Total Synthesis (1)

DOI: 10.1002/ange.200906121

Total Synthesis of Spirastrellolide F Methyl Ester—Part 1: Strategic Considerations and Revised Approach to the Southern Hemisphere[**]

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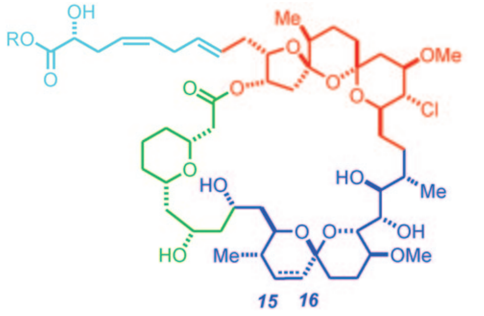
During a screening program for antimitotic agents using an innovative cell-based assay,[1] Anderson and co-workers recognized an unusual phenotypic response to the crude extract of the sponge *Spirastrella coccinea* collected off the coast of Dominica. Bioassay-guided fractionation led to the isolation of seven members of the spirastrellolide family as the active principles.[2–5] The methyl esters of these macrolides were found to exhibit uniformly strong activity that drives human breast cancer MCF-7 cells into premature mitosis before causing cell-cycle arrest. This activity is not mediated by interference with the tubulin or actin cytoskeletons, which serve as prominent targets for many other antimitotic agents, but rather by inhibition of the serine/threonine protein phosphatase PP2A.[2] The remarkable potency (IC_{50} ca. 1 nM) and selectivity for this key regulatory enzyme suggests that the spirastrellolides might represent valuable tools for chemical biology and/or possible leads in the quest for novel therapeutic agents for the treatment of cancer as well as various metabolic and neurological disorders.[6]

The promising biological activity of spirastrellolide A (**1a**) and F (**2a**) is encoded in a molecular architecture of exquisite complexity. These macrolides display 21 chiral centers on a linear polyketide chain of 47 carbon atoms, 20 of which reside within the 38-membered lactone that incorporates a tetrahydropyran ring, a [6,6]-spiroketal and an unusual chlorinated [5,6,6]-bisspiroketal subunit. The molecular intricacy is further increased by the labile *E*,*Z*-configured skipped diene embedded in the side chain.

All studies towards these enticing targets were severely hampered by a considerable uncertainty surrounding their structures. After an early revision of the originally proposed constitution of the macrocyclic frame,[2] only the relative configurations within the color-coded sectors of **1** could be established, whereas the relationship between the different domains remained unknown.[3] The resulting stereochemical puzzle enforced a high degree of strategic homology amongst the different synthetic approaches, since reasonable disconnections could only be made at the borders of the defined stereoclusters as long as their mutual relationship was unclear.[7,8] This situation lasted for more than four years after the initial disclosure of the spirastrellolides, which show relatively minor variations between the individual members of the family.[4,5] By then, enough material was collected from the natural source to allow for degradation studies and an X-ray structure analysis of a truncated derivative.[5] The deduced assignment of the relative and absolute configuration was confirmed by a monumental total synthesis of spirastrellolide A methyl ester (**1b**) published by Paterson et al. shortly after the open issues had been clarified.[9]



Spirastrellolide A (**1a**, R = H, $\Delta^{15,16}$)

Spirastrellolide A Methyl Ester (**1b**, R = Me, $\Delta^{15,16}$)

Spirastrellolide F (**2a**, R = H)

Spirastrellolide F Methyl Ester (**2b**, R = Me)

Our own studies toward the spirastrellolides soon led to concise and scalable approaches to all the required domains.[10,11] Of the approaches envisaged for their assembly, the esterification, the aldol reaction, and the elaboration of the side chain by a sequence of metathesis and π-allyl palladium chemistry[12] could be successfully reduced to practice (Scheme 1). However, the projected fragment coupling at the nonstereogenic C25–C26 bond by an inter- or intramolecular metathesis event met with failure, although more than 30 metathesis precursors with different protecting group patterns (R^1–R^4, X) were prepared and subjected to various catalysts and experimental set-ups; even the use of a "relay trigger" was to no avail, thus enforcing a redesign of the projected total synthesis.[13] This unfortunate outcome is thought to reflect the severe steric hindrance exerted by the

