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Natural Product Synthesis

Total Synthesis of Spirastrellolide A Methyl Ester—Part 2: Subunit Union and Completion of the Synthesis**

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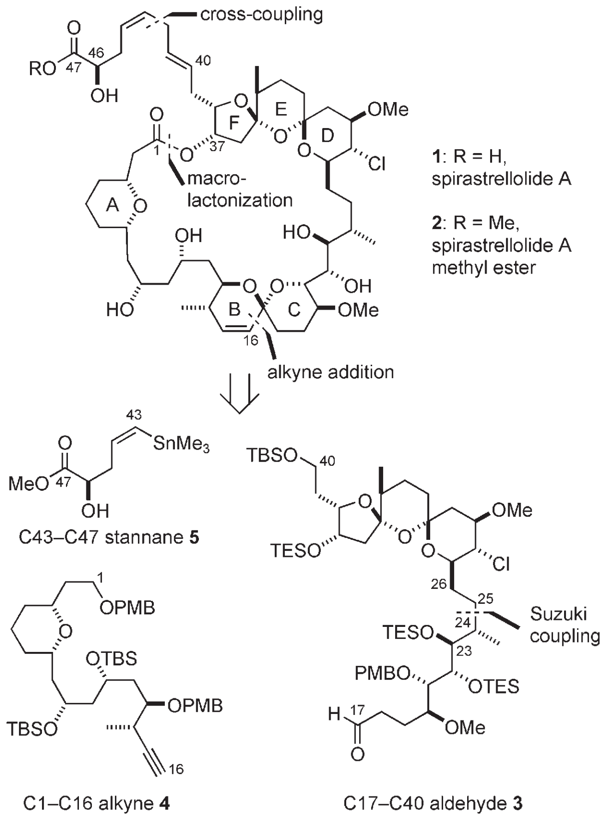
The marine macrolide spirastrellolide A (**1**, Scheme 1) is a potent and selective protein phosphatase inhibitor, causing premature cell entry into mitosis.[1] Synthetic interest[2] in the spirastrellolides derives not only from their unique molecular architecture, but also from their potential as lead structures for the development of novel anticancer agents.[3] In the preceding communication,[2] we described our optimized and scalable approach to the construction of the key C17–C40 bis-spiroacetal intermediate **3**, which forms the foundation of our strategy towards these challenging natural products. Herein, we report the completion of the first total synthesis of spirastrellolide A methyl ester (**2**, Scheme 1), as well as the single-crystal X-ray diffraction analysis of an advanced intermediate that reveals the conformation of the spirastrellolide macrocycle and plays a vital role in our end-game strategy.

A summary of our synthetic plan, which was designed to provide maximum flexibility in terms of fragment coupling and diastereomer selection, is outlined in Scheme 1. This optimized retrosynthesis leads to three key subunits—the C17–C40 aldehyde **3**, the C1–C16 alkyne **4**, and the C43–C47 stannane **5**. The planned completion of the total synthesis of spirastrellolide A methyl ester (**2**) would thus proceed through the union of aldehyde **3** with alkyne **4**, with subsequent elaboration to introduce the BC spiroacetal domain, and macrolactonization to generate the 38-membered macrolide core. A series of manipulations at C40 (in the truncated side chain) would precede the end game of the synthesis, which would involve a cross-coupling reaction with stannane **5** to install concurrently the 40*E* and 43*Z* double bonds as well as the terminal α-hydroxy ester in structure **2**.



