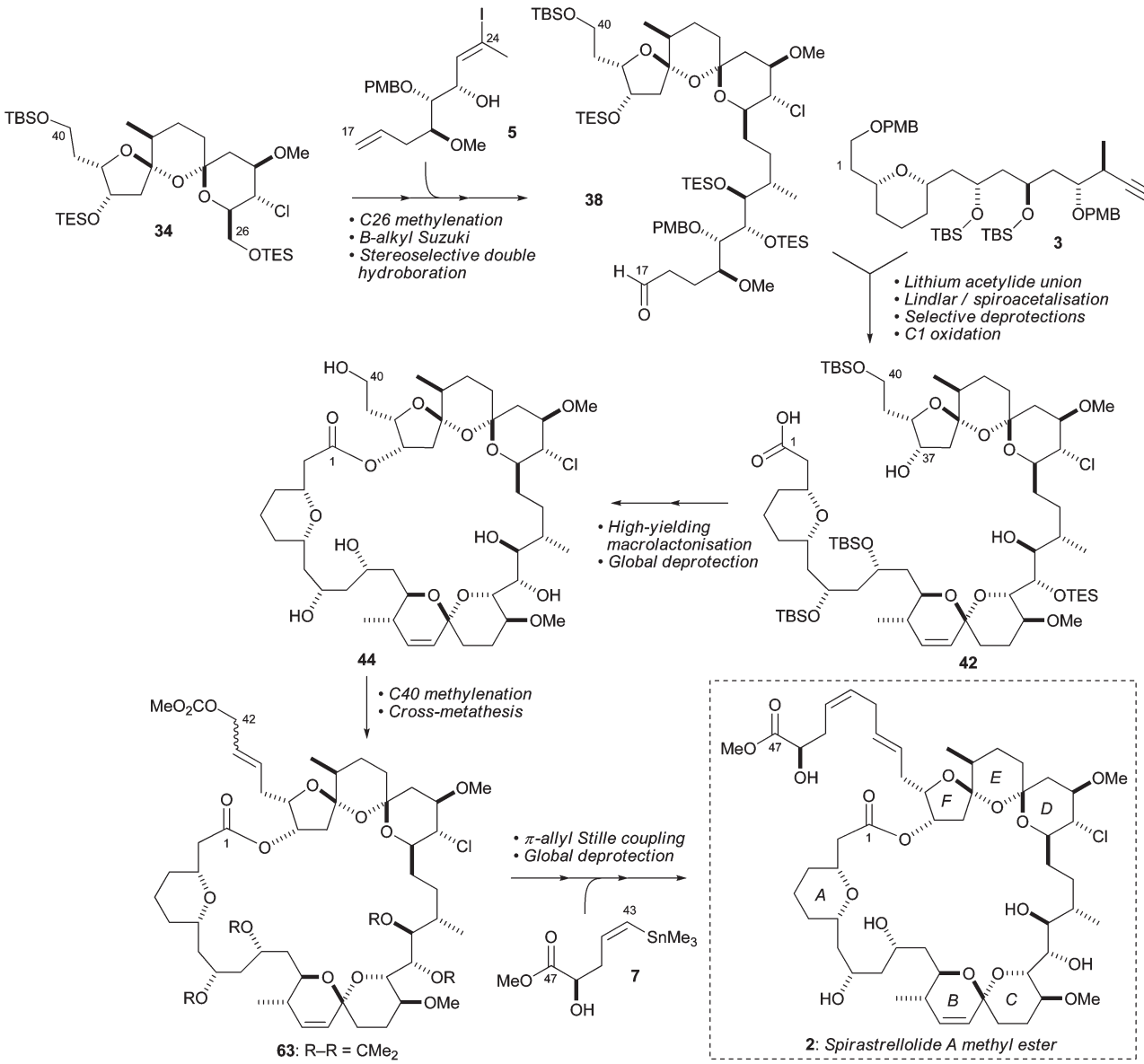
At this stage, we were ready to embark on the final stages of the total synthesis campaign having established the viability of the π-allyl Stille coupling process on northern hemisphere model systems. In order to test out some of the protocols for introducing the allylic carbonate appendage on the full macrolactone system, the alcohol **45** was oxidised by buffered Dess–Martin periodinane to cleanly afford aldehyde **61** (Scheme 11). Frustratingly, initial attempts to elaborate macrocyclic aldehyde **61** towards the targeted allylic carbonate proved unsuccessful. These included a Nozaki–Hiyama–Kishi reaction with vinyl iodide, a Grignard addition with vinylmagnesium bromide, and a stabilised Wittig olefination with $Ph_3P{=}CHCHO$. Although it is difficult to pinpoint a single cause of failure in a structure as complex as **61**, it was considered that steric effects from the macrocyclic cage-like environment around the C40 aldehyde (as revealed by the X-ray crystal structure of **44**, see Fig. 1) were reducing its reactivity. Fortunately, a Wittig olefination of **61** with $Ph_3P{=}CH_2$ was successful, giving the terminal alkene **62** cleanly (87%, 2 steps). Studies towards the side chain attachment were thus channelled towards olefin cross-metathesis[43] of **62** with **58**, which we hoped would afford a primary allylic carbonate. Further evidence for the reduced reactivity at this site is shown by the forcing conditions which were needed to achieve this cross-metathesis, requiring 20 mol% loading of Grubbs II catalyst and an elevated temperature of 80 °C. Moreover, the desired product **63** was isolated in a modest 58% yield after 16 h reaction, although fortunately the unreacted starting material **62**



