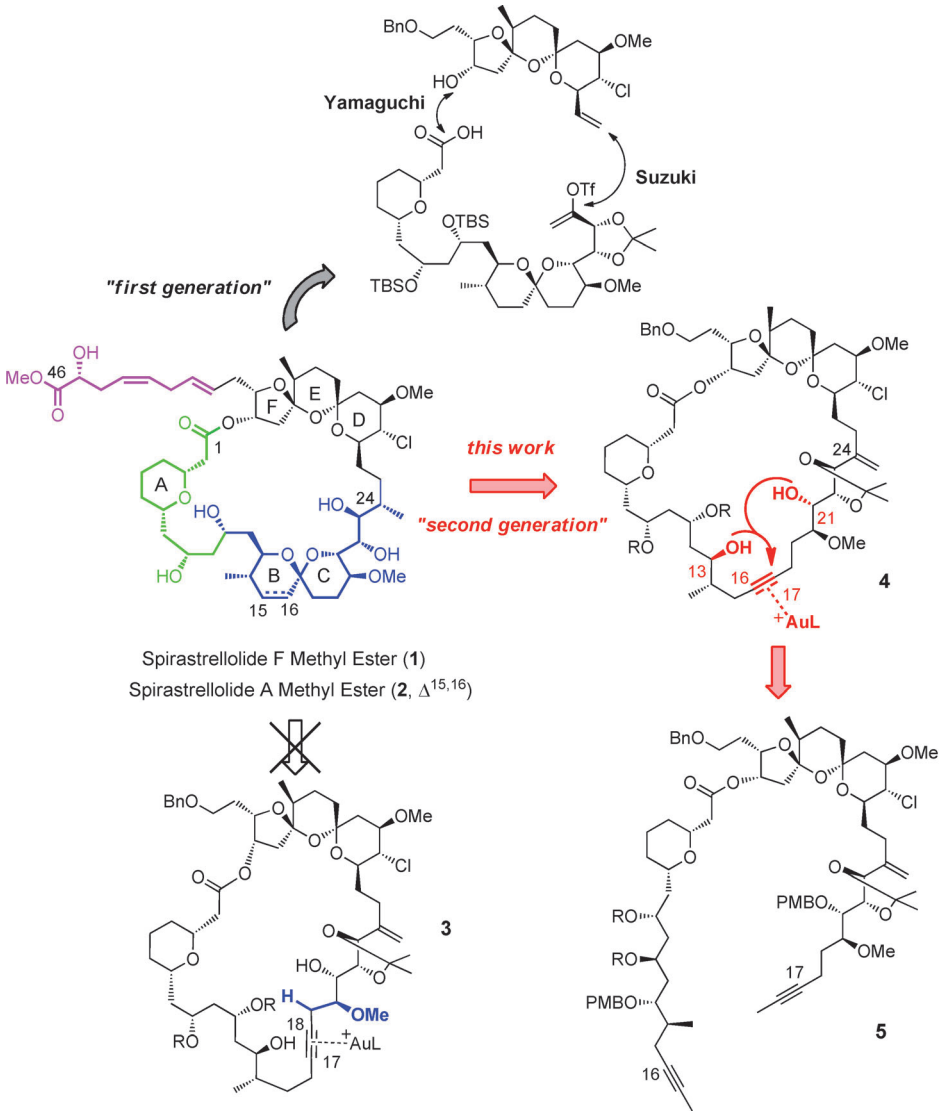
Natural Product Synthesis

DOI: 10.1002/anie.201103270

Second-Generation Total Synthesis of Spirastrellolide F Methyl Ester: The Alkyne Route**

*Stefan Benson, Marie-Pierre Collin, Alexander Arlt, Barbara Gabor, Richard Goddard, and Alois Fürstner**

The spirastrellolides are a small family of exquisitely potent antimitotic agents of marine origin which are reported to exert their function by selective inhibition of the serine/threonine protein phosphatase PP2 A (IC_{50} ca. 1 nM).[1] This activity predestines them as tools for chemical biology and as possible lead structures in the quest for novel therapeutic agents for the treatment of cancer and other metabolic disorders.[2] Although it took more than four years from the initial isolation to the full elucidation of the stereostructure of these compounds,[1] their intricate topology and very limited supply from the natural source aroused considerable interest in the synthetic community even before the molecular architecture had been fully elucidated.[3–5] These efforts culminated in the first total synthesis of spirastrellolide A methyl ester (**2**) by Paterson et al.,[6] followed by the conquest of the sister compound spirastrellolide F methyl ester (**1**) by our research group shortly thereafter (Scheme 1).[7] Since only the relative configuration of the four color-coded stereoclusters embedded into the framework of these macrolides but neither the stereochemical relationships between them nor their absolute configurations were known at the outset of these projects, both approaches could not help but envisage fragment coupling reactions at the boundaries of the known domains. Although quite distinct in their details, both the synthesis of **2** by Paterson et al. and our own successful route to **1** relied on a Suzuki cross-coupling, a macrolactonization, and a stepwise build-up of the side chain containing a fragile skipped *E*,*Z*-configured 1,4-diene motif (Scheme 1). Now