Scheme 1. Spirastrellolide A (**1**), its methyl ester (**2**), and retrosynthetic analysis leading to key building blocks **3**–**5**. PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

The first requirement for this synthetic plan was the preparation of the C1–C16 alkyne **4**. We have previously reported the synthesis of a close relative of this alkyne[4] by using Jacobsen's hydrolytic kinetic resolution of epoxides.[5] Building on this earlier work, installation of a PMB ether was now required at C1 such that our envisaged BC-spiroacetalization step would result in simultaneous deprotection at this position. The most convenient point to undertake this modification was deemed to be the vinyl dibromide **6** (Scheme 2). Thus, selective desilylation at C1 was followed by formation of the PMB ether under mild conditions by using PMB trichloroacetimidate. Subsequent conversion of the vinyl dibromide into the alkyne **4** proceeded uneventfully on treatment with base (66 % yield, over 3 steps).[6]

The union of the C1–C16 and C17–C40 subunits through addition of the lithium anion of alkyne **4** to the DEF aldehyde

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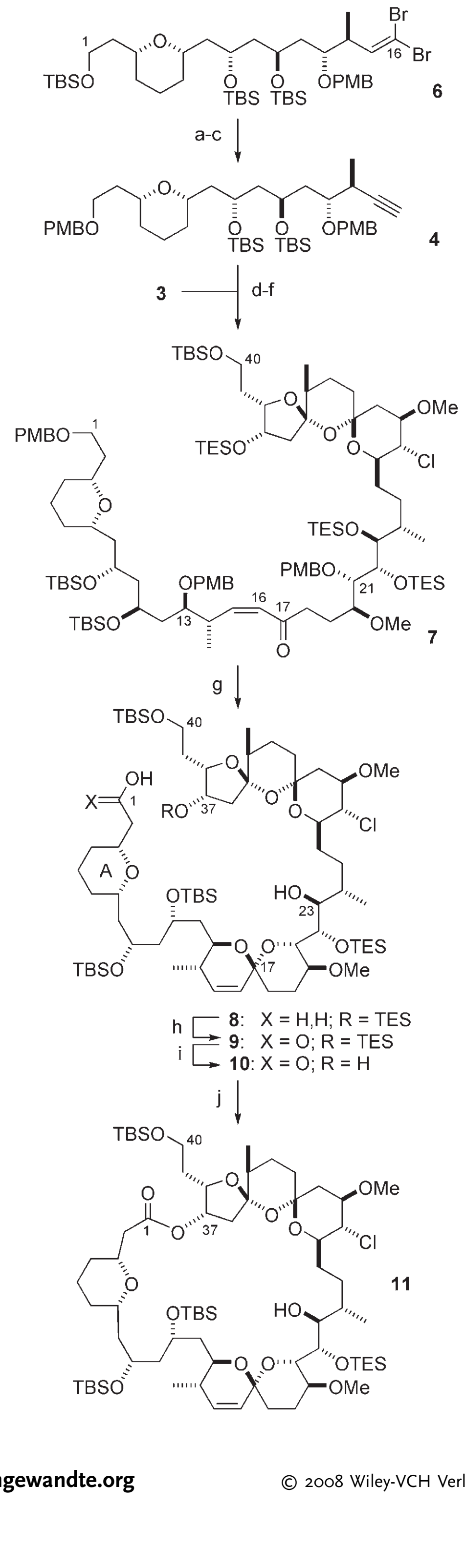
3 was now addressed. In this key step, deprotonation of **4** with *n*BuLi followed by addition to aldehyde **3** (THF, −78 °C to −20 °C) led cleanly to an inconsequential mixture of epimeric C17 alcohols in 92 % yield. Lindlar reduction of these propargylic alcohols, followed by oxidation (Dess–Martin periodinane), then provided the (*Z*)-enone **7** in 89 % yield.

