

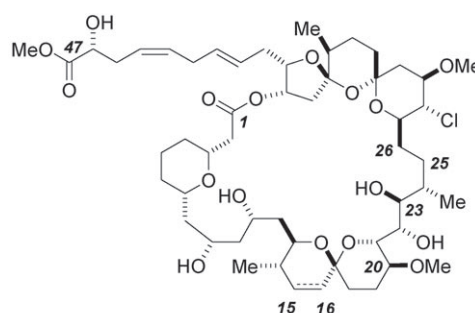
Total Synthesis of Spirastrellolide F Methyl Ester—Part 2: Macrocyclization and Completion of the Synthesis**

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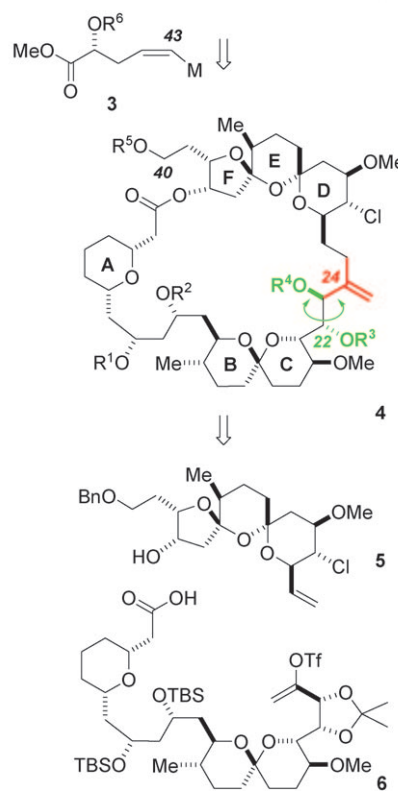
The remarkable antimitotic activity and intricate molecular architecture of the spirastrellolides have aroused considerable interest in the synthetic community ever since their discovery, even though the relative and absolute configuration of these macrolides remained uncertain for several years.^[1] These efforts^[2–5] culminated in the first and so far only total synthesis of the methyl ester of spirastrellolide A (**1**) as a prototype member of this small family of marine natural products published by Paterson et al. in 2008.^[6] We now report the conquest of its sister compound spirastrellolide F methyl ester (**2**), which differs from **1** only by incorporation of a saturated rather than an unsaturated B ring into the southern hemisphere.

Prompted by the failure to forge the 38-membered perimeter of the target by olefin metathesis at the non-stereogenic C25–C26 bond,^[5] we reconsidered the strategy for the assembly of the target. As outlined in the previous communication, this redesign led to a synthesis blueprint that envisages a highly convergent access to the macrocyclic core **4** (Scheme 1).^[7] In an attempt to streamline this critical manoeuvre and reduce any late-stage manipulation of protecting groups to a minimum,^[8] we devised an expeditious route to compound **6** as a surrogate of the southern hemisphere that carries an enol triflate and a free carboxylic acid at its termini. An alkyl-Suzuki cross coupling reaction^[9] and a lactonization event should join this fragment to the northern sector **5**, for which a highly productive and scalable synthesis had already previously been worked out.^[4b] However, this

scenario bears the risk that the course of the then necessary reduction of the resulting *exo*-methylene group in **4** cannot be predicted with certainty. This crucial transformation must occur from the olefin's *Re* face to set the correct configuration of the C24 stereogenic center. It was hoped that the protecting



Spirastrellolide A Methyl Ester (**1**, Δ^{15,16})
Spirastrellolide F Methyl Ester (**2**)



Scheme 1. Envisaged assembly of spirastrellolide F methyl ester (**2**). Bn = benzyl, Tf = trifluoromethanesulfonyl.

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groups for the adjacent secondary alcohols at C22 and C23 might provide a handle to determine the proper sense of induction during this substrate-controlled hydrogenation step. This diol ($R^3 = R^4 = H$, SiR_3) adopts an antiperiplanar orientation,^[10] whereas attachment of an acetal group as a cyclic constraint enforces a synclinal arrangement. The resulting change of the curvature of the macrocycle might eventually expose one or the other diastereotopic face of the alkene to a loaded hydrogenation catalyst.