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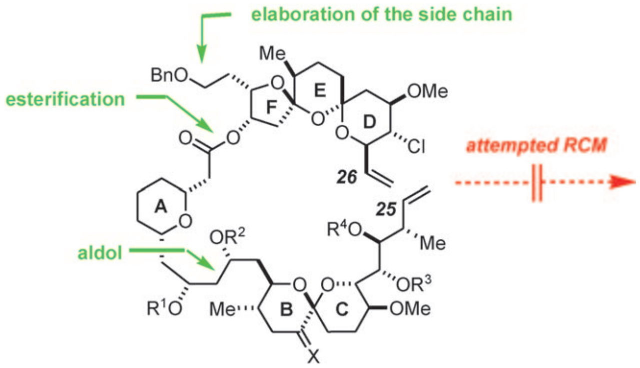
[**] Generous financial support by the MPG, the Chemical Genomics Center (CGC) of the MPG, the Fonds der Chemischen Industrie (Kekulé-stipend to S.B.), the Alexander-von-Humboldt Foundation (fellowship to G.O'N.), and F. Hoffmann–La Roche, Basel, is gratefully acknowledged. We sincerely thank the NMR, X-ray, and chromatography departments of our Institute for excellent support over the entire duration of this project.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200906121.

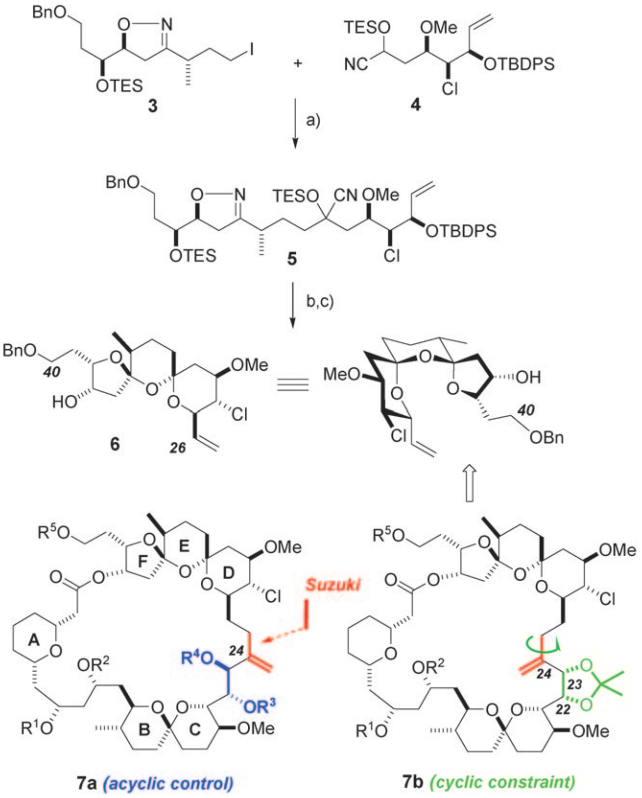


Scheme 1. Summary of our "first-generation" approach to the spirastrellolides.[10–13] The formation of the C25–C26 bond was not only attempted by ring-closing metathesis (RCM) but also in an intermolecular setting through olefin cross-metathesis. Bn = benzyl.

chlorinated bis(spiroketal) unit of the northern hemisphere on the adjacent olefin.[13]

This bis(spiroketal) entity DEF also turned out to be fairly sensitive and poised to furan formation.[8,11] Therefore it was planned to keep the northern segment as synthesized by the original route,[11,14] and rather modify the southern half in preparation for an alternative fragment coupling. Amongst the various possibilities that were contemplated and explored,[13] an alkyl-Suzuki reaction seemed particularly attractive (Scheme 2).[15–18] This transformation holds the promise of being productive because it allows the critical bond forming event to occur one carbon atom further away from the massive [5,6,6]-bis(spiroacetal) motif. At the same time, it might provide us with the unique opportunity to turn the steric hindrance exerted by the BC and DEF ring systems into a strategic advantage. Whereas these bulky and rigid substructures had ultimately prevented any productive metathesis from occurring, they are expected to shield one of the diastereotopic π faces of the *exo*-methylene group of the Suzuki product **7** during a subsequent hydrogenation step, and hence might ensure that the chiral center at C24 is established with high levels of selectivity.[17] Although the sense of induction could not be predicted with certainty at this stage, we were confident in gaining control over the course of the reduction by manipulation of the protecting groups R^3 and R^4 at the neighboring hydroxy functions at C22 and C23. This diol unit (**7a**; $R^3 = R^4 = H, SiR_3$) adopts an antiperiplanar conformation within the macrocycle,[19] whereas an isopropylidene acetal enforces a synclinal orientation (**7b**); distinctly different conformations of the macrocycle must ensue, which may help expose one or the other π face of the *exo*-methylene group to a suitable hydrogenation catalyst.

