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Total synthesis of (+)-spirastrellolide A methyl ester: Challenges and discoveries*

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Abstract: This review focuses on recent synthetic efforts by our group towards spirastrellolide A methyl ester, a complex marine macrolide containing two spiroacetal ring systems that shows promising anticancer properties. The evolution of a flexible, modular strategy leading to the first total synthesis of (+)-spirastrellolide A methyl ester, and the associated challenges overcome, are highlighted, particularly in dealing with the initial structural ambiguities. This work enabled the development of an improved second-generation synthesis, which revealed a critical dependence of the key macrolactonization step on the nature of the protecting groups in the linker region between the spiroacetal motifs.

Keywords: anticancer drugs; macrolides; natural products; protein phosphatases; stereocontrolled synthesis.

INTRODUCTION

Marine organisms, particularly sponge invertebrates and associated bacteria, continue to be a rich source of novel bioactive natural products for drug discovery [1]. In particular, marine polyketides that exhibit exceptional levels of antimitotic activity, combined with unique modes of action, represent valuable lead structures for the development of anticancer drug candidates [2]. However, as the promising biological activity exhibited by such polyketides is generally mirrored by their scarce natural abundance, chemical synthesis represents a critically important exercise to solve the supply problem, as well as to access novel analogues for structure–activity relationship (SAR) studies.

For example, the Novartis large-scale synthesis of discodermolide (**1**, Fig. 1), based on the synthetic work of Smith and ourselves, enabled this rare marine sponge-derived polyketide to advance into clinical trials as a novel tubulin-targeting anticancer drug [3]. Similarly, the clinical approval of Halaven (**2**), Eisai's analogue of the halichondrin family of marine polyether macrolides marketed for the treatment of metastatic breast cancer, owes much to the pioneering synthetic studies of the Kishi group [4].

Within our group, the stereocontrolled synthesis of biologically important polyketides of both marine and terrestrial origin, combined with the development of new synthetic methods and strategies, are of ongoing interest [5]. In this account, we give a critical overview of our efforts to develop an efficient total synthesis of spirastrellolide A, a structurally intriguing marine macrolide with promising anticancer activity.

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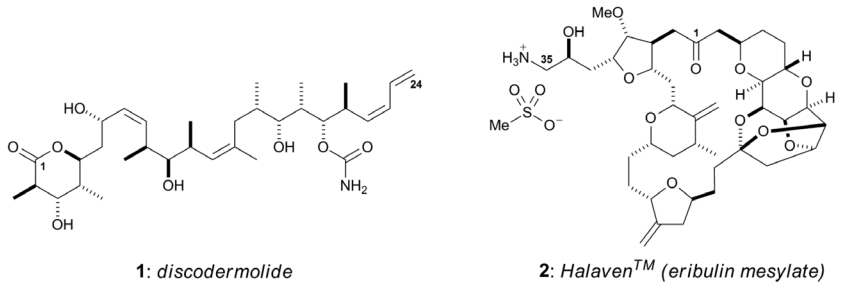


Fig. 1 Examples of medicinally significant marine-derived antimitotic agents.

THE SPIRASTRELLOLIDE FAMILY OF MARINE MACROLIDES

In 2003, the Andersen group reported the isolation and first tentative structural assignment of spirastrellolide A (**3**, Fig. 2), the active antimitotic agent found in extracts of the Caribbean sponge *Spirastrella coccinea* [6]. Isolated as the methyl ester derivative, spirastrellolide A has since been shown to exhibit potent and selective inhibition of protein phosphatase 2A, making this complex natural product an important candidate for anticancer therapeutics and a potential tool for investigating neurological disease. While the Andersen group were able to revise their original structural assignment to **4** in 2004, containing four isolated regions of undefined relative stereochemistry, it was not until late in 2007 that the relative and absolute configuration was unequivocally determined (**5**), following the isolation of six closely related congeners (spirastrellolides B–G) [7].

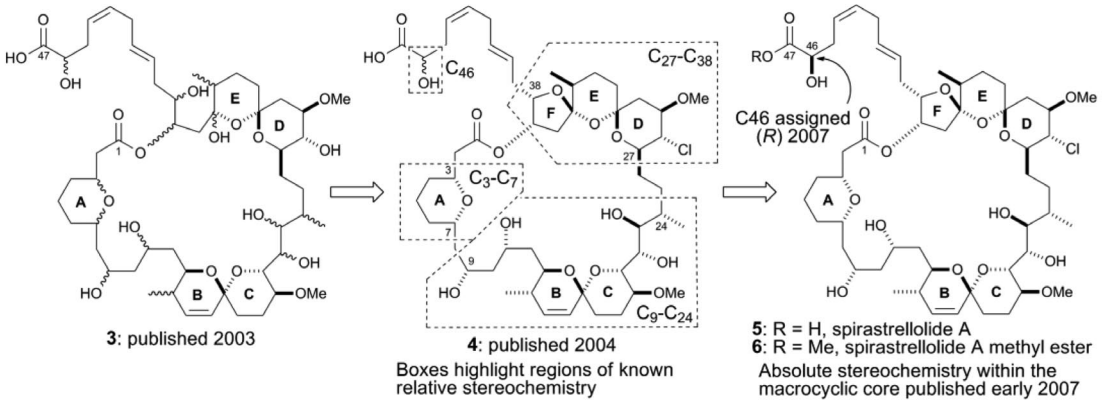


Fig. 2 An evolving structural understanding of spirastrellolide A.