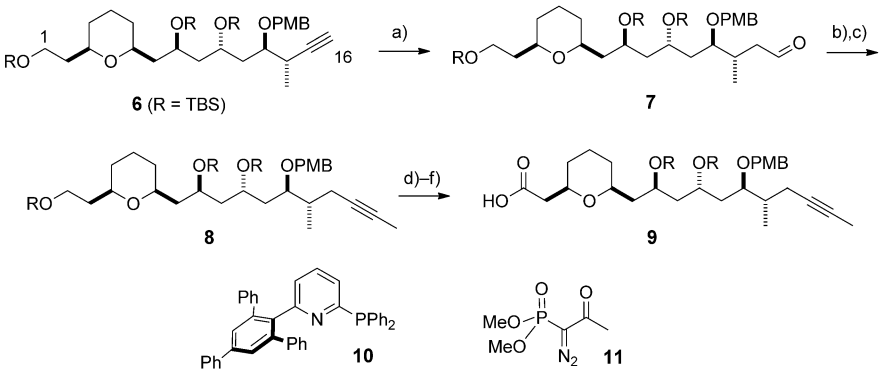
Scheme 1. Structures of spirastrellolide A and F methyl esters, together with our first- and second-generation retrosynthetic analysis of **1**. Bn = benzyl, PMB = *para*-methoxybenzyl.

[*] Dipl.-Chem. S. Benson, Dr. M.-P. Collin, Dipl.-Chem. A. Arlt, B. Gabor, Dr. R. Goddard, Prof. A. Fürstner
Max-Planck-Institut für Kohlenforschung
45470 Mülheim an der Ruhr (Germany)
E-mail: fuerstner@kofo.mpg.de

[**] Generous financial support by the MPG and the Fonds der Chemischen Industrie (Kekulé stipends to S.B. and A.A.) is gratefully acknowledged. We thank S. Schulthoff for skillful technical assistance.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103270.

that the stereochemistry of these targets has been established and confirmed, this major strategic constraint is no longer valid. We, therefore, present a conceptually different approach toward the macrocyclic edifice of **1** based on catalytic alkyne activation reactions. Moreover, an alternative end game is presented, which allows the side chain to be appended to the macrolide core in a single operation rather than by the incremental sequence previously used by the two research groups.



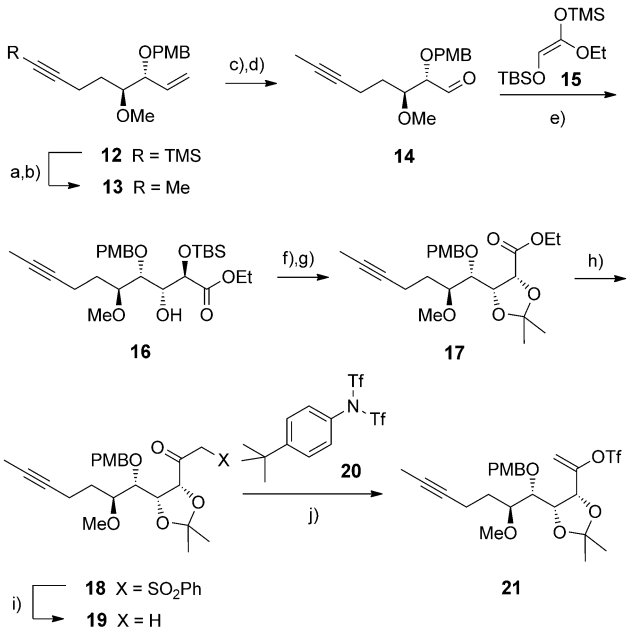
Scheme 2. a) $[CpRu(MeCN)_3]PF_6$ (5 mol%), **10** (10 mol%), MeCN, 60°C, then **6**, aq acetone, 60°C, 88%; b) **11**, K_2CO_3, MeOH, 96%; c) BuLi, MeOTf, THF, −78°C→0°C, 93%; d) HF·pyridine, pyridine, THF, −10°C, 76%; e) Dess–Martin periodinane, CH_2Cl_2; f) $NaClO_2$, NaH_2PO_4, *t*BuOH/H_2O (1:1), 2-methyl-2-butene, 92% (over both steps). TBS = *tert*-butyldimethylsilyl, Cp = cyclopentadienyl, Tf = trifluoromethanesulfonyl.

The strategic design element of this new approach is the late-stage unveiling of the spirocyclic BC ring system of **1** upon activation of a dihydroxy-alkyne precursor with a carbophilic Lewis acid catalyst such as Au^I or Pt^{II} (Scheme 1).[8,9] Of the two possible modes that can a priori be envisaged, it was decided not to follow the route via the C17–C18 cycloalkyne **3**, since this particular compound, upon activation of the triple bond, might be prone to elimination of MeOH with formation of a conjugated enyne; no such escape route exists for the regioisomer **4**, with the acetylene moiety at the C16–C17 position. This key intermediate for its part could derive from precursor **5** by what is arguably the most advanced application of ring-closing alkyne metathesis (RCAM)[10] reported to date and a particularly stringent test for the functional-group tolerance of the available catalysts.[11] Access to **5** can be secured from building blocks, for which scalable preparations have already been worked out during our previous total synthesis campaign.