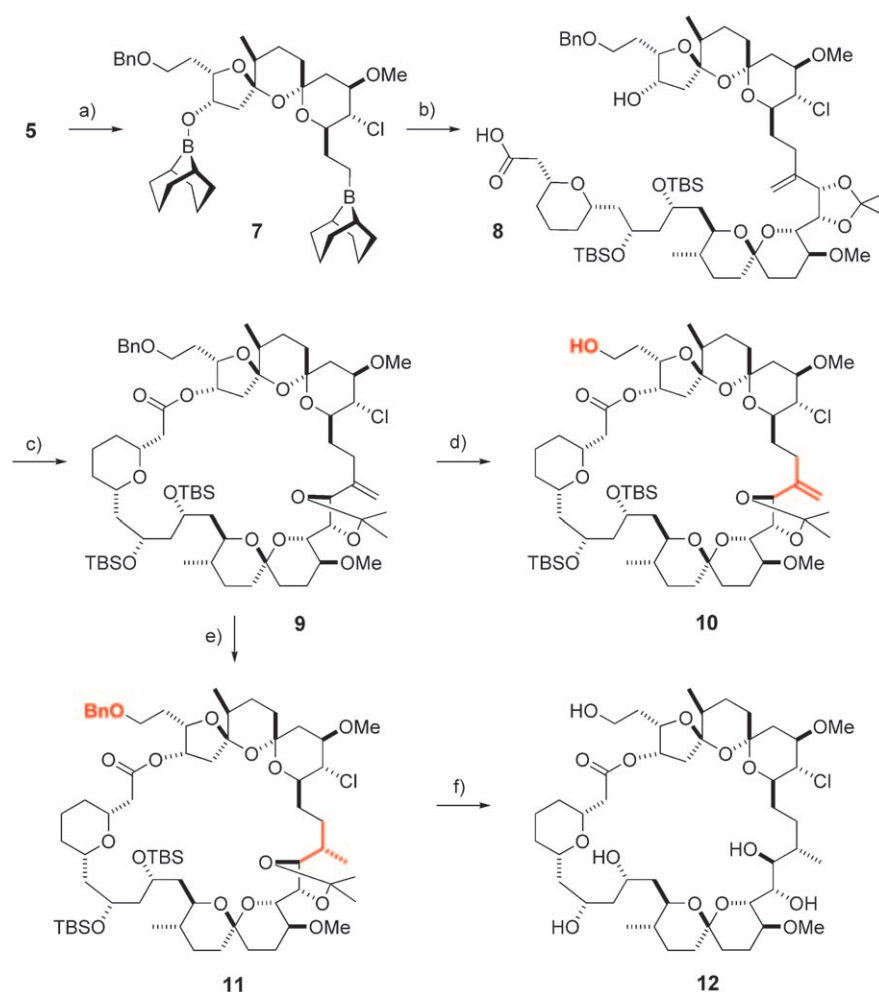
The assembly process commenced with the hydroboration of **5** with 1.2 equivalents of 9-H-9-BBN dimer (Scheme 2). In accord with our model studies,^[7] addition of aqueous NaOH to the resulting borane **7** generated a suitable borate nucleophile that readily engaged in a palladium-catalyzed cross-coupling reaction with the elaborate triflate **6**. After an oxidative work up with basic H_2O_2 to remove all boron impurities, the desired *seco*-acid **8** was isolated in a respect-

able 75% yield. After some experimentation it was found that the Yamaguchi protocol cleanly resulted in macrolactonization of this compound,^[11,12] provided that the mixed anhydride intermediate was slowly added to DMAP in toluene at reflux. The need for such harsh conditions is ascribed to a rather stiff and cyclization-unfriendly conformation imposed on the *seco* acid by the isopropylidene group and/or to transannular strain in the resulting macrocycle.