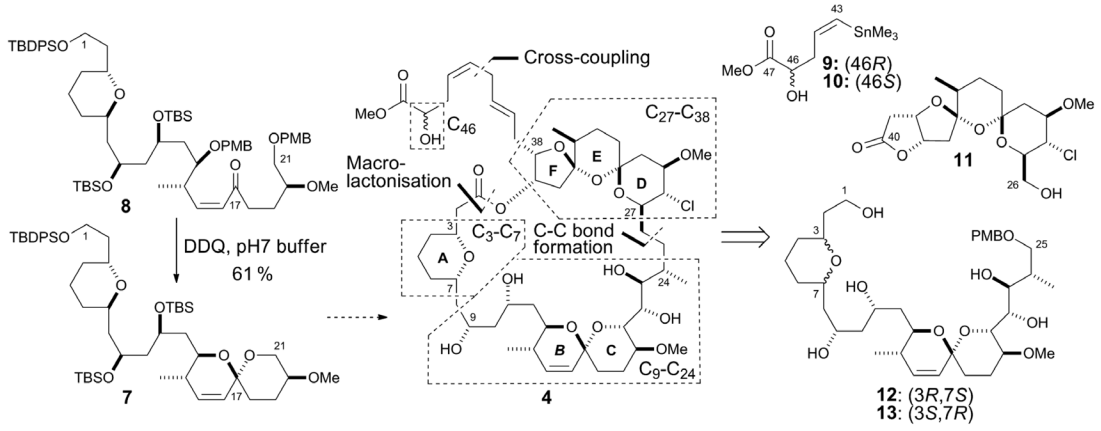
Spirastrellolide A contains several challenging and appealing structural features, including 21 stereocenters, a 38-membered macrolactone, and a 9-carbon side chain featuring a (*Z*,*E*)-1,4-diene. The macrocycle itself contains a tetrahydropyran (A ring), a bicyclic 6,6-spiroacetal (BC rings), and a tricyclic 5,6,6-spiroacetal (DEF rings) featuring a chlorine atom at C28. Notably, both the BC and DEF spiroacetal motifs benefit from stabilization by a maximum number of anomeric effects.

The incomplete stereochemical assignment of **3**, together with the scarce natural supply and complex structural features, make the spirastrellolides appealing targets for total synthesis. Despite intensive efforts worldwide from many research groups [8], there have only been four completed syntheses reported to date: the first total synthesis of spirastrellolide A methyl ester **6** (Paterson, 2008) [9], two completed syntheses of the 15,16-dihydro congener, spirastrellolide F methyl ester (Fürstner, 2009 and

2011) [10], and a second synthesis of **6** (Paterson, 2012) [11]. Herein, we present an updated critical review of our synthetic work directed towards spirastrellolide A.

Background to synthetic studies towards structure elucidation

Work in our group towards spirastrellolide A began in 2003, directly after publication of the originally proposed structure **3** [6a]. At this early stage, due to the structural ambiguities present in **3**, a full retrosynthetic analysis for spirastrellolide A was unfeasible. Instead, early efforts focused on an exploratory synthesis of a model C1–C21 subunit **7** [12], one of several plausible diastereomers based on **3** (Scheme 1). In the event, while spectroscopic comparison of this C1–C21 subunit with the natural product showed discrepancies, practical information regarding the ease of BC-spiroacetalization using a (DDQ-mediated) *p*-methoxybenzyl (PMB) deprotection and in situ cyclization, i.e., **8** → **7**, proved invaluable to the ultimate success of the project.



Scheme 1 Early retrosynthetic analysis based on spirastrellolide structure **4**.

With the advent of revised structure **4** [6b], which accounted for the discrepancies in the spectroscopic comparison between ABC subunit **7** and the natural product, it now became possible to consider an overarching strategy towards spirastrellolide A. To manage the considerable stereoconundrum presented in structure **4** (which is illustrated as one of 16 possible stereoisomers), a modular strategy was adopted such that regions of known relative stereochemistry could be generated in isolation, then combined to access any of the possible diastereomers of the natural product. Consequently, the remote C46 stereocenter in **4** was to be installed via Stille coupling of stannane **9** or **10** to the completed macrocycle, which in turn would arise from the union of DEF subunit **11** (or its enantiomer) and the two possible diastereomers of the southern hemisphere, **12** and **13**.

Continuing our work towards the construction of spirastrellolide fragments for spectroscopic comparison with the natural product, the two C1–C25 southern hemisphere diastereomers **12** and **13** were prepared using a similar deprotection/spiroacetalization strategy to that which generated the BC rings in fragment **7** [13]. Now a very clear ^{1}H NMR spectroscopic correlation was obtained between these synthetic diastereomers and the natural product, with a slightly better match observed for ABC segment **12** (3*R*,7*S*) over **13** (3*S*,7*R*). While this result was not sufficiently conclusive for unequivocal structural assignment, the stereochemical relationship in fragment **12** was pursued in our ongoing synthetic efforts, and ultimately proved to be correct.

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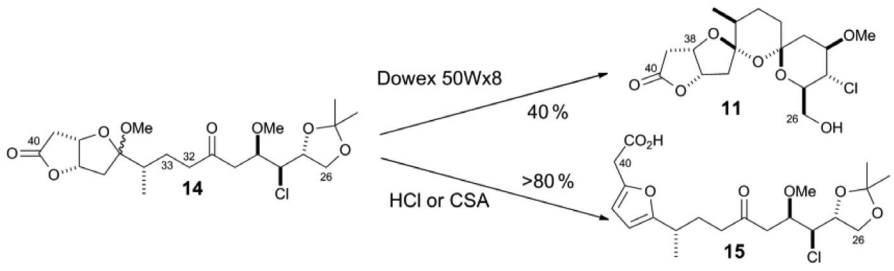
Armed with a synthetic entry into the southern hemisphere of spirastrellolide A, our attention turned to the synthesis of the northern hemisphere, containing the highly substituted and sterically congested DEF bis-spiroacetal region.

Synthesis of the DEF bis-spiroacetal

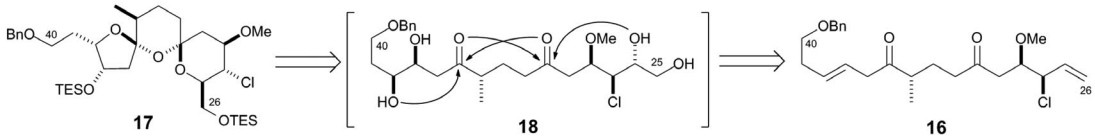
Our successful synthesis of DEF bis-spiroacetal **11** represented the first exploration of the delicate chemistry of the DEF rings [14]. Due to the complexity of the DEF region, a single enantiomeric series was arbitrarily pursued (corresponding to structure **4**), which fortuitously later turned out to correspond to the correct absolute configuration. A C40 γ-lactone was incorporated in **11** to provide a useful handle for our planned side-chain coupling. Following the success of the BC-ring formation strategies used to access the southern hemisphere fragments **7**, **12**, and **13**, an acid-mediated deprotection/spiroacetalization approach was initially favored (Scheme 2), which planned to exploit the double anomeric effect to set the C31 and C35 spiroacetal stereocenters.



Scheme 2 Completion of the first synthesis of C26–C40 DEF bis-spiroacetal **11**.