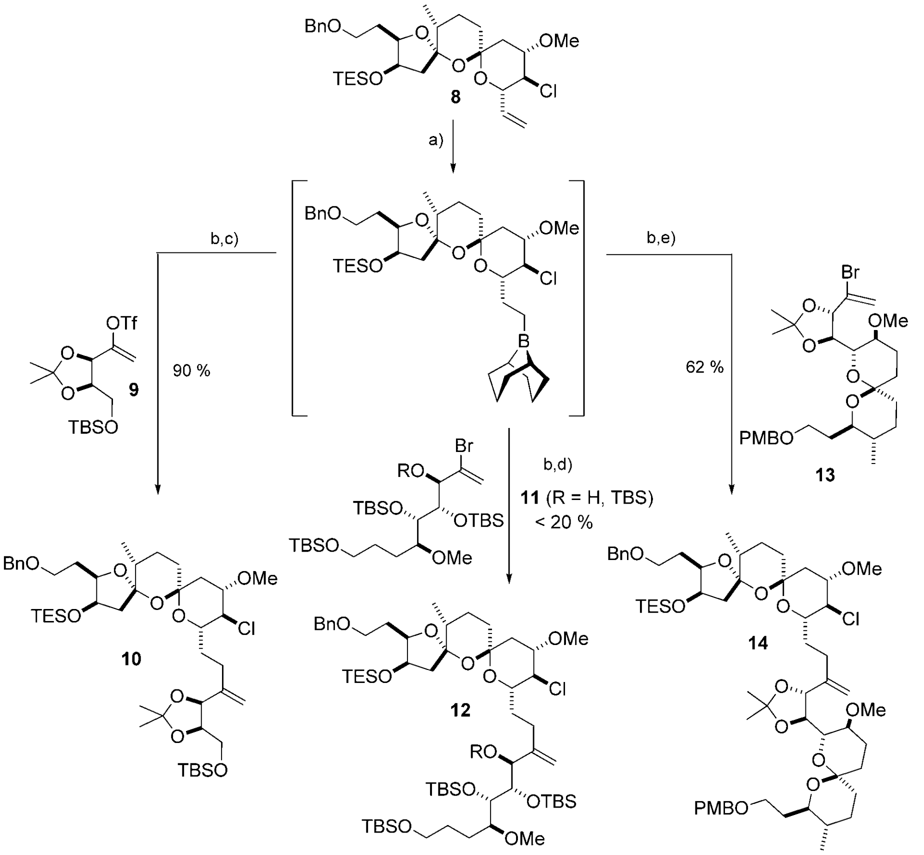
A high level of convergence was the other key design element of our revised synthesis plan. In particular, we envisaged a swift approach to the *seco* acid required for macrocyclization by stitching the northern fragment **6** together with a fully elaborate southern hemisphere, rather than a stepwise build-up of the cyclization precursor.[9] Moreover, efforts were made to minimize any post-lactonization interchange of protecting groups.



Scheme 2. Strategic fragment coupling at the C24–C25 bond by an alkyl-Suzuki reaction might provide strategic advantages, yet allow the sensitive northern sector **6** to be used unchanged. The hydrogenation of the *exo*-methylene group might be directed to the correct π face by proper choice of protecting groups for the adjacent hydroxy groups, which are expected to alter the conformation of the macrocyclic frame to a significant extent, see text; a) LDA, THF, −78 °C, 90-99 %; b) $[Mo(CO)_6]$, $MeCN/H_2O$ (10:1), 90 °C, 93 %; c) 1. TASF (aq), DMF, 94 %; 2. PPTS (cat.), CH_2Cl_2, 61 %. LDA = lithium diisopropylamide, PPTS = pyridinium *p*-toluenesulfonate, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl.