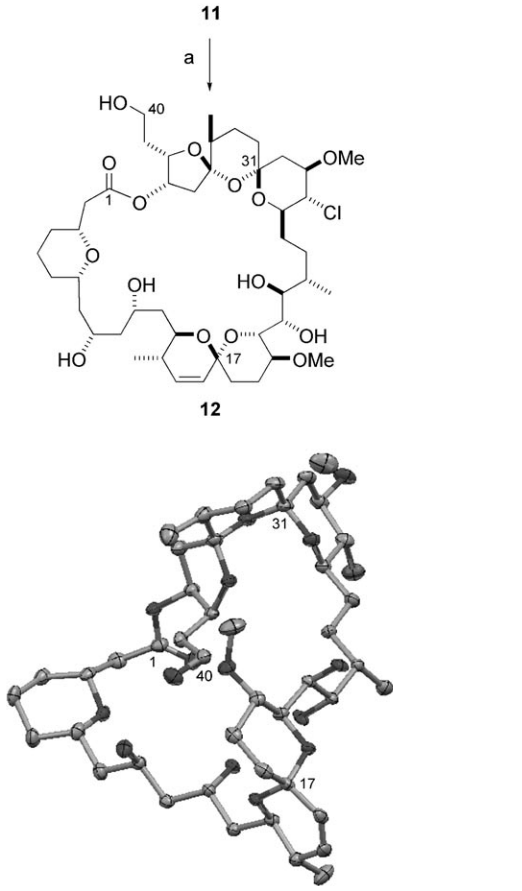
Formation of the BC spiroacetal domain, and the simultaneous liberation of the C1 hydroxy group in readiness for oxidation to the seco acid, was now required. Gratifyingly,



treatment of enone **7** with DDQ (CH_2Cl_2/pH 7 buffer, 0 °C) did indeed cleave all three PMB ethers, while also achieving selective BC spiroacetalization with complete control over the C17 acetal stereocenter (resulting from a double anomeric effect).[7] Unexpectedly, this transformation was accompanied by cleavage of the TES ether at C23, with some minor by-products detected in which this silyl ether had migrated to C1. Nevertheless, we were able to remove both these by-products and the minor C23,C24 diastereomer (arising from the earlier hydroboration reaction)[2] by flash chromatography, such that the pure ABCDEF hexacyclic diol **8** was isolated in 58 % yield from enone **7**. The synthesis of the seco acid **10** was completed through oxidation of the C1 hydroxy group in **8** to the corresponding acid **9** (TEMPO/BAIB; $NaClO_2$), and then selective cleavage of the C37 TES ether (TBAF, AcOH; 64 % brsm). The latter transformation was best halted prior to completion, as some over-deprotection involving the C40 TBS or C22 TES ether moieties occurred under prolonged reaction times.

At this point, we had reached the much anticipated and crucial macrolactonization step which would form the first fully synthetic spirastrellolide analogue. Gratifyingly, acid **10** underwent a rapid and efficient macrocyclization by using the Yamaguchi protocol,[8] to provide the corresponding 38-membered macrolide **11** in excellent yield (79 %), thus suggesting a favorable conformational preorganization of the seco acid. In principle, all that remained was a series of selective manipulations at C40 to install the required side chain. However, this proved fraught with difficulty, as it was not possible to selectively cleave the C40 TBS ether of **11** or indeed other intermediates. One apparent solution to this problem would be the complete cleavage of all the silyl ether groups, followed by reprotection or selective reaction at C40. We were able to achieve this global deprotection using HF·Py (Scheme 3), and recrystallization (CH_2Cl_2/heptane) of the crude product gave the remarkable pentaol **12** as colorless needles (83 %, m.p. 174 °C). Importantly, these crystals were of sufficient size and quality to obtain the X-ray crystal structure shown.[9] This structure served to confirm that the relative and absolute configuration was indeed as we had intended and corresponded to that recently reported for the natural spirastrellolide macrocycle.[1c] Notably, the pentaol **12** features a distinctive hydrogen-bond network, which leads to