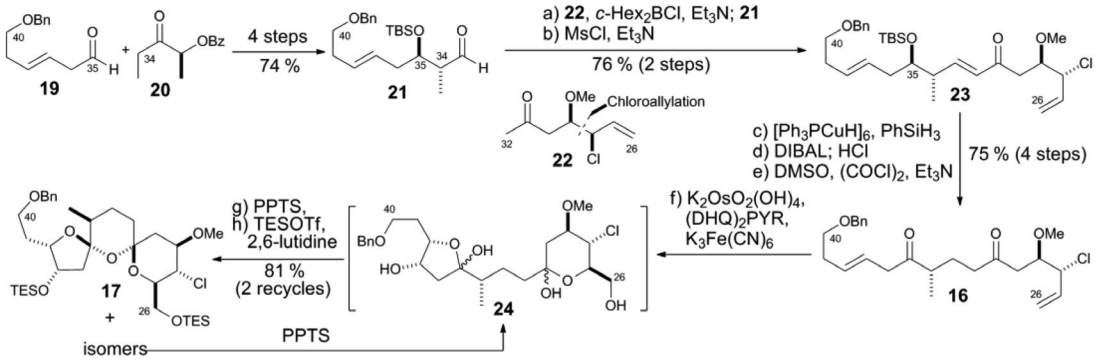
Unfortunately, attempts to cleave the acetonide in ketone **14** proved problematic, with the strongly acidic conditions required (e.g., HCl or CSA) leading to competitive elimination of the F-ring and formation of furan **15**. Even under optimized conditions (Dowex 50Wx8), only a modest and variable yield of the desired DEF subunit **11** could be obtained. To our satisfaction, ^{1}H and ^{13}C NMR spectroscopic comparison of **11** with spirastrellolide A methyl ester did, however, reveal excellent homology, supporting the structural and relative stereochemical assignment for this region.

Further attempts to optimize this approach to spiroacetal **11** proved equally frustrating, necessitating complete revision of our strategy towards the DEF bis-spiroacetal region (Scheme 3) [15], with the principle aim of reducing the susceptibility of the F ring to furan formation by removing the appended γ-lactone which we presumed promoted F ring elimination. It was recognized that the sense of asymmetric induction in the Sharpless dihydroxylation reactions [16] used to install the C37/C38 and C26/C27 diols was the same. Consequently, spiroacetalization might be induced under particularly mild conditions through double asymmetric dihydroxylation of the corresponding linear substrate, C26–C40 diene **16**, considerably streamlining the synthesis.



Scheme 3 Revised strategy to access C26–C40 DEF bis-spiroacetal **17**.

In the event, diene **16** was readily prepared from aldehyde **19** (Scheme 4) using our lactate aldol chemistry [17] and an Oehlschlager–Brown chloroallylation reaction [18]. A boron aldol reaction was used to unite ethyl ketone **20** and aldehyde **19**, setting the C34/C35 *anti*-relationship, leading on to **21**. A second boron aldol reaction then coupled aldehyde **21** with methyl ketone **22** incorporating the C27 methoxy and C28 chlorine substituents (installed by *syn*-chloroallylation of an aldehyde) [18]. Following controlled dehydration of the resulting aldol adducts to generate **23**, the enone was reduced using $[Ph_3PCuH]_6$ [19]. A further three-step sequence gave access to the targeted linear precursor **16**, which could be readily prepared on multigram scales.



Scheme 4 Efficient synthesis of C26–C40 DEF bis-spiroacetal **17**.

With **16** in hand, double Sharpless dihydroxylation of diene **16**, using $(DHQ)_2PYR$ as the ligand, initially gave **24** which was fully cyclized to the bis-spiroacetal diol on treatment with pyridinium *p*-toluenesulfonate (PPTS). *Per*-silylation afforded the desired DEF bis-spiroacetal **17**, which was separable from other spirocyclic isomers by chromatography. Clear ^{1}H NMR nuclear Overhauser effect (nOe) interactions between key protons in bis-spiroacetal **17** confirmed that it possessed the desired acetal configurations at C31 and C35. Importantly, the unwanted DEF diastereomers obtained could be recycled by mild acid treatment to generate further quantities of **17**. Using this sequence, the C26–C40 bis-spiroacetal **17** was now readily available in multigram quantities and excellent yield (81 % after two recycles). The success of this approach owed much to the increased stability of DEF spiroacetal **17** with respect to furan formation, which allowed access to the thermodynamic rather than kinetic ratio of products from the acetalization process. This efficient synthesis of **17** proved an important and timely breakthrough, enabling us to focus on devising a viable coupling strategy to connect the northern and southern hemisphere fragments.

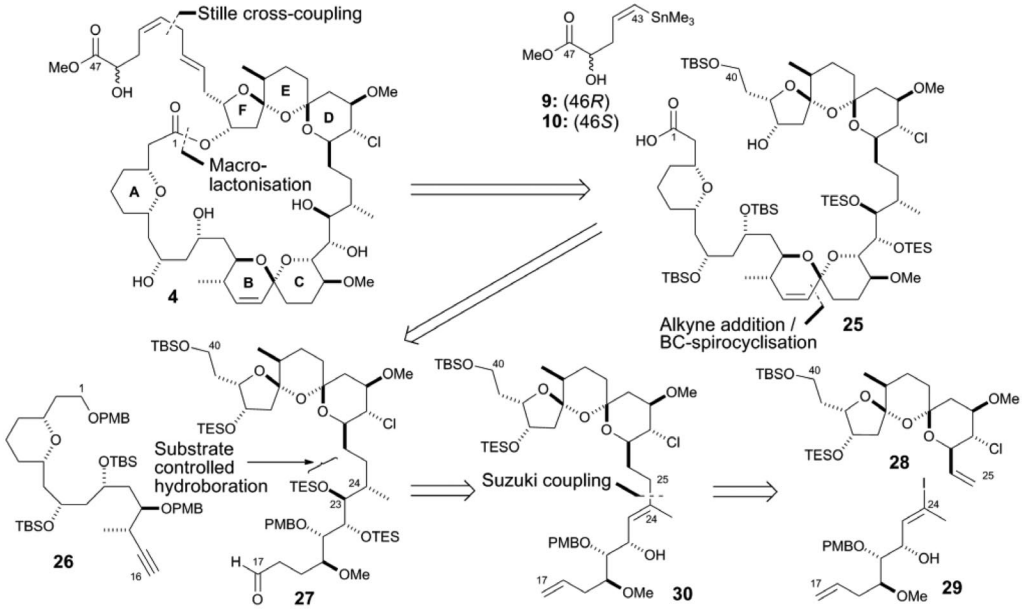
An efficient fragment coupling strategy

Preliminary investigations into fragment coupling at the C25–C26 bond concentrated on sulfur-mediated strategies such as sulfone alkylation or Julia olefination. However, these proved unsuccessful or low yielding, which we attributed to the steric demands of the DEF region and the sensitivity of substrates containing a C40 δ-lactone (derived from **11**) [20]. Furthermore, it was recognized that chemoselectivity issues could arise in our original strategy (based on union of preformed ABC and DEF subunits) if coupling methods were employed that would introduce unsaturation, as subsequent manipulation of such alkenes would be restricted by the presence of the C15–C16 alkene in the BC spiroacetal. For these reasons, a revised fragment coupling strategy was adopted based on forming the adjacent C24–C25 bond instead, which should alleviate the steric hindrance imposed by the DEF ring