To our surprise, however, attempted hydrogenation of the resulting product **9** over an assortment of catalysts under different conditions met largely with failure. While this transformation was initially thought to saturate the alkene and concomitantly deprotect the terminus in **9** for further elaboration, the cleavage of the primary benzyl ether occurs smoothly with the aid of $Pd(OH)_2$ to give the primary alcohol **10**, whereas the *exo*-methylene is exceptionally resistant to reduction over this and various other noble-metal contacts.^[13]

For the sake of the project, however, it was rewarding that crystals of **10** suitable for X-ray structure analysis could be grown (Figure 1). This authenticated the constitution of the macrocycle and its constituent A–F rings and confirmed the assignment of all 19 stereogenic centers in place at this stage. Even more gratifyingly, the structure of **10** in the solid state reveals that the isopropylidene acetal orients the adjacent *exo*-methylene group such that the *Si* face is effectively shielded by the southern [6,6]-spiroketal entity, whereas the *Re* face seems wide open. While this analysis certainly forecasts that the hydrogenation should occur with the correct facial bias, a closer look at the structure also explains the difficulties in hydrogenating the olefin, which experiences very tight transannular contacts to the BC ring system; in particular, H13 stands directly in the way.^[14] Moreover, the spiroacetal cage, because of its rigidity, can hardly accommodate any further move of the substituent into this crowded space, which accompanies the reduction of the methylene to a methyl group.

In fact, considerable experimentation was necessary to accomplish the seemingly trivial hydrogenation of **9**. Only the use of a modified Crabtree complex escorted by the poorly coordinating tetrakis(3,5-bis-trifluoromethylphenyl)borate (BARF) anion (rather than the conventional PF_6^-) gave reproducible results at 200 atm hydrogen pressure under rigorously anhydrous conditions,^[16,17] within the limits of detection, **11** was the only product formed. In addition to the



Scheme 2. Assembly of the macrocycle: a) 9-H-9-BBN₂, THF; b) 1. aq NaOH (1 M); 2. **6**, [PdCl₂-(dppf)] (20 mol %), Ph₃As (20 mol %), THF, 75%; c) 1. 2,4,6-trichlorobenzoyl chloride, Et₃N, toluene; 2. DMAP, toluene, reflux, 80%; d) Pd(OH)₂ (30% w/w), H₂ (1 atm), EtOAc, 87%; e) [Ir(cod)(PCy₃)(pyridine)][BARF] (20 mol %), H₂ (200 atm), 1,2-dichloroethane, 59% (83% brsm); f) 1. Pd(OH)₂ (25% w/w), H₂ (1 atm), EtOAc; 2. PPTS (cat.), MeOH/Et₂O/H₂O (7:2:1), 50°C, 43% (over two steps, not optimized). BARF = tetrakis(3,5-bis-trifluoromethylphenyl)borate, 9-BBN = 9-borabicyclo[3.3.1]nonane, brsm = based on recovered starting material, cod = cycloocta-1,5-diene, DMAP = 4-dimethylaminopyridine, dppf = 1,1'-bis(diphenylphosphino)ferrocene, PPTS = pyridinium *p*-toluenesulfonate, TBS = *tert*-butyldimethylsilyl.

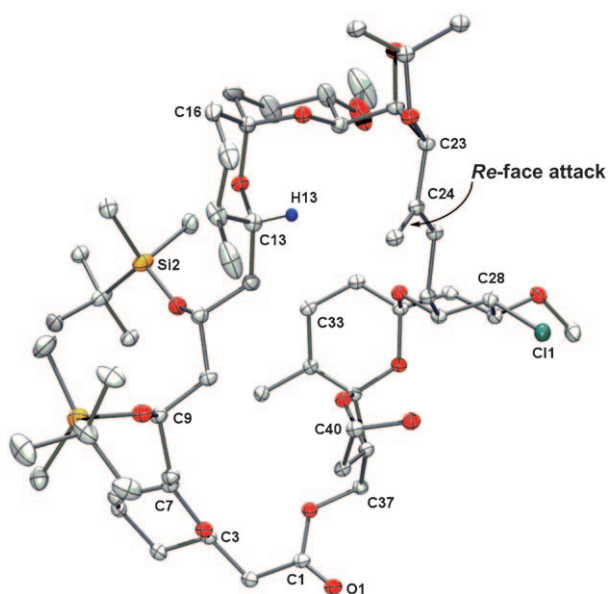


Figure 1. Structure of **10** in the solid state.^[15]

inherent reluctance of the alkene moiety, one also has to bear in mind that the catalytically competent 12-electron iridium center generated in situ from this precursor has a high affinity for donor sites.^[18] Thus, the many acetal and ether groups in **9** may compete with productive binding of the 1,1-disubstituted olefin to the catalytically active metal template and hence further impede the reaction, so that even this powerful catalyst must be forced to attack this particular substrate.