To achieve these ambitious goals, it was necessary to gather intelligence in a series of model reactions.[20,21] Following our initial report on a Suzuki reaction of **8** with 2-bromopropene,[13] considerable efforts were made to determine the optimal conditions for this key transformation using more elaborate electrophilic partners. From the representative examples shown in Scheme 3 it was concluded that 1) enol triflates such as **9** engage much more effectively in the cross-coupling with the 9-BBN adduct derived from **8** than the corresponding alkenyl bromides **11** and **13**, and 2) protection of the secondary hydroxy groups flanking the reaction center as an isopropylidene acetal furnishes significantly better yields than their masking in the form of silyl ethers.

Based on this knowledge, a suitably functionalized southern hemisphere was prepared as shown in Schemes 4–6. The palladium-catalyzed, Et_2Zn-induced Marshall propargylation[22] between **15** and **16**[23,24] furnished 10 g batches of product **17** in excellent yield and high selectivity, and hence qualified as the starting point for the synthesis. Routine protecting-group manipulations allowed this material to be



Scheme 3. Model studies on the Suzuki coupling:[20,21] a) $[9\text{-H-9-BBN}]_2$ (0.5 equiv), THF; b) aq NaOH (1 M); c) **9**, $[PdCl_2(dppf)]$ (10 mol%), Ph_3As (20 mol%), RT→65 °C; d) **11**, $[PdCl_2(dppf)]$ (10 mol%), Ph_3As (20 mol%), Cs_2CO_3, 65 °C; e) **13**, $[PdCl_2(dppf)]$ (10 mol%), Ph_3As (20 mol%), Cs_2CO_3, 65 °C. dppf = 1,1′-bis(diphenylphosphino)ferrocene, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

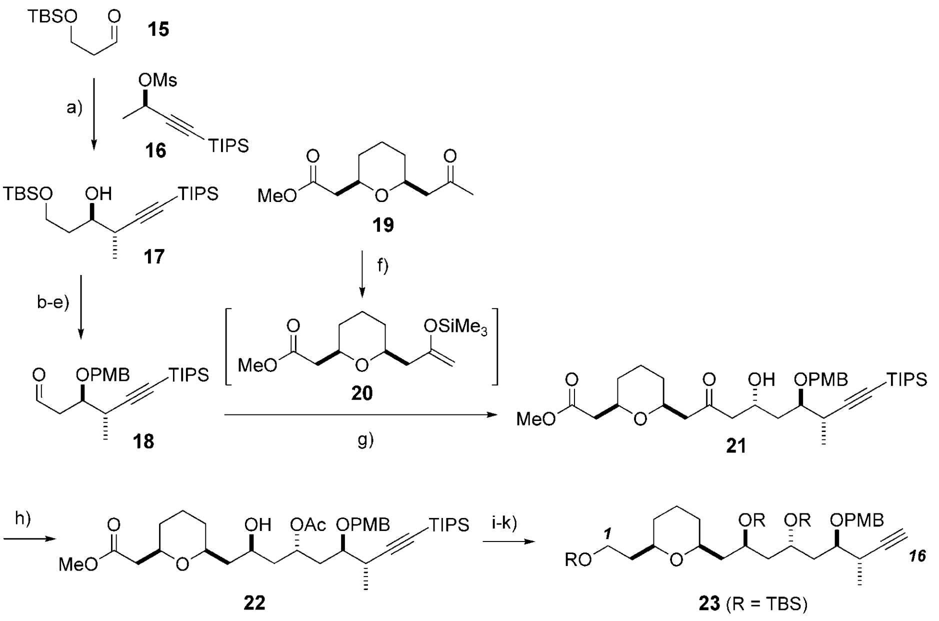
converted into aldehyde **18**, which underwent a modified Mukaiyama aldol reaction[25] with silyl enol ether **20** derived from the A-ring fragment **19** previously described by our research group.[26] In line with our experiences from earlier studies,[10] this transformation was highly diastereoselective, providing multigram amounts of product **21** as a single isomer. Its seemingly routine 1,3-*anti* reduction, however, was troublesome as the use of $[Me_4N][BH(OAc)_3]$ led to a disappointing 1.6:1 mixture of diastereomers; this problem was solved by recourse to the Evans–Tishchenko protocol,[27] which gave essentially a single product (d.r. ≥ 95:5) in 98% yield on a 4.3 g scale; its *anti-anti* configuration was proven by derivatization[28] and confirmed by crystal-structure analyses of more advanced intermediates.[29] Simultaneous reduction of both esters in **22**, cleavage of the remaining C-silyl group, and persilylation of the alcohol functions delivered the C1–C16 fragment **23**.