system, and the introduction of the BC spiroacetal and its associated C15–C16 alkene was delayed to a later stage of the synthesis.

As shown in Scheme 5, spirastrellolide A would again arise from the late-stage attachment of side chain **9** (or **10**) to a preformed macrocycle, obtained by macrolactonization between C1 and C37 of *seco*-acid **25**. Now, however, C1–C16 alkyne **26**, containing the C15–C16 unsaturation, was excised revealing C17–C40 aldehyde **27**. Coupling of **27** with alkyne **26** and formation of the BC ring system would rely on bis-PMB deprotection (C13 and C17) and in situ spiroacetalization. A B-alkyl Suzuki coupling reaction [21] of DEF alkene **28** with vinyl iodide **29** would provide diene **30**, upon which it was anticipated that the C23/C24 stereocenters, and C17/C23 oxygenation might be installed through a substrate-controlled double hydroboration reaction.

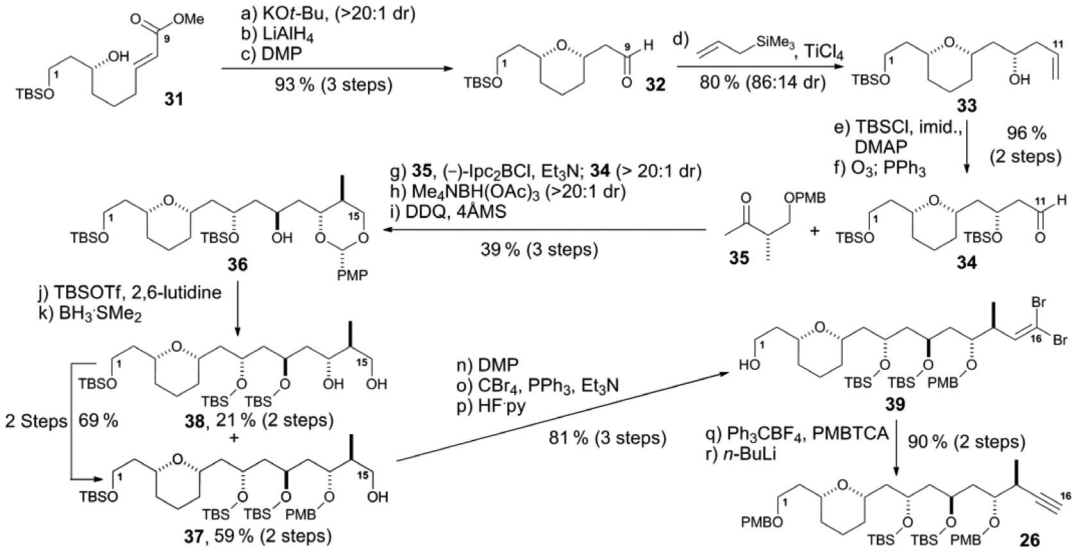
Overall, the anticipated benefits of this revised strategy lay in the mild and reliable nature of the Suzuki coupling and alkyne addition reactions for complex fragment union, although the strategy would ultimately depend on the success of the hydroboration at C23/C24.



Scheme 5 Revised retrosynthetic analysis of spirastrellolide A methyl ester.

Synthesis and coupling of the fragments to assemble the macrocycle

Based on this revised synthesis plan, the targeted fragments **26**, **28**, and **29** were prepared. The optimized synthesis of alkyne fragment **26** containing six stereocenters evolved from our earlier work on the related systems **7**, **12**, and **13**, with efficient installation of stereochemistry now achieved primarily by substrate control (Scheme 6). Starting from enone **31** [13b], a *cis*-selective hetero-Michael reaction followed by oxidation state adjustment afforded aldehyde **32**, which was allylated under Sakurai conditions to set the C9 stereocenter in **33** through chelation control using $TiCl_4$ as Lewis acid. Silylation of alcohol **33** and ozonolysis gave aldehyde **34**, which then underwent efficient boron-mediated aldol coupling with Roche ester-derived methyl ketone **35** to set the C11 stereocenter in **36** [22]. A 1,3-*anti* reduction followed by protecting group manipulation provided the differentiated C1–C15 fragment **36**, the C15 hydroxyl of which was deprotected using $BH_3 \cdot SMe_2$ to reveal alcohol **37** (together with over-reduced, but readily recycled diol **38**). Following oxidation at C15, Corey–Fuchs alkynylation afforded