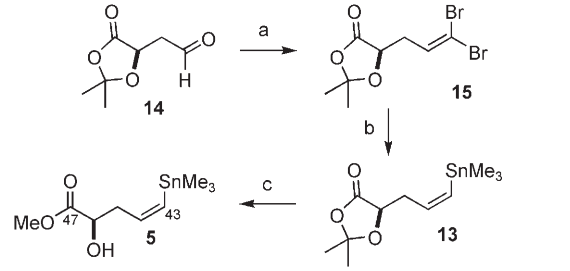
Scheme 2. Preparation of the C1–C16 alkyne **4**, its union with the C17–C40 aldehyde **3**, and conversion into the macrocycle **11**. a) HF·Py/Py, THF, 73 %; b) PMBTCA, Ph_3CBF_4, THF, 0 °C, 90 %; c) *n*BuLi, THF, −78 °C to −20 °C, 100 %; d) *n*BuLi, THF, −20 °C; **3**, −78 °C to −20 °C, 92 %; e) $Pd/CaCO_3/Pb$, quinoline, H_2, EtOAc; f) DMP, $NaHCO_3$, CH_2Cl_2, 89 % (over 2 steps); g) DDQ, CH_2Cl_2/pH 7 buffer (9:1), 0 °C, 58 %; h) TEMPO, BAIB, CH_2Cl_2/pH 7 buffer (5:1); $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, 2-methyl-2-butene, *t*BuOH/H_2O (1:1), 88 %; i) TBAF, AcOH, THF, 49 % (64 % brsm); j) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene; DMAP, toluene, 79 %. BAIB = [bis(acetoxy)iodo]benzene, brsm = based on recovered starting material, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-(dimethylamino)pyridine, DMP = Dess–Martin periodinane, PMBTCA = *para*-methoxybenzyl-2,2,2-trichloroacetimidate, Py = pyridine; TBAF = tetra-*n*-butylammonium fluoride, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical.



Scheme 3. Deprotection of the macrocycle **11** to the crystalline pentaol **12** and X-ray crystal structure of **12** (shown with ellipsoids at 50% probability). a) HF·Py/Py, THF, 83%.

a well-defined conformation of the macrolide core. Interestingly, an inexact match between **12** and the macrolide region of spirastrellolide A was revealed in the ^{1}H NMR spectrum.[10] This finding is consistent with our observations that small changes in the side chain could lead to substantial differences in the chemical shifts in the ^{1}H NMR spectrum of the macrocycle, thereby emphasizing its proximity to this ring and hence restricting its accessibility.

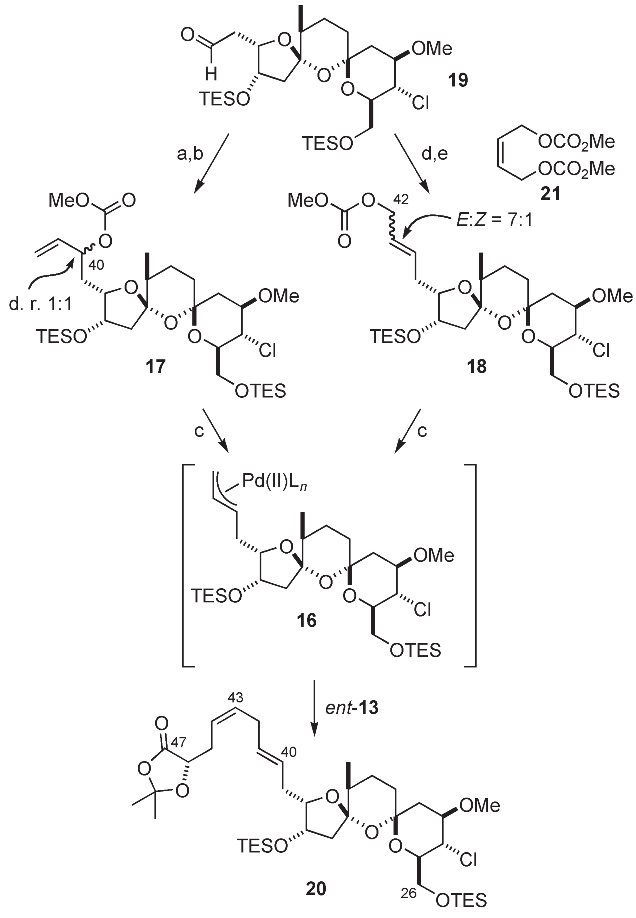
Attachment of the full side chain of the spirastrellolides was planned (Scheme 1) using a π-allyl Stille cross-coupling reaction[11] of stannane **5** with a suitable allylic carbonate derived from the advanced intermediate **12**. It was decided to first model this crucial transformation with a simplified DEF analogue. At this stage of the project, rapid access to both enantiomers of stannane **5** and its acetonide derivative **13** were required (Scheme 4). To this end, the aldehyde **14**, prepared in three steps from (*R*)-malic acid,[12] was converted into the corresponding vinyl dibromide **15** (81%).[6] Pleasingly, a palladium-catalyzed one-pot debromination/stannylation protocol, which exploits the differing reactivity of the *trans*- and *cis*-bromides through selective reductive (*E*)-debromination[13] ([Pd(PPh$_3$)$_4$], Bu$_3$SnH, 40°C) followed by buffered bromine-tin exchange (Me$_6$Sn$_2$, 80°C),[14] provided solely the (*Z*)-alkenyl stannane **13** (74%); the antipodal stannane *ent*-**13** was obtained in an analogous fashion from