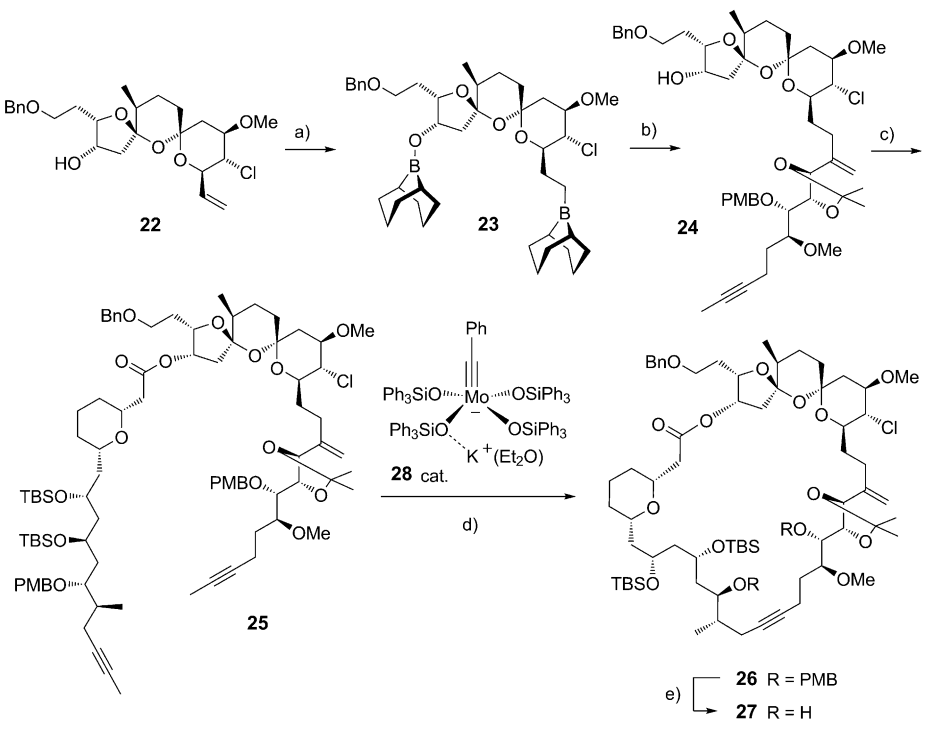
To this end, the known terminal alkyne **6**[7a] was homologated by first subjecting it to a ruthenium-catalyzed anti-Markovnikov hydration according to the method developed by Hintermann and co-workers (Scheme 2).[12] This procedure furnished the desired aldehyde **7** in 88% yield. This product was treated with the Ohira–Bestmann reagent **11**[13] and the resulting terminal alkyne end-capped with a methyl group. Selective desilylation of the primary alcohol in **8** with buffered HF·pyridine, followed by stepwise oxidation, readily furnished the required carboxylic acid segment **9**.

Access to the C17–C24 sector was similarly straightforward starting from compound **12**, which had previously been prepared on a multigram scale (Scheme 3).[7] Replacement of the silyl group by a methyl substituent followed by oxidative cleavage of the alkene terminus in **13** gave aldehyde **14**, which was subjected to a Mukaiyama aldol reaction with the TMS-ketene acetal **15**.[14] Under the aegis of $MgBr_2{\cdot}OEt_2$, this transformation provided product **16** with a diastereomeric ratio of >10:1 in a highly reproducible 70% yield.[7,15] Its elaboration to the isopropylidene acetal **17**, which later plays an essential role as a conformational control element for setting the stereocenter at C24,[7b] was uneventful, as was the conversion of the methyl ester group into the required enol triflate **21**. This transformation was best achieved by addition of lithiated methyl phenyl sulfone[16] and subsequent cleavage of the $PhSO_2$ group in **18** under free-radical conditions; the resulting ketone **19** then gave triflate **21** on deprotonation with LiHMDS and quenching of the generated enolate with triflimide **20** as the preferred electrophile.[17]

The assembly of these fragments to the required RCAM precursor benefitted from the intelligence gathered in our first-generation total synthesis of spirastrellolide F.[4,7] Specif-