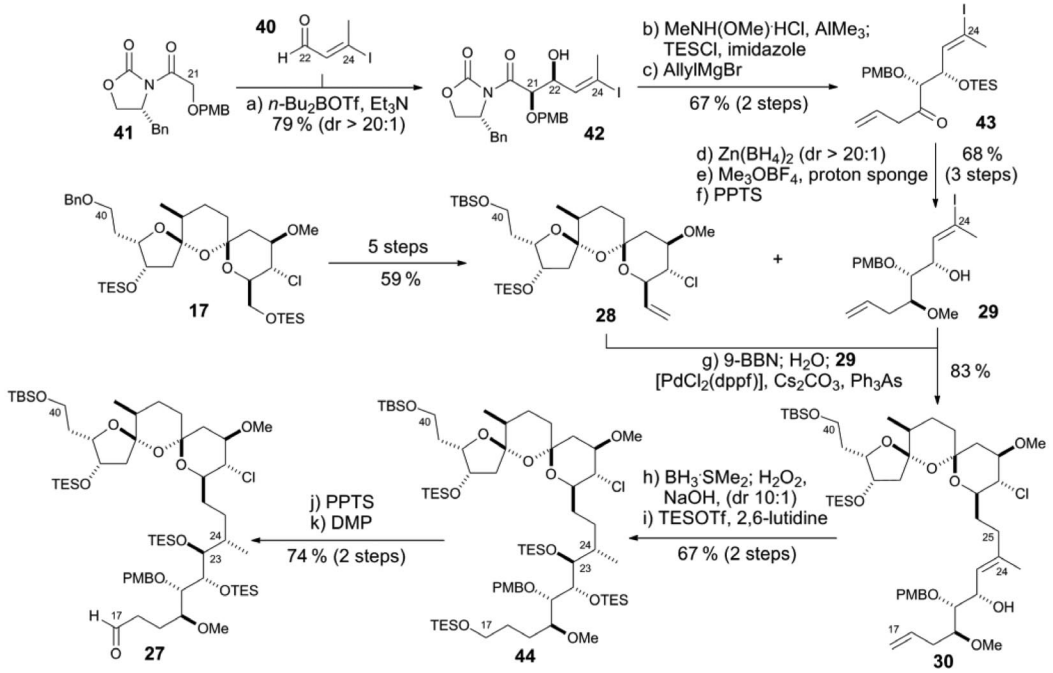


Scheme 6 Synthesis of C1–C16 alkyne **26**.

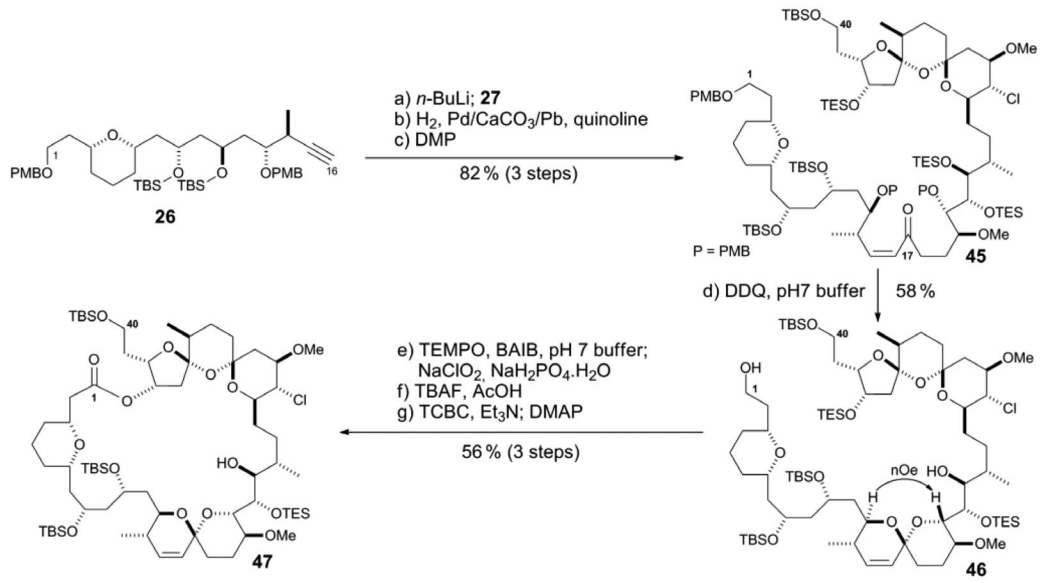
alkyne fragment **26** (with a protecting group exchange at C1). This route proved robust and enabled the multigram scale preparation of the C1–C16 alkyne fragment **26**.

The C17–C24 vinyl iodide **29** was readily obtained in 6 steps from iodoenal **40** using an aldol/reduction sequence to install the three contiguous stereocenters (Scheme 7). An Evans glycolate aldol coupling [23] with imide **41** gave the *syn*-adduct **42**, with the required C21 PMB ether installed for projected BC spiroacetalization. Transamination of **42** and silyl protection gave the Weinreb amide, which was advanced to C17–C24 allyl ketone **43**. Chelation-controlled reduction with $Zn(BH_4)_2$ [24] then set the C20 stereocenter. Vinyl iodide fragment **29** was completed through methylation of the C20 alcohol and desilylation. The corresponding Suzuki coupling partner C26–C40 **28** was prepared from bis-spiroacetal **17** via Wittig methylenation of the derived aldehyde. Initial hydroboration of DEF olefin **28** with 9-BBN, followed by Pd-catalyzed coupling with iodide **29**, generated the pivotal C17–C40 diene **30** in excellent yield. With the C24–C25 bond successfully forged, the crucial double hydroboration of diene **30** to install hydroxyl groups at C17 and C23 in **44** was achieved with high selectivity (10:1 dr) using $BH_3 SMe_2$. This desired stereochemical outcome at C23/C24 was attributed to both induction by the neighboring stereocenters and steric shielding of one face of the olefin by the DEF spiroacetal, as model substrates lacking this region showed little or no stereoselectivity [18]. Following this welcome result, cleavage of the primary C17 TES ether and oxidation completed the synthesis of C17–C40 aldehyde **27**.

With aldehyde **27** and alkyne **26** available in useful quantities, completion of the spirastrellolide macrolide core could advance (Scheme 8). Following the generalized approach, coupling of lithiated alkyne **26** and **27** provided the corresponding propargylic alcohol. Lindlar reduction and Dess–Martin oxidation afforded C1–C40 (*Z*)-enone **45** as a prelude to BC-spiroacetalization. Treatment of tris-PMB ether **45** with buffered DDQ effected tris-PMB deprotection and in situ cyclization to form the BC rings of **46** with complete stereocontrol. Surprisingly, spiroacetalization also resulted in concomitant, selective desilylation at C23. Although seemingly irrelevant to the completion of the synthesis (the C23 alcohol remained unprotected for the subsequent steps), it was later demonstrated that this innocuous deprotection would be critical to the success of the macrolactonization step (see second-generation synthesis).



Scheme 7 *B*-Alkyl Suzuki coupling/hydroboration approach to C17–C40 aldehyde **27**.