Scheme 4. Preparation of the side chain stannanes **13** and **5**. a) CBr$_4$, PPh$_3$, Et$_3$N, CH$_2$Cl$_2$, 0°C, 81%; b) *n*Bu$_3$SnH, [Pd(PPh$_3$)$_4$], benzene, 40°C; (Me$_3$Sn)$_2$, *i*Pr$_2$NEt, 80°C, 74%; c) K$_2$CO$_3$, MeOH, 81%.

(*S*)-malic acid. Methanolysis of **13** then provided the free α-hydroxy ester **5**.

Our exploratory Stille cross-coupling studies are shown in Scheme 5. We were mindful that the intermediate π-allylpalladium complex **16** could arise from the two regioisomeric carbonates **17** and **18**, and furthermore that the configuration of both the internal C40 carbonate of **17** (at the allylic stereocenter) and terminal C42 carbonate of **18** (olefin

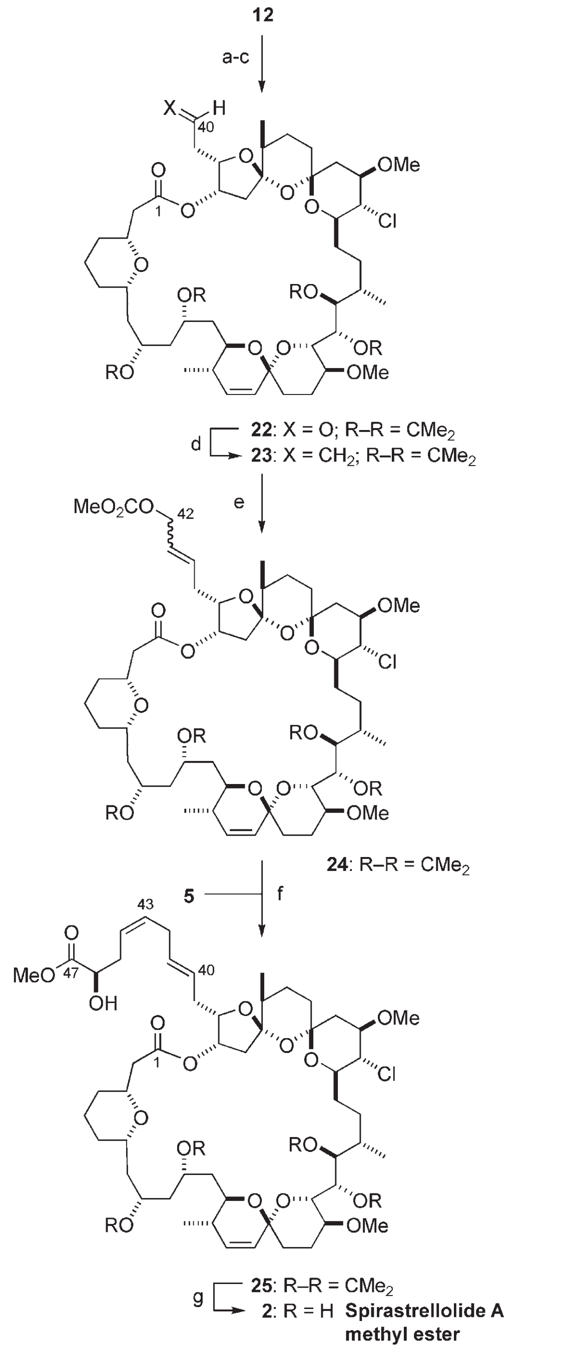


Scheme 5. Synthesis of carbonates **17** and **18**, and their coupling with stannane *ent*-**13**. a) H$_2$C=CHI, CrCl$_2$, NiCl$_2$, DMF, 71%; b) ClCO$_2$Me, Py, CH$_2$Cl$_2$, 43%; c) [PdCl$_2$(MeCN)$_2$], *ent*-**13**, DMF/H$_2$O (4:1), 59% (for **17**), 80% (for **18**); d) Ph$_3$P=CH$_2$, THF, −78°C to RT, 71%; e) 2nd generation Grubbs catalyst, **21**, CH$_2$Cl$_2$, 40°C, 99% (*E*/*Z* 7:1). DMF = *N*,*N*-dimethylformamide.

isomers) may well be important, as the rate of isomerization of π-allyl species derived from such precursors depend strongly on the choice of reaction conditions.