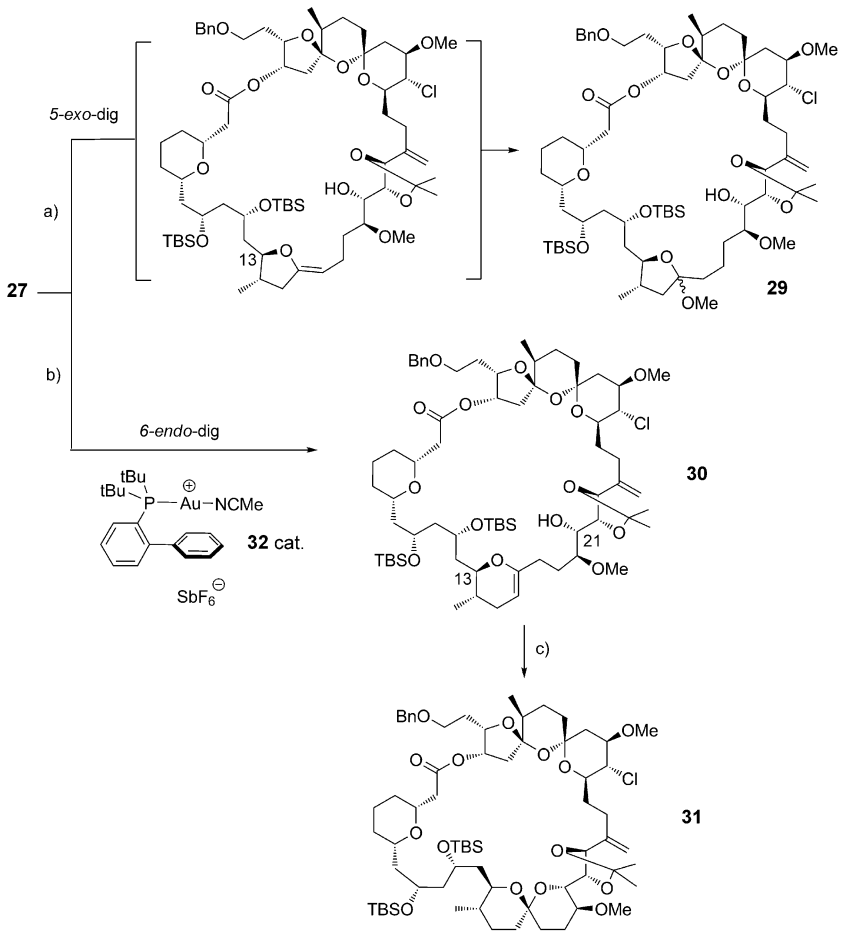
Scheme 3. a) K_2CO_3, MeOH, 89%; b) BuLi, THF, −78°C→0°C, then MeOTf, −78°C, 80%; c) OsO_4 cat., $(DHQ)_2PYR$, $K_3[Fe(CN)_6]$, K_2CO_3, *t*BuOH, H_2O, 0°C→RT, 77% (brsm); d) $Pb(OAc)_4$, CH_2Cl_2, 88%; e) $MgBr_2{\cdot}OEt_2$, toluene, −78°C→RT, 70% (d.r. ≥ 10:1); f) TBAF, THF, 0°C→RT, 88%; g) 2,2-dimethoxypropane, camphorsulfonic acid cat., CH_2Cl_2, 0°C →RT, 87%; h) $PhSO_2Me$, BuLi, THF, then **17**, −78°C→0°C; i) azoisobutyronitrile, Bu_3SnH, toluene, reflux, 79% (over two steps); j) **20**, LiHMDS, THF, −78°C→RT, 57%. LiHMDS = lithium hexamethyldisilazide, $(DHQ)_2PYR$ = hydroquinine-(2,5-diphenyl-4,6-pyrimidindiyl) diether, TBAF = tetrabutylammonium fluoride.



Scheme 4. a) 9-H-9-BBN dimer, THF; b) aq NaOH (1 M), [$PdCl_2$(dppf)] (20 mol%), Ph_3As (20 mol%), **21**, THF, 76%; c) 1. **9**, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, 0°C; 2. **24**, DMAP, toluene, 0°C→RT, 85%; d) **28** (8 mol%), 5 Å M.S., toluene, 87%; e) DDQ, CH_2Cl_2, 0°C→RT, 91%. 9-BBN = 9-borabicyclo[3.3.1]nonane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, DMAP = 4-dimethylamino-pyridine; M.S. = molecular sieves.

ically, the well accessible "northern" hemisphere **22**[4] was hydroborated with 9-H-9-BBN dimer and the resulting borane **23** subjected to an alkyl-Suzuki cross-coupling reaction with alkenyl triflate **21** (Scheme 4).[18] The resulting alcohol **24** was esterified with acid **9** under Yamaguchi conditions[19] to give diyne **25** in readiness for ring closure. Gratifyingly, this elaborate substrate cyclized smoothly to cycloalkyne **26** when exposed to catalytic amounts of the molybdenum alkylidyne complex **28**, which is arguably the most efficient and, at the same time, most functional group tolerant alkyne metathesis catalyst currently available.[20,21] Product **26** was formed in a spot-to-spot reaction and isolated in 87% yield. The excellent application profile of **28** is ascribed to its triphenylsilanolate ligands. These impart a well-balanced level of Lewis acidity on the Mo^{VI} center, which is high enough to ensure an outstanding catalytic performance, yet sufficiently tempered not to endanger any of the acid-labile motifs in **25**.[20] Most notable is its compatibility with the secondary chloride substituent and the fragile bis(spiroacetal) that forms the northern hemisphere; likewise, the strictly chemoselective metathetic activation of the alkynes in the presence of the alkene moiety is noteworthy.

With cycloalkyne **26** in hand, the stage was set for the spirocyclization meant to forge the BC ring system. To this end, the two PMB ethers in **26** were cleaved with DDQ and the resulting diol **27** treated with catalytic amounts of AuCl or AuCl·SMe_2 in CH_2Cl_2. Although this simple carbophilic Lewis acid had already been used successfully in some advanced spirocyclization reactions,[8,22–24] we were disappointed to find that it furnished exclusively the wrong



Scheme 5. a) AuCl·SMe_2 (10 mol%), CH_2Cl_2, then MeOH, PPTS cat., 36%, see text for details; b) **32** (10 mol%), CH_2Cl_2, 4 Å M.S., 62% (*endo*/*exo* = ca. 5:1); c) PPTS cat., toluene, 80°C, 81%. PPTS = pyridinium *p*-toluenesulfonate.