The second building block was prepared from epoxide **25**, which is available on large scale by Sharpless kinetic resolution (Scheme 5).[30] Even though rarely used in advanced synthesis, we found that the lithium reagent derived from TMS-propyne and *n*BuLi/TMEDA was highly suited for the opening of the oxirane ring.[31] Following an O-methylation of the resulting alcohol **26** with MeOTf/LiHMDS, the alkene terminus was oxidatively cleaved[32] to aldehyde **27** in preparation for a glycolate aldol reaction with silyl ketene acetal **28**[33] using freshly prepared $MgBr_2{\cdot}Et_2O$ as the mediator. In line with a literature precedent,[34] this transformation turned out to be highly 2,3-*anti*-3,4-*syn* selective (d.r. ≥ 10:1),[28] which is best explained by assuming a nonchelated open transition state.

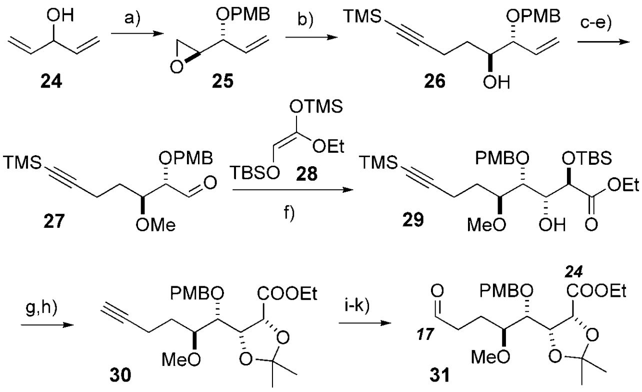
In preparation for an effective Suzuki cross-coupling reaction, compound **29** thus obtained was desilylated and the resulting diol converted into the isopropylidene acetal **30**. At this stage, Lindlar reduction of the alkyne in the presence of quinoline and sacrificial 1-hexene, followed by oxidative cleavage of the resulting terminal olefin unmasked the carbonyl group in **31**, which represents the C17–C24 segment of spirastrellolide F. From a conceptual viewpoint it is noteworthy that the double and the triple bond in **26** had thus served as strictly orthogonal aldehyde surrogates.

With multigram amounts of the two building blocks in hand, the southern hemisphere was elaborated as shown in Scheme 6. Addition of **31** to a cold solution of the alkynyl lithium reagent derived from **23** resulted in a chemoselective attack on the aldehyde while keeping the ester group intact. Oxidation of alcohols **32** with Dess–Martin periodinane[35] set the stage for the subsequent spirocyclization. Note that alkynones such as **33** are a priori amenable to the total synthesis of spirastrellolide A (**1**) and spirastrellolide F (**2**) alike, which differ from each other only in the presence or absence of the C15–C16 double bond in ring B; at this stage of our program, however, we decided to chase the latter compound as our initial target. To this end, **33** was hydrogenated over $Pd(OH)_2$ in EtOAc. It was gratifying to note that this simple operation resulted in saturation of the alkyne, cleavage of both PMB ethers at O13 and O21 and an exquisitely stereoselective spiroketalization of the released dihydroxyketone in a single operation.[36] This cascade turned out to be well reproducible and could be executed on a ≥ 2.3 g scale.