[11a] In the present system, the combination of a hindered *Z* stannane combined with the bulky nature of the tricyclic DEF system was anticipated to favor terminal substitution and formation of an *E* olefin. Thus, we addressed the formation of the π-allylpalladium complex **16** by both routes, starting from the common C26–C40 aldehyde **19** obtained from the corresponding alcohol.[15] The preparation and reaction of the internal carbonate **17** was first examined. Aldehyde **19** underwent a smooth Nozaki–Hiyama–Kishi coupling[16] with vinyl iodide to provide an epimeric mixture of internal allylic alcohols, which were then converted into **17**. We were now faced with the key π-allyl Stille cross-coupling reaction,[11] for which (because the C46 configuration was unknown at the time of these studies) we arbitrarily employed the (*S*)-stannane *ent*-**13**. Treatment of the carbonates **17** with *ent*-**13** and $[PdCl_2(MeCN)_2]$ led to the isolation of a single product **20** (59%), which corresponds to the desired 40*E*,43*Z* diene ($J_{H40,H41} = 14.6$ Hz). The regioisomeric carbonates **18** were prepared by Wittig methylenation of aldehyde **19**, followed by cross-metathesis[17] with the bis-methyl carbonate **21** to generate the terminal allylic carbonates **18** as a 7:1 *E*/*Z* mixture. (*E*)-**18** was also prepared exclusively through Wittig olefination (Ph_3PCHCO_2Me), followed by reduction with DIBALH and carbonate formation. Pleasingly, these carbonates **18** also proved to be viable substrates for the cross-coupling reaction with *ent*-**13**, and the C26–C47 diene **20** was again isolated as a single isomer, in an improved yield of 80%.