regioisomer in our case. Indeed, only the highly labile five-membered enol ether was formed by a 5-*exo*-dig cyclization of the C13-OH group onto the alkyne unit (Scheme 5). This compound had to be transformed to the corresponding furanoid methyl glycoside **29** (d.r. = 2.3:1) to avoid decomposition upon work up. No trace of the regioisomeric enol ether **30** formed by 6-*endo* cyclization or the desired spiroacetal could be detected in the crude mixture.[25]

Gratifyingly though, a screening of catalysts showed that this inherent bias of the substrate could be overridden with more advanced gold catalysts bearing bulky ancillary ligands. The best results were obtained with complex **32**,[26] which furnished the six-membered enol ether derivative **30** as the major product. Although the *exo/endo* ratio was somewhat variable in different runs,[27] this result paved the way to spiroketal **31** upon treatment of **30** with catalytic amounts of PPTS in toluene at 80 °C. Under these forcing conditions, the hindered OH group at C21 was found to attack the enol ether bond of **30**, with the formation of the correct doubly anomeric BC ring system in 81 % yield. An X-ray structure analysis of product **31** confirmed its constitution as well as the correct configuration of all the 19 chiral centers set at this stage (Figure 1).

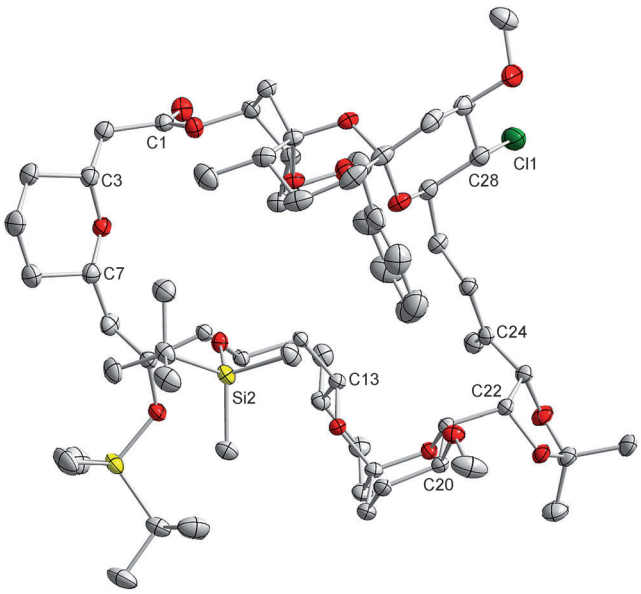
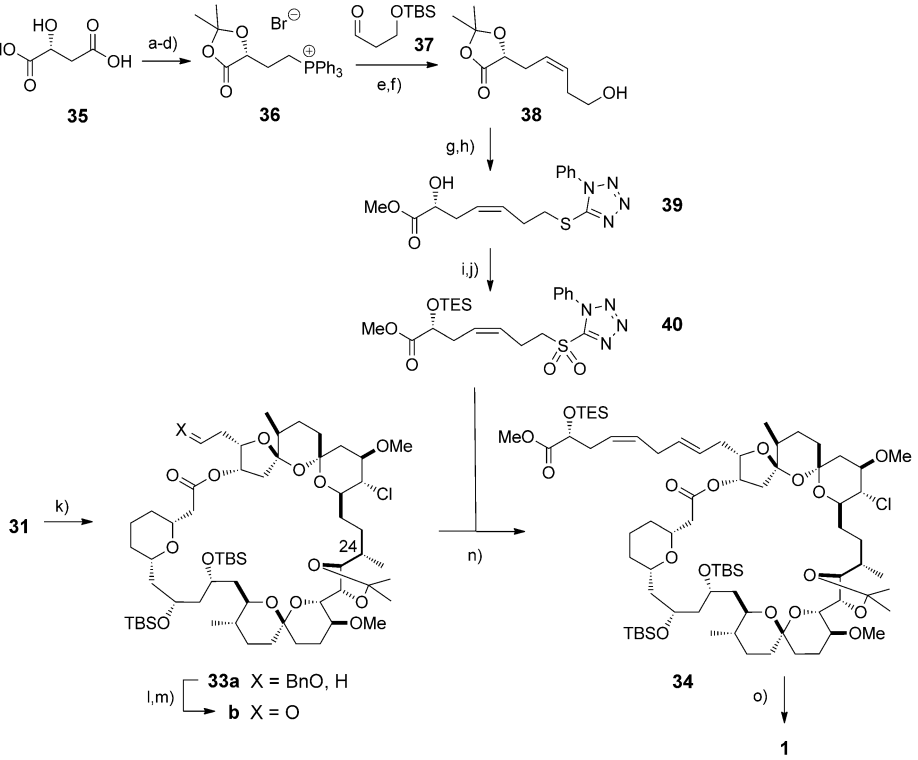


Figure 1. Structure of **31** in the solid state.[28]