Scheme 11 Completion of the total synthesis of spirastrellolide A methyl ester.

could be recovered in 42% yield (99% brsm for **63**), this low conversion again likely reflecting the steric encumbrance imposed by the macrocycle on the truncated side chain. The stereoselectivity of this coupling mirrored that of our earlier model study, with allylic carbonate **63** being obtained as a 6 : 1 mixture of *E*/*Z*-isomers.

At this late stage of the campaign, the configuration of the last remaining stereocentre at C46 was assigned in a timely



Scheme 12 Summary of the intermediates and synthetic journey to spirastrellolide A methyl ester (**2**).

publication by the Andersen group.[2b] By oxidative degradation of a newly found congener, spirastrellolide D methyl ester, and subsequent methyl ester formation within the fragmentation product, dimethyl malate was obtained as the (*R*)-enantiomer.

Consequently, spirastrellolide D was shown to have (*R*)-configuration at C46 and hence, by analogy, it was assumed that spirastrellolide A would be the same.

With this knowledge of the full configuration of spirastrellolide A, the side chain attachment could now be completed with confidence that the correct stereochemistry would be introduced. Stille coupling was initiated between macrocyclic allylic carbonates **63** and (46*R*)-stannane **7** using identical conditions to those in the model system ($PdCl_2(MeCN)_2$ in wet DMF). From the previous work to chain-extend at C40, it was expected that the reactivity of the allylic carbonate would be lower than for the model system. As such, it was disappointing yet unsurprising to discover that once stannane **7** was added to a pre-mixed solution of **63** and palladium catalyst in degassed DMF–H_2O, the desired cross-coupling reaction seemed to be prevented by competing decomposition pathways, with more rapid formation of the homo-coupling product of **7** and deposition of palladium black, preventing productive turnover in the catalytic cycle. Fortunately, this could be circumvented by the slow (portionwise) addition of solutions of $PdCl_2(MeCN)_2$ catalyst and stannane **7** to substrate **63**, which provided the desired coupled product **64** in 96% yield. As expected from the model system, both isomers of the $\Delta^{40,41}$ olefin in **63** produced the desired (40*E*)-olefin following Stille coupling. At this stage, a direct comparison could be made to an identical bis-acetonide prepared by the Andersen group from natural spirastrellolide A.[1b] Gratifyingly, this synthetic bis-acetonide **64** correlated in all respects (^1H and ^{13}C NMR, mass spectra, and optical rotation, see ESI‡) with the data reported, unequivocally validating the complete stereostructure proposed by the Andersen group.[46]

To complete the total synthesis, the final acetonide deprotection was carried out on **64**. With an excess of PPTS in MeOH, spirastrellolide A methyl ester (**2**) could be obtained following 16 h reaction at 35 °C. At this stage, a sample of authentic methyl ester of spirastrellolide A was made available to us by the Andersen group for correlation purposes. However, ^{1}H NMR comparison of the purified synthetic and natural samples proved an inexact match on initial analysis. Even more remarkably, repeated analysis of the *same sample* in benzene-d_6 gave varied spectra depending on the sample treatment. For example, spectra of this sample differed before and after storage at −20 °C for 16 h, despite both spectra being recorded at room temperature. Purification by HPLC also caused changes to the resonances in the 3.1–4.8 ppm region of the ^{1}H NMR spectra (see ESI‡). This observation may suggest the adoption of different stable conformers (*i.e.*, atropisomers) of spirastrellolide in benzene-d_6, where the barrier to interconversion is set by the hydrogen bond-stabilised framework. It is entirely conceivable that reverse phase HPLC purification could interconvert such isomers *via* temporary disruption of this hydrogen bond network (polar/aqueous conditions), and that the process of temporary incorporation of the natural product in a frozen benzene matrix could exert similar effects. Similar discrepancies between samples had been observed by Andersen,[47] and subsequent to our work by the Fürstner group[4b] in their total synthesis of spirastrellolide F methyl ester, as well as in our earlier NMR analysis of macrocyclic pentaol **44**.[40] To reinforce this hypothesis, a more polar NMR solvent was used in order to disrupt the hydrogen-bonding network. In acetonitrile-d_3, despite the poorer dispersion, all chemical shifts were now readily reproducible in both the synthetic and natural sample. By careful trials, it was discovered that an exact correlation in benzene-d_6 could only be achieved by subjecting both synthetic and natural samples to an identical NMR sample preparation protocol. Thus, purification by HPLC, preparation of NMR samples, and running of the NMR spectra was carried out in parallel under identical conditions with both samples. Gratifyingly, in this case, both the natural and synthetic NMR spectra were now identical. Correlation was also obtained in mass spectra, CD spectra, optical rotation and HPLC retention time, thus confirming unequivocally the success of our total synthesis, and providing for the first time a synthetic means to access this captivating and important natural product.