To establish the stereochemical course of the reduction, **11** was globally deprotected as shown in Scheme 2. Fine acicular crystals of the resulting product **12** could be grown. Their X-ray diffraction analysis confirmed that the configurations of all the stereogenic centers adorning the macrolactone ring—including the newly set center at C24—correspond to those of spirastrellolide F (Figure 2). Furthermore it is of note that the unprotected diol at C22 and C23, relieved from the constraints of the isopropylidene acetal, indeed shows the

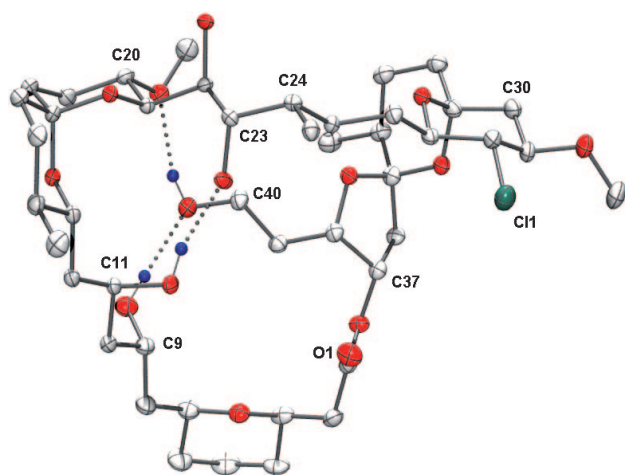
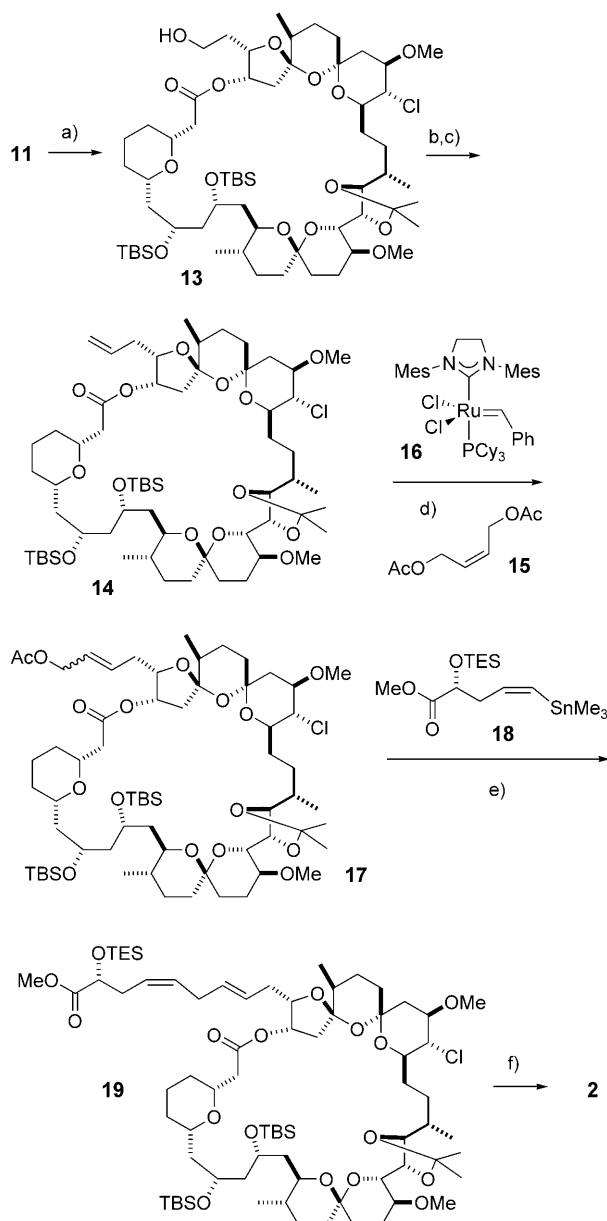