Since **31** intercepts our initial total synthesis of **1**,[7b] its elaboration into spirastrellolide F could follow the previously disclosed route based on a fully diastereoselective reduction of the exocyclic double bond at C24. This transformation is directed by the adjacent isopropylidene acetal as the conformational control element, which ensures that hydrogen can be delivered only from the open *Re* face (see Figure 1).[7] Routine management of the protecting groups and oxidation state then allowed the primary benzyl ether in the resulting product **33a** to be cleaved and the released alcohol to be oxidized to aldehyde **33b** as the starting point for the introduction of the side chain. This end game, however, had previously been accomplished in a stepwise manner.[7] Therefore, we chose to revisit this final phase in an attempt to improve on the convergence of the total synthesis (Scheme 6). Accordingly, D-(+)-malic acid (**35**) was transformed into phosphonium salt **36** and the derived ylide treated with the known aldehyde **37**[4] to give *Z*-alkene **38**, which was swiftly converted into sulfone **40**. A Julia–Kocienski olefination[29] between this product and the macrocyclic aldehyde **33b** afforded fully protected spirastrellolide F **34** as a single isomer in 76 % yield. The deprotection of this material to



Scheme 6. a) 2,2-dimethoxypropane, PPTS cat., 84 %; b) BH_3·THF, THF, 0 °C→RT; c) Ph_3PBr_2, imidazole, CH_2Cl_2, 0 °C→RT, 68 % (over two steps); d) PPh_3, MeCN, microwave, 150 °C; e) KHMDS, THF/CH_2Cl_2 (2:1), −78 °C, then **37**, −78 °C→0 °C; f) TBAF, NH_4F, THF, 0 °C→RT, 56 % (over three steps); g) 1-phenyltetrazole-5-thiol, PPh_3, DIAD, THF, 0 °C→RT; h) NaOMe cat., MeOH/CH_2Cl_2 (1:4), 0 °C→RT, 86 % (over both steps); i) $(NH_4)_6Mo_7O_{24}$·$4H_2O$, aq H_2O_2, EtOH, 5 °C, 65 %; j) TESCl, imidazole, CH_2Cl_2, 0 °C→RT, 90 %; k) see Ref. [7]; l) $Pd(OH)_2$ cat., H_2 (1 atm), EtOAc; m) Dess–Martin periodinane, CH_2Cl_2, $NaHCO_3$, 0 °C→RT, 67 % (over two steps); n) **40**, KHMDS, THF, −78 °C→−60 °C, then **33b**, −65 °C, 76 %; o) PPTS cat., MeOH/Et_2O/H_2O (7:2:1), 50 °C, 55 %. KHMDS = potassium hexamethyldisilazide, DIAD = diisopropylazodicarboxylate, TES = triethylsilyl.

the targeted marine natural product as its methyl ester was performed with PPTS in a mixed solvent system, as previously described.[7]

In summary, a concise second-generation total synthesis of the complex antimitotic macrolide spirastrellolide F methyl ester (**1**) has been achieved. It features the power of contemporary metal-catalyzed alkyne chemistry in the metathetic closure of the macrocyclic scaffold and the subsequent formation of the southern acetal domain by carbophilic activation of the π bond. Together with an improved strategy for the introduction of the labile side chain, this conceptually new route to **1** opens the door for further investigations into this demanding family of target molecules. At the same time, this case study helps to widen the scope of ring-closing alkyne metathesis beyond the formation of stereodefined cycloalkenes by semireduction of the products primarily formed, which previously constituted the major application of this powerful transformation.[30,31]

Received: May 12, 2011
Published online: July 26, 2011

Keywords: alkyne metathesis · gold · molybdenum · natural products · total synthesis

[1] a) D. E. Williams, M. Roberge, R. Van Soest, R. J. Andersen, *J. Am. Chem. Soc.* **2003**, *125*, 5296 – 5297; b) D. E. Williams, M. Lapawa, X. Feng, T. Tarling, M. Roberge, R. J. Andersen, *Org. Lett.* **2004**, *6*, 2607 – 2610; c) D. E. Williams, R. A. Keyzers, K. Warabi, K. Desjardine, J. L. Riffell, M. Roberge, R. J. Andersen, *J. Org. Chem.* **2007**, *72*, 9842 – 9845; d) K. Warabi, D. E. Williams, B. O. Patrick, M. Roberge, R. J. Andersen, *J. Am. Chem. Soc.* **2007**, *129*, 508 – 509.

[2] For reviews on phosphatase inhibitors, see a) A. McCluskey, A. T. R. Sim, J. A. Sakoff, *J. Med. Chem.* **2002**, *45*, 1151 – 1175; b) R. E. Honkanen, T. Golden, *Curr. Med. Chem.* **2002**, *9*, 2055 – 2075; c) L. Bialy, H. Waldmann, *Angew. Chem.* **2005**, *117*, 3880 – 3906; *Angew. Chem. Int. Ed.* **2005**, *44*, 3814 – 3839.