As a prelude to the Suzuki coupling, an expedient transformation of the ester group in **34** into an enol triflate was sought. To this end, exposure of **34** to the lithium anion of $PhSO_2Me$ furnished β-keto sulfone **35**,[37] which gave the required methyl ketone **36** in excellent overall yield on treatment with AIBN and Bu_3SnH in toluene at reflux. In view of its brevity and efficiency, this two-step protocol for the



Scheme 4. Preparation of the C1–C16 fragment: a) Et_2Zn, $Pd(OAc)_2$ (5 mol%), PPh_3 (5 mol%), THF, −78 °C, 92% (d.r. ≥ 9:1); b) TBAF, THF, −5 °C, 87%; c) $MeOC_6H_4CH(OMe)_2$, PPTS (cat.), CH_2Cl_2, −5 °C, 94%; d) Dibal-H, CH_2Cl_2, −5 °C, 97%; e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 92%; f) TMSOTf, $i\mathrm{Pr}_2\mathrm{NEt}$, CH_2Cl_2, −78 °C; g) $BF_3\cdot Et_2O$, CH_2Cl_2, −78 °C, 77% (over two steps); h) SmI_2 (15 mol%, 0.1 M in THF), MeCHO, THF, −10 °C, 98%; i) Dibal-H, toluene, 99%; j) TASF, THF, 0 °C → RT; k) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, quant. Dibal-H = diisobutylaluminum hydride, TBAF = tetra-*n*-butylammonium fluoride, TIPS = triisopropylsilyl, TMS = trimethylsilyl.



Scheme 5. Preparation of the C17–C24 fragment: a) Ref. [30]; b) TMSC≡CMe, *n*BuLi, TMEDA, Et_2O, −25 °C → −5 °C, 81%; c) MeOTf, LiHMDS, THF, 84%; d) OsO_4 (cat.), $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH, 0 °C → RT, 64% (74% brsm); e) $Pb(OAc)_4$, CH_2Cl_2; f) $MgBr_2\cdot Et_2O$, toluene, −78 °C → RT, 81% (over both steps, d.r. ≥ 10:1); g) TBAF, THF, 0 °C, quant.; h) acetone dimethylacetal, camphorsulfonic acid (cat.), 0 °C → RT, 90%; i) Lindlar catalyst (50% w/w), H_2 (1 atm), quinoline, EtOAc/1-hexene (1:1); j) OsO_4 (cat.), NMO, 89% (over two steps); k) $Pb(OAc)_4$, CH_2Cl_2, 86%; brsm = based on recovered starting material; $(DHQ)_2PYR$ = hydroquinine-(2,5-diphenyl-4,6-pyrimidinediyl) diether; HMDS = hexamethyldisilezene.

conversion of esters into methyl ketones should be of wider interest.[38] Next, deprotonation of **36** with KHMDS at −78 °C followed by quenching of the kinetic enolate with freshly sublimed *N*-(4-*tert*-butylphenyl)-bis(trifluoromethanesulfon imide)[39] afforded enol triflate **37**, which turned out to be stable enough to allow for the selective deprotection of the primary TBS ether at the other end with the aid of HF·pyridine under buffered conditions. This rewarding result opened the possibility to install the *free* carboxylic acid required for the envisaged macrolactonization prior to the Suzuki event and hence reduce late-stage manipulation of the protecting groups to a minimum. In fact, the oxidation of **38** gave compound **39**, with an enol triflate and a free carboxylic acid at its termini, in almost quantitative yield. This surprisingly robust product constitutes the fully functional southern domain of **2** and holds the promise of being stitched together with the northern sector to give the intact macrocyclic framework of the target in only two operations. The reduction of this plan to practice and the completion of the total synthesis of spirastrellolide F methyl ester are reported in the following report.

Received: October 30, 2009

Keywords: natural products · phosphatase inhibitors · synthesis design · total synthesis