Confident that we were now equipped with two complementary strategies for installing the side chain, we refocused our attention on the pentaol **12**, and embarked on the concluding steps of the total synthesis (Scheme 6). These steps commenced with formation of the corresponding trisacetonide of **12** (which contained a mixed acetal at C40) by warming **12** with 2,2-dimethoxypropane and PPTS. It was then possible to cleave the C40 mixed acetal—a reaction that was inevitably accompanied by some competing deprotection at C9 or C11 to give a recyclable monoacetonide—giving the bis-acetonide in an overall yield of 78% after one recycle. The residual primary alcohol at C40 was oxidized using Dess–Martin periodinane to give aldehyde **22**, which represented the point at which to test our two coupling strategies. In the event, our concerns over this side chain introduction proved justified, as the Nozaki–Hiyama–Kishi vinyl iodide addition, which had proved facile in our model system **19**, failed in the current setting. Fortunately, we were able to exploit our alternative strategy through Wittig methylenation of aldehyde **22** to provide the terminal alkene **23**. In contrast, attempts to extend the sterically encumbered side chain further using stabilized Wittig reagents (e.g. $Ph_3P{=}CHCHO$) proved unrewarding, despite the remarkable thermal stability of the aldehyde **22** (e.g. prolonged heating to 110°C in toluene).

At this point we were faced with a narrow window of synthetic opportunity, as our plan now relied on the success of a contemporary cross-metathesis reaction[17] to overcome the limitations of classical olefination chemistry. The steric



Scheme 6. Completion of the total synthesis of spirastrellolide A methyl ester (**2**). a) PPTS, $(MeO)_2CMe_2/CH_2Cl_2$ (2:1), 35°C, 95%; b) PPTS, CH_2Cl_2/MeOH (12:1), 0°C, 78% after one recycle; c) DMP, $NaHCO_3$, CH_2Cl_2, 80%; d) $Ph_3P{=}CH_2$, THF, −78°C to RT, 75%; e) 2nd generation Grubbs catalyst, **21**, benzene, 80°C, 57% (99% brsm); f) $[PdCl_2(MeCN)_2]$, **5**, DMF/H_2O (4:1), 35°C, 96%; g) PPTS, MeOH, 35°C, 60%. PPTS = pyridinium *para*-toluenesulfonate.

demands of the C40–C41 terminal alkene were again in evidence, as the cross-metathesis of **23** required substantially harsher conditions than had our model substrates. Pleasingly, and despite the requirement for elevated temperatures (second-generation Grubbs catalyst, 80°C, benzene, 4 h) and excess **21** (16 equiv), the reaction afforded the desired product **24** (99% brsm, typical conversion 60%, *E*/*Z* 6:1). Crucially, the resulting allylic carbonate **24** then underwent a π-allyl Stille cross-coupling reaction with the (*R*)-stannane **5** to give the (40*E*,43*Z*)-bis-acetonide **25**, which was isolated as the sole geometric isomer in excellent yield (96%). The benefit of our late-stage protecting group switch was now revealed, as this bis-acetonide correlated in all respects (^{1}H and ^{13}C NMR spectra, mass spectra, and optical rotation) with that formed by Andersen and co-workers from spirastrellolide A itself,[1b,10] thereby confirming the 46*R* configuration.[1d]

With **25** in hand, the completion of the total synthesis required only the cleavage of the acetonide groups. Heating a solution of **25** in methanol in the presence of PPTS (35°C, 12 h) did indeed remove both acetonide groups, and provided (+)-spirastrellolide A methyl ester (**2**) in 60% yield, $[\alpha]_D^{20} = +28.6$ ($c = 0.007$, CH_2Cl_2). Comparison with an authentic sample (provided by Professor Andersen) revealed matching NMR spectra (in several solvents), IR and mass spectra, HPLC retention time, optical rotation, and CD spectra, thereby conclusively defining the full configuration of the spirastrellolides.[10]

In conclusion, we have completed the first total synthesis of spirastrellolide A methyl ester by using a modular and convergent strategy, which proceeds in 36 linear steps, with a 19-step sequence from the C26–C40 DEF subunit.[18] We anticipate that this work will in turn allow the preparation of significant quantities of spirastrellolide A itself for detailed biological evaluation as well as leading to the synthesis of its congeners spirastrellolides B–G[1d] along with unnatural analogues for structure–activity relationship studies. Furthermore, the X-ray crystal structure of the unprotected macrolide core of spirastellolide A should enable protein phosphatase 2A docking studies to be performed, thereby permitting the rational design of analogues with improved efficacy.

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