[3] a) I. Paterson, E. A. Anderson, S. M. Dalby, O. Loiseleur, *Org. Lett.* **2005**, *7*, 4121 – 4224; b) I. Paterson, E. A. Anderson, S. M. Dalby, O. Loiseleur, *Org. Lett.* **2005**, *7*, 4125 – 4128; c) J. Liu, R. P. Hsung, *Org. Lett.* **2005**, *7*, 2273 – 2276; d) Y. Pan, J. K. De Brabander, *Synlett* **2006**, 853 – 856; e) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, P. Maltas, C. Moessner, *Chem. Commun.* **2006**, 4186 – 4188; f) C. Wang, C. J. Forsyth, *Org. Lett.* **2006**, *8*, 2997 – 3000; g) J. Liu, J. H. Yang, C. Ko, R. P. Hsung, *Tetrahedron Lett.* **2006**, *47*, 6121 – 6123; h) I. Paterson, E. A. Anderson, S. M. Dalby, J. Genovino, J. H. Lim, C. Moessner, *Chem. Commun.* **2007**, 1852 – 1854; i) A. B. Smith, D.-S. Kim, *Org. Lett.* **2007**, *9*, 3311 – 3314; j) C. Wang, C. J. Forsyth, *Heterocycles* **2007**, *72*, 621 – 632; k) K. A. Keaton, A. J. Phillips, *Org. Lett.* **2008**, *10*, 1083 – 1086; l) S. Chandrasekhar, C. Rambabu, A. S. Reddy, *Org. Lett.* **2008**, *10*, 4355 – 4357; m) J.-H. Yang, J. Liu, R. P. Hsung, *Org. Lett.* **2008**, *10*, 2525 – 2528; n) J. L.-Y. Chen, M. A. Brimble, *Chem. Commun.* **2010**, *46*, 3967 – 3969; o) A. B. Smith, H. Smits, D. S. Kim, *Tetrahedron* **2010**, *66*, 6597 – 6605; p) G. Sabitha, A. S. Rao, J. S. Yadav, *Synthesis* **2010**, 505 – 509.

[4] a) A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout, K. Radkowski, *Angew. Chem.* **2006**, *118*, 5632 – 5636; *Angew. Chem. Int. Ed.* **2006**, *45*, 5506 – 5510; b) A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout, K. Radkowski, *Angew. Chem.* **2006**, *118*, 5636 – 5641; *Angew. Chem. Int. Ed.* **2006**, *45*, 5510 – 5515; c) A. Fürstner, B. Fasching, G. W. O'Neil, M. D. B. Fenster, C. Godbout, J. Ceccon, *Chem. Commun.* **2007**, 3045 – 3047.

[5] I. Paterson, S. M. Dalby, *Nat. Prod. Rep.* **2009**, *26*, 865 – 873.

[6] a) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, J. Genovino, P. Maltas, C. Moessner, *Angew. Chem.* **2008**, *120*, 3058 – 3062; *Angew. Chem. Int. Ed.* **2008**, *47*, 3016 – 3020; b) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, J. Genovino, P. Maltas, C. Moessner, *Angew. Chem.* **2008**, *120*, 3063 – 3067; *Angew. Chem. Int. Ed.* **2008**, *47*, 3021 – 3025; c) I. Paterson, S. M. Dalby, P. Maltas, *Isr. J. Chem.* **2011**, *51*, 406 – 419.

[7] a) G. W. O'Neil, J. Ceccon, S. Benson, M.-P. Collin, B. Fasching, A. Fürstner, *Angew. Chem.* **2009**, *121*, 10124 – 10129; *Angew. Chem. Int. Ed.* **2009**, *48*, 9940 – 9945; b) S. Benson, M.-P. Collin, G. W. O'Neil, J. Ceccon, B. Fasching, M. D. B. Fenster, C. Godbout, K. Radkowski, R. Goddard, A. Fürstner, *Angew. Chem.* **2009**, *121*, 10130 – 10134; *Angew. Chem. Int. Ed.* **2009**, *48*, 9946 – 9950.

[8] a) K. Utimoto, *Pure Appl. Chem.* **1983**, *55*, 1845 – 1852; b) B. Liu, J. K. De Brabander, *Org. Lett.* **2006**, *8*, 4907 – 4910; c) A. Aponick, C.-Y. Li, J. A. Palmes, *Org. Lett.* **2009**, *11*, 121 – 124; d) review: B. Alcaide, P. Almendros, J. M. Alonso, *Org. Biomol. Chem.* **2011**, *9*, 4405 – 4416.

[9] a) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478 – 3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410 – 3449; b) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395 – 403; c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326 – 3350; d) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180 – 3211.

[10] a) A. Fürstner, G. Seidel, *Angew. Chem.* **1998**, *110*, 1758 – 1760; *Angew. Chem. Int. Ed.* **1998**, *37*, 1734 – 1736; b) A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, *121*, 11108 – 11113; c) A. Fürstner, C. Mathes, C. W. Lehmann, *Chem. Eur. J.* **2001**, *7*, 5299 – 5317.

[11] a) A. Fürstner, P. W. Davies, *Chem. Commun.* **2005**, 2307 – 2320; b) W. Zhang, J. S. Moore, *Adv. Synth. Catal.* **2007**, *349*, 93 – 120; c) R. R. Schrock, C. Czekelius, *Adv. Synth. Catal.* **2007**, *349*, 55 – 77; d) X. Wu, M. Tamm, *Beilstein J. Org. Chem.* **2011**, *7*, 82 – 93.

[12] a) A. Labonne, T. Kribber, L. Hintermann, *Org. Lett.* **2006**, *8*, 5853 – 5856; b) L. Hintermann, T. T. Dang, A. Labonne, T. Kribber, L. Xiao, P. Naumov, *Chem. Eur. J.* **2009**, *15*, 7167 – 7179; c) F. Boeck, T. Kribber, L. Xiao, L. Hintermann, *J. Am. Chem. Soc.* **2011**, *133*, 8138 – 8141; d) L. Hintermann in *C-X Bond Formation*, *Vol. 31* (Ed.: A. Vigalok), Springer, Berlin, *Top. Organomet. Chem.* **2010**, pp. 123 – 155.