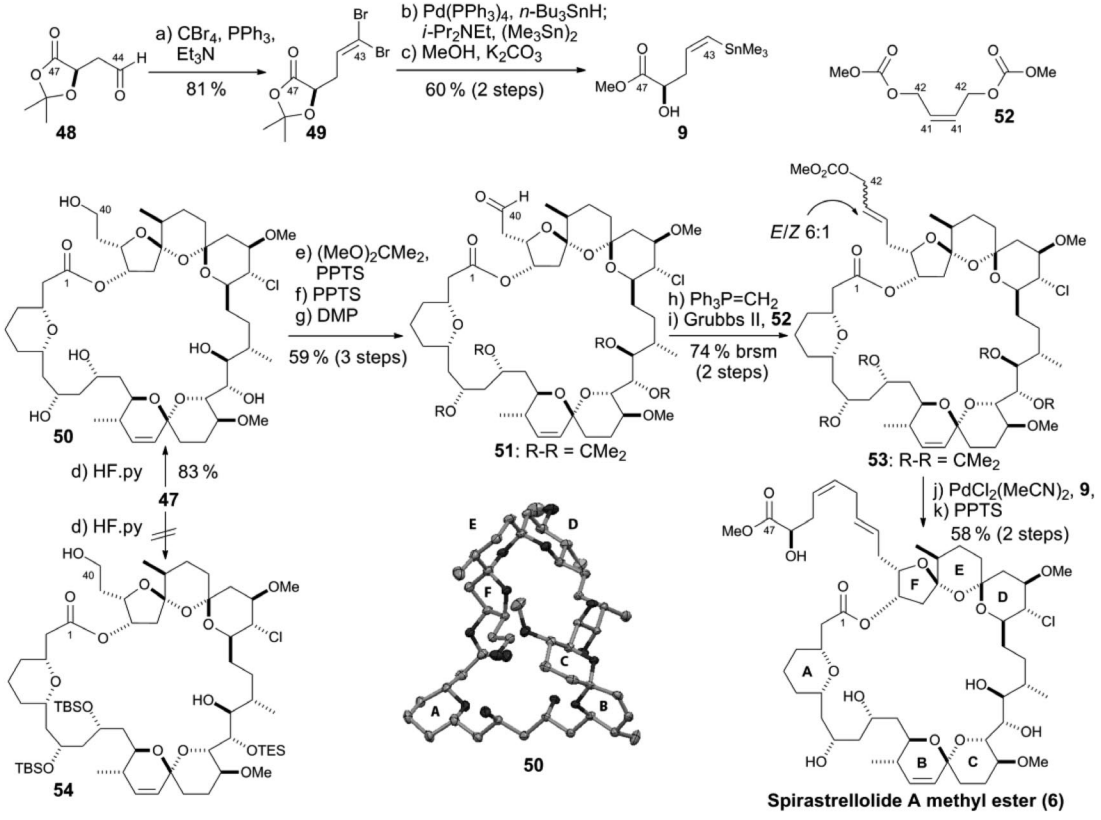
Scheme 8 Formation of the macrocyclic core **47** of spirastrellolide A.

With the complete ABCDEF ring system in place, attention turned to the crucial macrolactonization step. In preparation, oxidation of the primary alcohol in **46** to the acid was followed by selective removal of the C37 TES ether. Gratifyingly, application of the Yamaguchi protocol [25] to this hydroxy-

acid afforded 38-membered macrolactone **47** in remarkably high yield (77–99 %), suggesting a favorable conformational preorganization in the macrolactone precursor.

Completion of the first total synthesis of spirastrellolide A methyl ester

Having assembled the macrocyclic core **47**, completion of the total synthesis of spirastrellolide A methyl ester required the incorporation of a side-chain subunit containing the remaining C46 stereocenter. A π-allyl Stille cross-coupling reaction [26] was employed as a mild and selective method for this purpose. Stannane **9** was prepared from (*R*)-malic acid as a convenient source for the C46 stereocenter (Scheme 9). Following homologation of the derived aldehyde **48** to vinyl dibromide **49**, a one-pot, Pd-catalyzed, reductive debromination [27]/Wulff–Stille reaction [28], gave the corresponding (*Z*)-vinyl stannane. Methanolysis then provided the targeted stannane **9**.



Scheme 9 Completion of the first total synthesis of spirastrellolide A methyl ester (**6**).

The first step for side-chain attachment to macrocycle **47** was the removal of the C40 protecting group. Unfortunately, despite significant effort, selective desilylation at C40 in macrocycle **47**, to form diol **54**, proved surprisingly difficult to achieve. A solution to this problem was ultimately found whereby the macrolide was completely desilylated using HF·pyridine, which fortuitously provided crystalline polyol **50** (Scheme 8). At this point, X-ray crystallography confirmed the stereochemistry within the macrocycle to match that of the natural product, allowing our total synthesis to continue with confidence [29]. Despite the structural similarity of **50** to spirastrellolide A, significant NMR spectro-

scopic differences were still observed, which we attributed to through-space interactions of the side chain with the macrolide core.

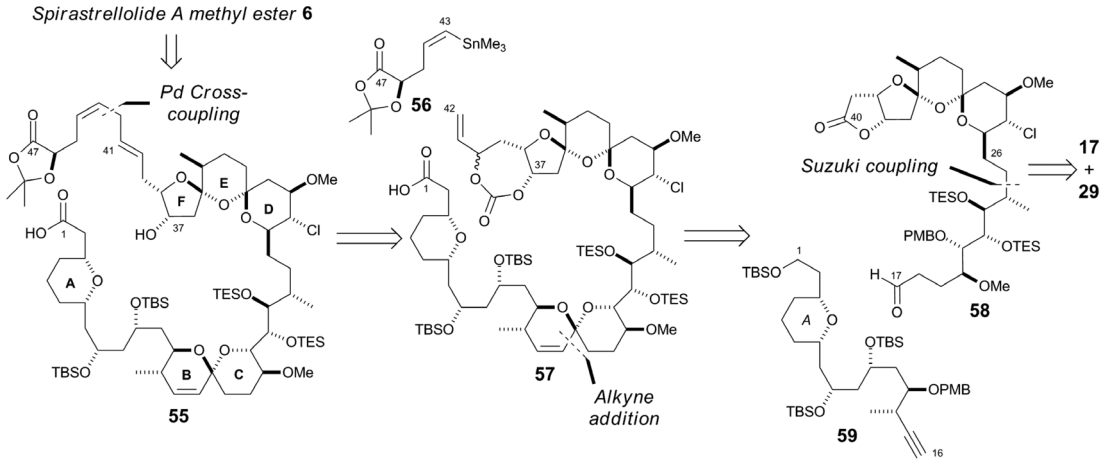
Acetonide protection of pentaol **50**, followed by hydrolysis of the resulting C40 mixed acetal, allowed oxidation at C40 to give aldehyde **51**. Considerable difficulties were encountered in extending the side chain due to the steric constraints imposed by the macrocycle. In the event, a Wittig methylenation of **51** was used to form the corresponding terminal olefin, which was subjected to cross-metathesis with dimeric carbonate **52** to generate allylic carbonate **53**. Treatment of **53** and stannane **9** with $PdCl_2(MeCN)_2$ effected π-allyl Stille coupling, affording the bis-acetonide of spirastrellolide A methyl ester with the expected (*E*)-$\Delta^{40,41}$, (*Z*)-$\Delta^{43,44}$ olefin configurations. Much to our satisfaction, this compound was identical in all respects with the bis-acetonide prepared by Andersen and co-workers from natural spirastrellolide A methyl ester [6]. Finally, global deprotection with methanolic PPTS gave our first precious sample of spirastrellolide A methyl ester (**6**).