Figure 2. Structure of **12** in the solid state.^[15] The dotted lines represent the intramolecular hydrogen-bonding network, see text.

expected *anti* orientation. The macrocycle embraces this substructure by adopting a triangular shape that is entirely different from the more-extended conformation of its protected precursor **10** displayed in Figure 1.

The final stages largely followed our earlier model studies^[19] and also resemble the endgame independently pursued by the Paterson group (Scheme 3).^[6] Specifically, hydrogenolysis of the primary benzyl ether in **11** followed by an oxidation/Wittig olefination sequence provided alkene **14** in 89% yield over three steps and a single chromatographic purification. Cross-metathesis (CM)^[20] with **15** installed an



Scheme 3. Completion of the total synthesis: a) Pd(OH)₂ (25% w/w), H₂ (1 atm), EtOAc; b) Dess–Martin periodinane, CH₂Cl₂, 0°C → RT; c) Ph₃P=CH₂, THF, 89% (over three steps); d) **15** (15 equiv), complex **16** (20 mol%), toluene, 60°C, 47% (98% brsm, *E/Z* ≥ 8:1); e) **18**, [Pd₂(dba)₃] (20 mol%), LiCl, *N*-methylpyrrolidone, 60°C; f) PPTS (cat.), MeOH/Et₂O/H₂O (7:2:1), 50°C, 50% (over both steps). dba = dibenzylideneacetone, Mes = 2,4,6-trimethylphenyl, TES = triethylsilyl.

allylic acetate motif as an $\geq 8:1$ mixture of isomers. It is of note that the CM reaction had worked exceedingly well on several advanced models,^[21] but never gave more than 47% yield (98% brsm) of the desired product with the fully elaborate substrate **14** because of incomplete conversion, even if a large excess of **15** and high loadings of catalyst **16** were used; a similar observation had been made by the Paterson research group.^[6b] Compound **17** was then subjected to a modified allylic Stille reaction^[22] with stannane **18**, which installed the skipped *E,Z* diene.^[23] Final cleavage of all the residual protecting groups in a single operation using pyridinium *p*-toluenesulfonate in a mixed solvent system completed our endeavor.

The analytical and spectral properties of spirastrellolide F (**2**) also deserve comment. Our synthetic sample is a white solid rather than a “clear oil” as stated in the literature.^[1c] The ¹³C NMR data (150 MHz) are in excellent agreement with the published ones, with the signals of the hydroxylated C atoms being somewhat broadened;^[24] the ¹H NMR spectra (600 MHz) also match well, but show a striking dynamic behavior, which has not been described before. Over the course of days, the compound reorganizes an intricate hydrogen-bonding network (see Figure 2), which engages not only the lateral hydroxy groups but also traces of water from the medium, as confirmed by extensive NOESY studies.^[24] As a result, the shift of the hydroxy groups is time- and concentration-dependent. Even more strikingly, the ensuing conformational changes and/or the slow motion of the macrocycle have an impact on the shape of several signals: a particularly strong effect is observed for the C20-OMe group, which appears as the expected singlet but evolves into an unusually broad resonance (Figure 3). Careful analysis by MS and ¹³C NMR spectroscopy show no sign of decomposition when this stage is reached. This stunning phenomenon is the subject of further study in our laboratory. With the constitution and stereochemistry of the macrocycle being unambiguously confirmed by two independent crystal-structure analyses and in view of the comprehensive and fully consistent NMR data set obtained during our investigation,^[24] there is no

doubt whatsoever about the structure and integrity of synthetic spirastrellolide F methyl ester obtained through our campaign, even though a natural sample of **2** could not be made available for direct comparison.^[25]

In summary, we have accomplished the first total synthesis of the potent antimitotic macrolide spirastrellolide F methyl ester. The chosen approach is highly convergent and productive and involves a minimum number of late-stage manipulations of protecting groups. It allows assembly of the macrocyclic perimeter in a “stitching” mode from two advanced intermediates and provides exquisite control over all the stereogenic centers of this challenging target. Further investigations, including an alternative strategy for the elaboration of the side chain, studies on the fascinating conformational behavior in solution, as well as evaluations of the biological properties of these marine polyketides are underway and will be reported in due course.