[13] a) S. Ohira, *Synth. Commun.* **1989**, *19*, 561 – 564; b) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521 – 522.

[14] K. Hattori, H. Yamamoto, *J. Org. Chem.* **1993**, *58*, 5301 – 5303.

[15] M. S. M. Timmer, A. Abidekian, P. H. Seeberger, *Angew. Chem.* **2005**, *117*, 7777 – 7780; *Angew. Chem. Int. Ed.* **2005**, *44*, 7605 – 7607.

[16] Y.-G. Suh, B.-A. Koo, E.-N. Kim, N.-S. Choi, *Tetrahedron Lett.* **1995**, *36*, 2089 – 2092.

[17] Triflimide **20** was preferred over $PhN(Tf)_2$ or Comins reagent because the by-products formed were more readily separable from the enol triflate. Moreover, this reagent can be sublimed, thus ensuring dryness and hence high yields in the reaction with the enolate, cf. Ref. [7].

[18] a) N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314 – 321; b) review: S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676 – 4701; *Angew. Chem. Int. Ed.* **2001**, *40*, 4544 – 4568.

[19] Review: A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.* **2006**, *106*, 911 – 939.

[20] J. Heppekausen, R. Stade, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 11045 – 11057.

[21] a) V. Hickmann, M. Alcarazo, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 11042 – 11044; b) K. Micoine, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 14064 – 14066.

[22] a) Y. Li, F. Zhou, C. J. Forsyth, *Angew. Chem.* **2007**, *119*, 283 – 286; *Angew. Chem. Int. Ed.* **2007**, *46*, 279 – 282; b) B. M. Trost, B. M. O′Boyle, *J. Am. Chem. Soc.* **2008**, *130*, 16190 – 16192; c) B. M. Trost, B. M. O′Boyle, D. Hund, *J. Am. Chem. Soc.* **2009**, *131*, 15061 – 15074; d) C. Fang, Y. Pang, C. J. Forsyth, *Org. Lett.* **2010**, *12*, 4528 – 4531.

[23] For a leading study on the formation of enol ethers in the context of natural product synthesis from hydroxy-alkynes by means of gold catalysis, see a) B. M. Trost, G. Dong, *Nature* **2008**, *456*, 485 – 488; b) B. M. Trost, G. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 16403 – 16416.

[24] A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208 – 3221.

[25] Other catalysts such as $AuCl_3$ or $PtCl_4$ decomposed the starting material.

[26] C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178 – 6179.

[27] This is ascribed to the instability of the furanoid product; its decomposition may alter the observed ratio.

[28] Anisotropic displacement parameters are drawn at the 50% probability level. CCDC 824552 contains 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.

[29] P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley, *Synlett* **1998**, 26 – 28.

[30] For further applications of RCAM to the formation of products other than stereodefined olefins, see a) A. Fürstner, A.-S. Castanet, K. Radkowski, C. W. Lehmann, *J. Org. Chem.* **2003**, *68*, 1521 – 1528; b) A. Fürstner, O. Larionov, S. Flügge, *Angew. Chem.* **2007**, *119*, 5641 – 5644; *Angew. Chem. Int. Ed.* **2007**, *46*, 5545 – 5548; c) A. Fürstner, S. Flügge, O. Larionov, Y. Takahashi, T. Kubota, J. Kobayashi, *Chem. Eur. J.* **2009**, *15*, 4011 – 4029.

[31] For representative total syntheses relying on an RCAM/semi-reduction, see Ref. [21] and the following: a) V. V. Vintonyak, M. E. Maier, *Angew. Chem.* **2007**, *119*, 5301 – 5303; *Angew. Chem. Int. Ed.* **2007**, *46*, 5209 – 5211; b) B. J. Smith, G. A. Sulikowski, *Angew. Chem.* **2010**, *122*, 1643 – 1646; *Angew. Chem. Int. Ed.* **2010**, *49*, 1599 – 1602; c) M. G. Nilson, R. L. Funk, *Org. Lett.* **2010**, *12*, 4912 – 4915; d) A. Fürstner, M. Bindl, L. Jean, *Angew. Chem.* **2007**, *119*, 9435 – 9438; *Angew. Chem. Int. Ed.* **2007**, *46*, 9275 – 9278; e) A. Fürstner, D. De Souza, L. Turet, M. D. B. Fenster, L. Parra-Rapado, C. Wirtz, R. Mynott, C. W. Lehmann, *Chem. Eur. J.* **2007**, *13*, 115 – 134; f) A. Fürstner, L. Turet, *Angew. Chem.* **2005**, *117*, 3528 – 3532; *Angew. Chem. Int. Ed.* **2005**, *44*, 3462 – 3466; g) A. Fürstner, K. Radkowski, J. Grabowski, C. Wirtz, R. Mynott, *J. Org. Chem.* **2000**, *65*, 8758 – 8762; h) A. Fürstner, K. Grela, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **2000**, *122*, 11799 – 11805.