The final correlation of our synthetic material with a natural sample of spirastrellolide A methyl ester proved challenging. Initial NMR comparisons of synthetic and natural **6** revealed an inexact match of ^{1}H NMR spectral data. Moreover, repeated analysis of the same synthetic sample led to varied NMR results. Careful observation of these effects showed that the NMR spectra of spirastrellolide A methyl ester are susceptible to subtle variations in temperature and purity, with an exact match between authentic and synthetic samples only proving possible when both are treated under identical conditions: ultimately, parallel high-performance liquid chromatography (HPLC) purification and characterization of both synthetic and natural samples of **6** indeed provided identical NMR spectroscopic data [30].

A second-generation total synthesis of spirastrellolide A methyl ester

Our initial total synthesis of spirastrellolide A methyl ester evolved alongside structure determination studies undertaken by the Andersen group in the period 2003–2007. Stereochemical ambiguities enforced a modular approach to the macrocycle, and a late-stage side-chain attachment. A number of opportunities for streamlining the synthesis were now identified, leading to the development of a revised, second-generation synthesis. In addition to taking advantage of available fragments, we aimed to improve the convergency with respect to side-chain attachment and avoid unproductive protecting group manipulations.

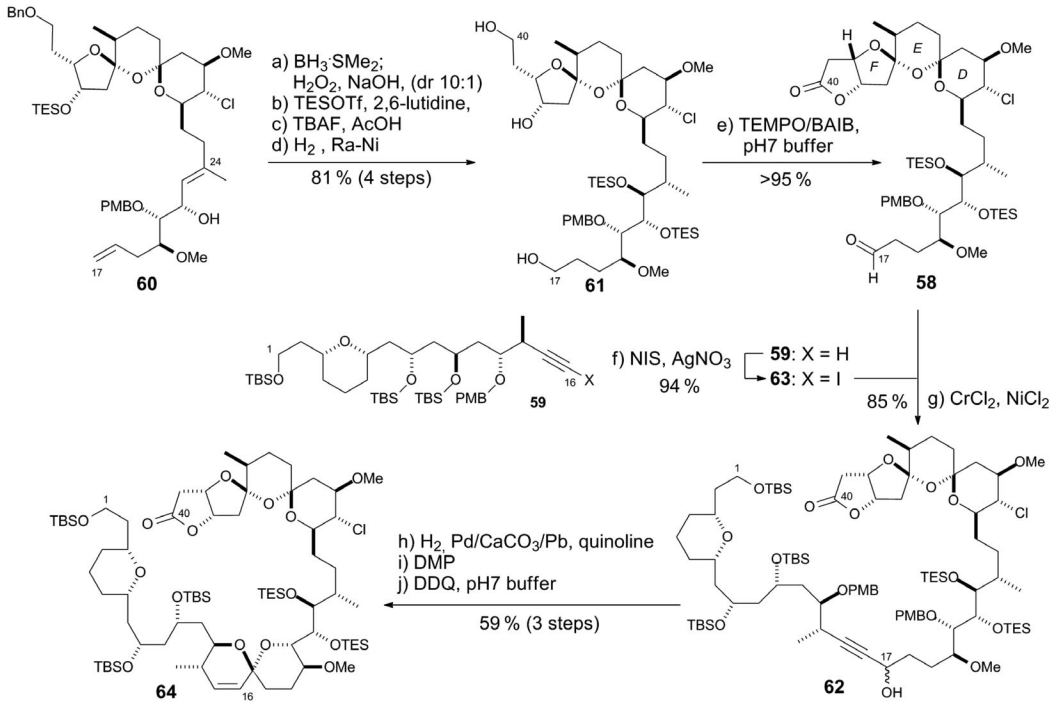
With the above goals in mind, we sought to now establish the complete C1–C47 carbon backbone prior to macrolactonization (Scheme 10). As such, *seco*-acid **55** would be accessed using a π-allyl Stille



Scheme 10 A revised retrosynthetic analysis of spirastrellolide A.

cross-coupling reaction between stannane **56** and C1–C42 carbonate **57** [31]. Cyclic carbonate **57** would in turn be generated from a C40 γ-lactone, which would be installed in C17–C40 aldehyde **58**, prior to coupling with alkyne **59**. Notably, the use of a γ-lactone, which acts both as a protecting group for alcohols at C37/C40 and a vehicle for side-chain installation, represents a return to the originally proposed strategy for the northern hemisphere [14a].

Starting from C17–C40 diene **60** (now avoiding a protecting group exchange at C40), double hydroboration efficiently installed the C17 and C23 hydroxyl groups and established the C23/C24 *anti*-stereochemistry (Scheme 11). Selective deprotection removed the more labile C17 and C37 TES ethers, and debenzylation gave triol **61**. Aldehyde **58** was then completed using a high-yielding one-pot triple oxidation, through treatment of **61** with catalytic 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) and $PhI(OAc)_2$ [32].