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Keywords: cross-coupling · hydrogenation · macrolides · natural products · total synthesis

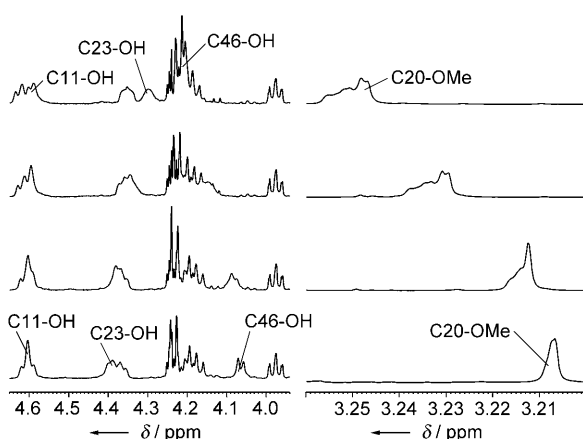
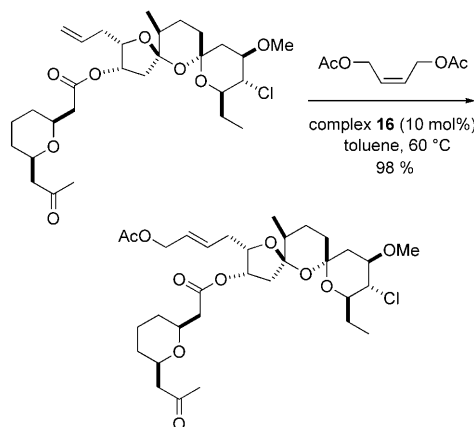


Figure 3. The slow reorganization of the hydrogen-bonding network between the peripheral hydroxy groups of **2** and external water dramatically changes the chemical shift as well as the shape of several signals.

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- [14] The distance from H13 to the centroid of the C=C bond is only 2.794 Å and the C13...C58 distance is remarkably short (3.61 Å) in spite of a C13–H13–C58 angle of 158°. There are no crystal structures in the Cambridge Database (September 2009) containing similar structural elements that have shorter intermolecular C...C distances with such a large C–H angle. Furthermore, the C13–H13 bond is calculated to be only 1.001 Å.
- [15] For the sake of clarity, anisotropic displacement parameters are drawn only at the 5% (**10**) and 20% (**12**) probability level. CCDC 749791 (**10**) and 752194 (**12**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Additional views of the structures and short crystallographic summaries are also found in the Supporting Information.
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compound **14** undergo CM, remain unclear. Preliminary data, however, suggest that the oxygen atom of the tetrahydrofuran ring in **14** coordinates with the Ru center and hence likely interferes with the performance of the metathesis catalyst, see A. Fürstner, K. Langemann, *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136. Details will be reported in a future full paper.

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- [23] In our previous study, we have described a donor analogous to **18** protected by a TBS group. It was found, however, that this particular silyl group cleaves much slower than the secondary TBS groups at O9 and O1 as well as the isopropylidene acetal. Prolonged stirring of the material with PPTS, however, leads to partial decomposition of the final product. Therefore, the donor fragment **18** was prepared, which carries a more labile TES group as shown in Scheme 3. Furthermore, attempted coupling with the analogous donor featuring a free hydroxy group, as used by Paterson et al.,^[6] did not work well in our hands.
- [24] For details and a comprehensive data set, see the Supporting Information.
- [25] It is of note that the NMR spectrum of synthetic spirastrellolide A methyl ester reported by Paterson and coworkers is identical to that of an authentic sample recorded under the same conditions on the same spectrometer,^[6] but is distinctly different from the spectrum depicted in the Supporting Information of the isolation paper.^[1]