Conclusions

Due to a combination of their promising anticancer properties, the limited supply from the marine sponge source and their unprecedented 38-membered macrolactone scaffold, the spirastrellolides represent attractive yet challenging synthetic targets. By adopting a modular and flexible strategy, a highly stereocontrolled total synthesis of (+)-spirastrellolide A methyl ester (**2**) was completed in 36 steps (*ca*. 0.3% overall yield, Scheme 12). Following optimised syntheses of the key building blocks (C1–C16 alkyne **3**, C17–C24 vinyl iodide **5** and C25–C40 bis-spiroacetal **6**), controlled fragment coupling to access the macrocyclic core of spirastrellolide A proceeded with high efficiency. In the preferred route, vinyl iodide **5** was coupled to bis-spiroacetal **34** using *B*-alkyl Suzuki coupling methodology, followed by double hydroboration to install the C23/C24 stereocentres. The derived C17 aldehyde **38** then underwent smooth coupling with the lithium acetylide of alkyne **3**. A DDQ-mediated BC-spiroacetalisation was followed by a remarkably high yielding macrolactonisation of a truncated seco-acid **42** to give, after exhaustive desilylation, the crystalline macrocyclic core **44** of the spirastrellolides. Finally, after investigations to chain-extend the sterically hindered C40 region, a π-allyl Stille coupling was employed to install the required skipped diene from a diastereomeric mixture of allylic carbonates **63**. Global deprotection and purification then afforded fully synthetic (+)-spirastrellolide A methyl ester (**2**), which was validated by careful NMR correlation with an authentic sample.

This first total synthesis of spirastrellolide A methyl ester evolved alongside structure determination studies by the Andersen group. As such initial stereochemical ambiguities influenced our synthetic strategy, resulting in a modular approach to the macrocyclic core and a late-stage side-chain attachment. We anticipate that with the full configuration now secure, a more streamlined and higher yielding synthetic route to the spirastrellolides might evolve from the extensive groundwork reported in these two papers.[48] In closing, we emphasise that pursuing such complex natural products as the spirastrellolides by total synthesis has proved to be a learning experience par excellence, as well as enabling a sustainable supply and access to novel designed analogues to further explore the biology and therapeutic potential of these fascinating molecules.

Experimental

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

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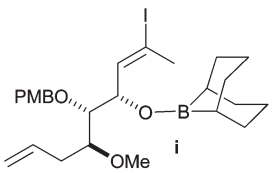

i

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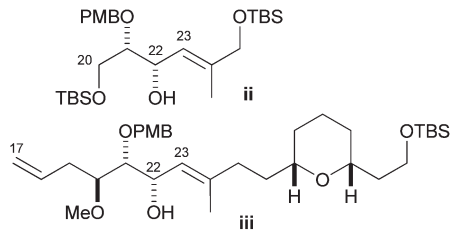

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ascribed to a disadvantageous conformation imposed by having the C22/C23 hydroxyls protected as an acetonide; see ref. 4*b*.
39 CCDC 669312 contains the supplementary crystallographic data for **42**.‡
40 Detailed ^{1}H NMR analysis of **44** in C_6D_6 solution proved to be a demanding task, where several different conformations of the macrocyclic pentaol may be present. The observation of variable chemical shifts of some resonances on repeated submission of the same sample and an inexact match between **44** and the macrolactone region of spirastrellolide A methyl ester meant that the definitive evidence from the X-ray structure was invaluable. All of the erratic ^{1}H NMR signals correlate to the protons, which could be part of the hydrogen-bonding network, based on the solid-state structure of **44**.
41 A change in diastereomeric ratio at C40 in forming carbonates **48** is attributed to differential reactivity between the epimeric allylic alcohols.
42 I. Paterson, K.-S. Yeung and J. B. Smaill, *Synlett*, 1993, 774.
43 (*a*) A. K. Chatterjee, T. L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360; (*b*) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4490.
44 T. Tsuda, T. Kiyoi and T. Saegusa, *J. Org. Chem.*, 1990, **55**, 3388.
45 See ESI‡ for structures and details.
46 Independently to the degradation study by the Andersen group (ref. 2*b*), it was considered that the side-chain configuration could be established through the synthesis of both C46-epimers and comparison to the reported spectral data. To this end, we also prepared the 46-*epi*-bis-acetonide of spirastrellolide A methyl ester by carrying out the Stille coupling with *ent*-7; this product showed a distinctly different ^{1}H NMR spectrum to that of **64** and so could be ruled out.
47 D. E. Williams, personal communication, University of British Columbia, November 2008.
48 I. Paterson, P. Maltas, S. M. Dalby, J. H. Lim and E. A. Anderson, *Angew. Chem., Int. Ed.*, 2012, **51**, 2749.