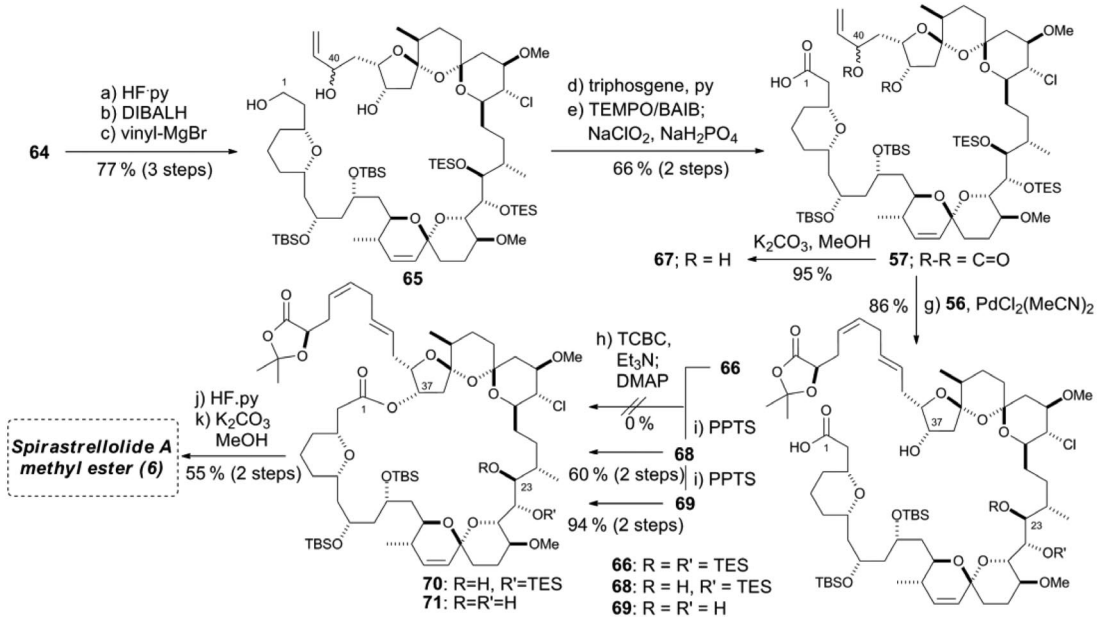


Scheme 11 Synthesis of C1–C40 lactone **64**.

Adoption of the alkynyllithium/aldehyde coupling procedure afforded propargylic alcohol **62** from **58** and **59**, but only in variable yield (21–57 %), this key coupling step now proving to be highly capricious due to chemoselectivity issues arising from the δ-lactone. Fortunately, a more efficient fragment union could be achieved using Nozaki–Hiyama–Kishi coupling conditions [33]. As such, alkyne **59** was converted to the corresponding iodoalkyne **63**, which on treatment with freshly activated $NiCl_2/CrCl_2$ and aldehyde **58** now afforded propargylic alcohol **62** in a reliable 85 % yield.

With coupled product **62** in hand, construction of the BC-spiroacetal ring system was carried out on the derived (*Z*)-enone. PMB deprotection and in situ cyclization then provided C1–C40 BC spiroacetal **64**. Now, however, the C23 silyl protecting group was retained by using suitably mild reaction conditions. This seemingly innocent deviation from the first-generation route would have a considerable impact on the closing stages of the synthesis.

Unaware of the challenges that would yet be met, C1 desilylation followed by diisobutylaluminum (DIBAL) reduction of the C40 lactone and addition of vinylmagnesium bromide afforded allylic alcohol **65** (Scheme 12). Treatment of **65** with triphosgene with subsequent oxidation at C1 formed the C37–C42 allylic cyclic carbonate/C1 carboxylic acid **57** in readiness for installation of the full side chain. Using our standard conditions, a π-allyl Stille coupling between cyclic carbonate **57** and stannane **56** afforded the complete C1–C47 carbon framework **66**. Now, with *seco*-acid **66** in hand, spirastrellolide A methyl ester appeared to be within easy reach—but this was not to be the case! Much to our dismay, no macrocyclic products were isolated when **66** was submitted to the previously successful Yamaguchi conditions [25]. Repeated attempts to promote macrolactonization, including use of the alternative conditions developed by the Shiina group [34], also failed. Assuming that the side chain in C1–C47 *seco*-acid **66** was impeding macrolactonization, methanolysis of allylic carbonate **57** gave diol **67**. Even now, **67** failed to macrocyclize. The failure of both hydroxy-acids to undergo macrolactonization, despite their similarity to the hydroxy-acid derived from **46** (see Scheme 8), suggested that the C23 protecting group might be the root of the problem. While this silyl ether is remote to the reaction centers, it was conjectured that it might be responsible for enforcing conformations of the linker region between the spiroacetal ring systems that are unfavorable to macrocyclization.



Scheme 12 Completion of the second-generation synthesis of spirastrellolide A methyl ester **6**.

In the event, C1–C47 carboxylic acid **66** was treated under mildly acid conditions (PPTS), giving access to either diol **68** (mono-desilylation) or triol **69** (bis-desilylation). Gratifyingly, submission of either **68** or **69** to Yamaguchi macrolactonization now afforded the corresponding macrocycles **70** (60 %) and **71** (94 %), respectively. The subtle structural requirements for this macrocyclization emphasizes the often unpredictable constraints imposed by remote functionality. Furthermore, by structural analogy, it is highly probable that the successful macrocyclization to form **47** was entirely dependent on the serendipitous C23 desilylation during BC spiroacetalization. Finally, silyl ether cleavage gave the corresponding tetraol, which was converted to spirastrellolide A methyl ester on treatment with K_2CO_3 in MeOH, thus completing the second-generation total synthesis in 23 linear steps and 6 % yield from C26–C40 bis-spiroacetal **17**. Overall, this synthesis represents a considerable improvement in both step

and yield efficiency over our first-generation strategy, which was completed in 25 steps and ca. 1 % yield from common intermediate **17**.

CONCLUSION AND OUTLOOK

Our synthetic endeavors towards spirastrellolide A have enabled the development of scaleable routes towards all of the key fragments, and efficient coupling protocols for assembling the characteristic spiroacetal motifs and the 38-membered macrolactone. The first total synthesis of spirastrellolide A methyl ester evolved from the requirement to separate regions of unknown relative stereochemistry such that the side chain was introduced on to a preformed macrolactone. An improved, second-generation synthesis refined the protecting group and end-game strategies through targeting a C1–C47 open-chain precursor to spirastrellolide A, the macrolactonization of which revealed a remarkable sensitivity to remote functionality.

The completion of these two highly convergent syntheses of spirastrellolide A methyl ester will not only allow ready access to a supply of this biologically potent natural product, but will also provide a starting point for systematic structure variation to gain an understanding of the SARs for this family of macrocycles. To this end, we have already observed the importance of the C47 carboxy moiety, as pentaol **50** displayed no cytotoxicity at up to 5 μM concentration when tested against four different human cell lines [30,35].

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