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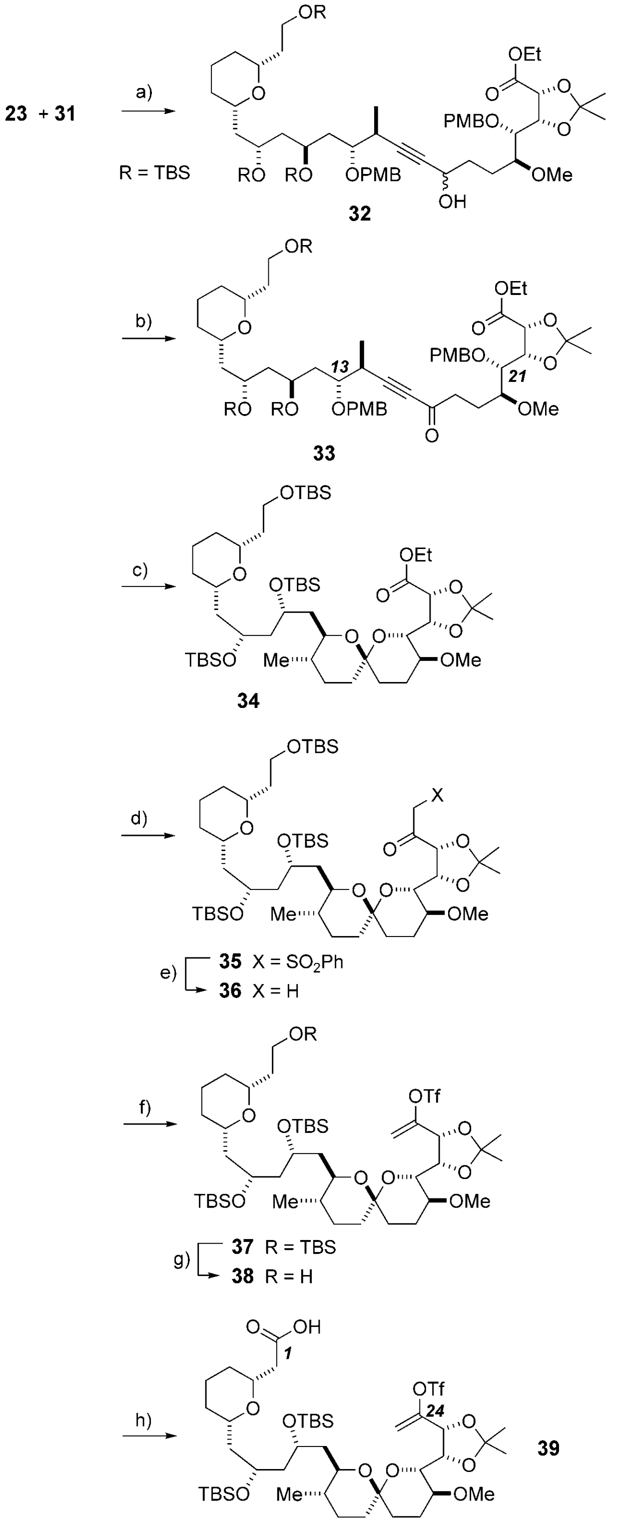

Scheme 6. Preparation of the southern hemisphere in readiness for macrocyclization: a) 1. **23**, *n*BuLi, THF, −78 °C→−50 °C; 2. **31**, −78 °C, 81 %; b) Dess–Martin periodinane, CH_2Cl_2, 0 °C→RT, 99 %; c) $Pd(OH)_2$ (25 mol % w/w), H_2 (1 atm), EtOAc, 80 %; d) $PhSO_2Me$, *n*BuLi, THF, −78 °C, 90 %; e) AIBN, Bu_3SnH, toluene, reflux, 80 %; f) KHMDS, THF, then *N*-(4-*tert*-butylphenyl)-bis(trifluoromethanesulfonimide), −78 °C; g) HF·pyridine, THF, pyridine, −10 °C, 60 % (75 % brsm, over 2 steps); h) 1. Dess–Martin periodinane, CH_2Cl_2, 0 °C→RT; 2. $NaClO_2$, NaH_2PO_4, *t*BuOH, H_2O, 2-methyl-2-butene, 95 % (over two steps). AIBN = 2,2′-azobis(2-methylpropionitrile).

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[20] These experiments had been carried out before the absolute configuration of the spirastrellolides was assigned; they were performed with what turned out to be the non-natural enantiomer of the DEF ring system.

[21] Note that the configuration of the chiral center corresponding to C23 in **13** is opposite to that of the spirastrellolides.

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[38] For comparison, the conventional route involving reduction/oxidation to form the aldehyde, MeMgBr addition, and re-oxidation gave ketone **36** in only 25 % yield over four operations.

[39] *N*-(4-*tert*-Butylphenyl)-bis(trifluoromethanesulfonimide) was preferred over $PhN(Tf)_2$ or Comins reagent because the by-products formed are more readily separable from enol triflate **37**. Moreover, this reagent can be sublimed, thus ensuring dryness and hence high yields in the reaction with the potassium enolate.