CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201203965

VIP

A Total Synthesis of Spirastrellolide A Methyl Ester

Alexander Arlt, Stefan Benson, Saskia Schulthoff, Barbara Gabor, and Alois Fürstner*[a]

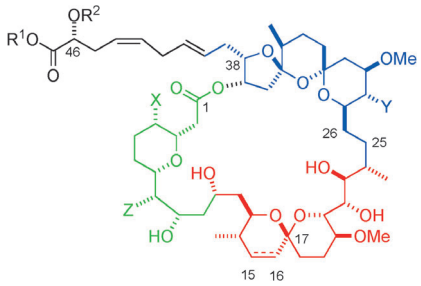
Abstract: A concise total synthesis of spirastrellolide A methyl ester (**1a**, R^1 = Me) as the parent compound of a series of highly cytotoxic marine macrolides is disclosed, which exploits and expands the flexibility of a synthesis plan previously developed by our group en route to the sister compound spirastrellolide F methyl ester (**6a**, R^1 = Me). Key to success was the masking of the signature $\Delta^{15,16}$-bond of **1a** as a C16-carbonyl group until after the stereogenic center at C24 had been properly set by a highly selective hydrogenation of the C24 *exo*-methylene precursor **66**. Conformational control over the macrocyclic frame allowed the proper stereochemical course to be dialed into this reduction process. The elaboration of the C16 ketone to the C15–C16 double bond was accomplished by a chemoselective alkenyl triflate formation followed by a palladium-catalyzed hydride delivery. The role of the ketone at C16 as a strategic design element is also evident up-stream of the key intermediate **66**, the assembly of which hinged upon the addition of the polyfunctionalized dithiane **37** to the similarly elaborate aldehyde fragment **46**. Other crucial steps of the total synthesis were an alkyl-Suzuki coupling and a Yamaguchi lactonization that allowed the Northern and the Southern sector of the target to be stitched together and the macrocyclic perimeter to be forged. The lateral chain comprising the remote C46 stereocenter was finally attached to the core region by a modified Julia–Kocienski olefination. The preparation of the individual building blocks led to some methodological spin-offs, amongst which the improved procedure for the N–O-bond cleavage of isoxazolines by zero-valent molybdenum and the ozonolysis of a double bond in the presence of other oxidation-prone functionality are most noteworthy. Preliminary biological data suggest that the entire carbon framework, that is the macrocyclic core plus the lateral chain, might be necessary for high cytotoxicity.

Keywords: antitumor agents · macrolides · natural products · phosphatase inhibitors · total synthesis

Introduction

An innovative cell-based assay for antimitotic agents allowed the Anderson group to perform a high-throughput evaluation of more than 24000 extracts from marine and terrestrial organisms of the animal and plant kingdoms.[1] One of the hits of this screening campaign was the methanol extract of the marine invertebrate *Spirastrella coccinea* collected in the Atlantic off Dominica, which elicited an unusual phenotypic response. A total of seven closely related macrolides, dubbed spirastrellolides A–G (**1–7**), were isolated from these extracts in form of the corresponding methyl esters (R^1 = Me) (Table 1). The individual family members were found similarly potent in triggering premature cell cycle arrest.[2–4] Unlike many other antimitotic agents, however, they do not interfere with tubulin dynamics but rather seem to target protein phosphatases (PP), in particular PP2A, which is inhibited by the parent compound **1** with an IC_{50} of ≈1 nM.[5] Because of this remarkable potency, the

Table 1. Structures of the spirastrellolides; the color-coded sectors indicate the stereoclusters, the relative stereochemistry of which could originally be assigned in 2004, but the mutual relationship between them remained unknown.[7] The full stereostructure of the natural products was established as shown only in late 2007.[3,4]



	△[15,16]	R^1	R^2	X	Y	Z
spirastrellolide A (**1**)	√	H	H	H	Cl	H
spirastrellolide B (**2**)	–	H	H	H	H	H
spirastrellolide C (**3**)	–	H	H	H	H	OH
spirastrellolide D (**4**)	√	H	H	Cl	Cl	H
spirastrellolide E (**5**)	√	H	H	H	H	H
spirastrellolide F (**6**)	–	H	H	H	Cl	H
spirastrellolide G (**7**)	√	H	Me	H	Cl	H

[a] Dipl.-Chem. A. Arlt, Dr. S. Benson, S. Schulthoff, B. Gabor, Prof. A. Fürstner
Max-Planck-Institut für Kohlenforschung
45470 Mülheim/Ruhr (Germany)
Fax: (+49) 208306-2994
E-mail: fuerstner@kofo.mpg.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201203965.

spirastrellolides might qualify as tools for chemical biology and eventually even as lead structures in the quest for novel therapeutic agents for the treatment of metabolic disorders and/or cancer, if the supply problem can be overcome. In this context, it is important to note that the free acids **1** and **2** ($R^1=H$) have lately been re-isolated from an *Epipolasis* sponge harvested in the East China Sea.[6] This finding strongly suggests that the spirastrellolides might not be innate secondary metabolites of the sponges themselves but rather be of bacterial origin. With the re-extracted materials, it was also possible to show that the free acids ($R^1=H$) and the derived methyl esters ($R^1=Me$) exhibit similarly high levels of cytotoxicity against the tested HeLa cell line.[6]

The very intriguing biological profile of the spirastrellolides is encoded in a molecular framework of exquisite complexity. The elucidation of their intricate topology and the unusual stereochemical features was highly challenging, not least because of the small amounts of material available from the natural sources. While advanced NMR spectroscopy had allowed the relative configuration of the color-coded segments within the polyketide frame to be established early on (Table 1),[7] the relationship between these domains could be unraveled only more than four years after the first report. At this point, a re-isolation campaign had provided enough material for chemical derivatization. Specifically, a truncated derivative of **2** could be crystallized, allowing the absolute stereochemistry of the macrocyclic perimeter to be determined by X-ray diffraction;[3] the configuration of the lateral stereocenter at C46 had to be elucidated via chemical correlation.[4]

Although the spirastrellolides aroused considerable interest immediately after their disclosure and prompted remarkable chemical creativity, the lasting uncertainty about their identity imposed severe constraints upon any synthetic endeavor. As long as the relationship between the color-coded stereoclusters of **1** (or congeners) was unclear, no less than 16 possible isomers had to be considered as the potential target and all approaches until late 2007 could not help but envisage fragment coupling processes at or close to the borders of these domains. This notion is evident from the exploratory studies published by a sizeable number of research groups.[8–10] Even the first total syntheses of spirastrellolide A methyl ester (**1a**, $R^1=Me$) published by Paterson and co-workers in 2008 and of spirastrellolide F methyl ester (**6a**, $R^1=Me$) disclosed by our group in 2009 still reflect this limited freedom to operate.[11,12] Once the uncertainty had vanished and the structures were established and confirmed, both teams followed up with "second-generation" total syntheses of the very same targets, which took advantage of the acquired greater strategic flexibility. Notably, the Paterson group postponed the macrolactonization event until after completion of the entire carbon framework.[13] This tactics was clearly more productive than the originally pursued attachment of the lateral chain to a truncated macrocycle, which had turned out to be more challenging than anticipated. Our own second-generation synthesis of **6a** features an even more profound change, as the site of ring closure was shifted away from the lactone to the C16–C17 bond flanking the conspicuous spiroketal center at C17.[14] This ambitious plan could be successfully reduced to practice by recourse to the power of ring-closing alkyne metathesis[15,16] in concert with a gold-catalyzed activation of the resulting triple bond toward a transannular spiroacetalization reaction (Scheme 1).[17]

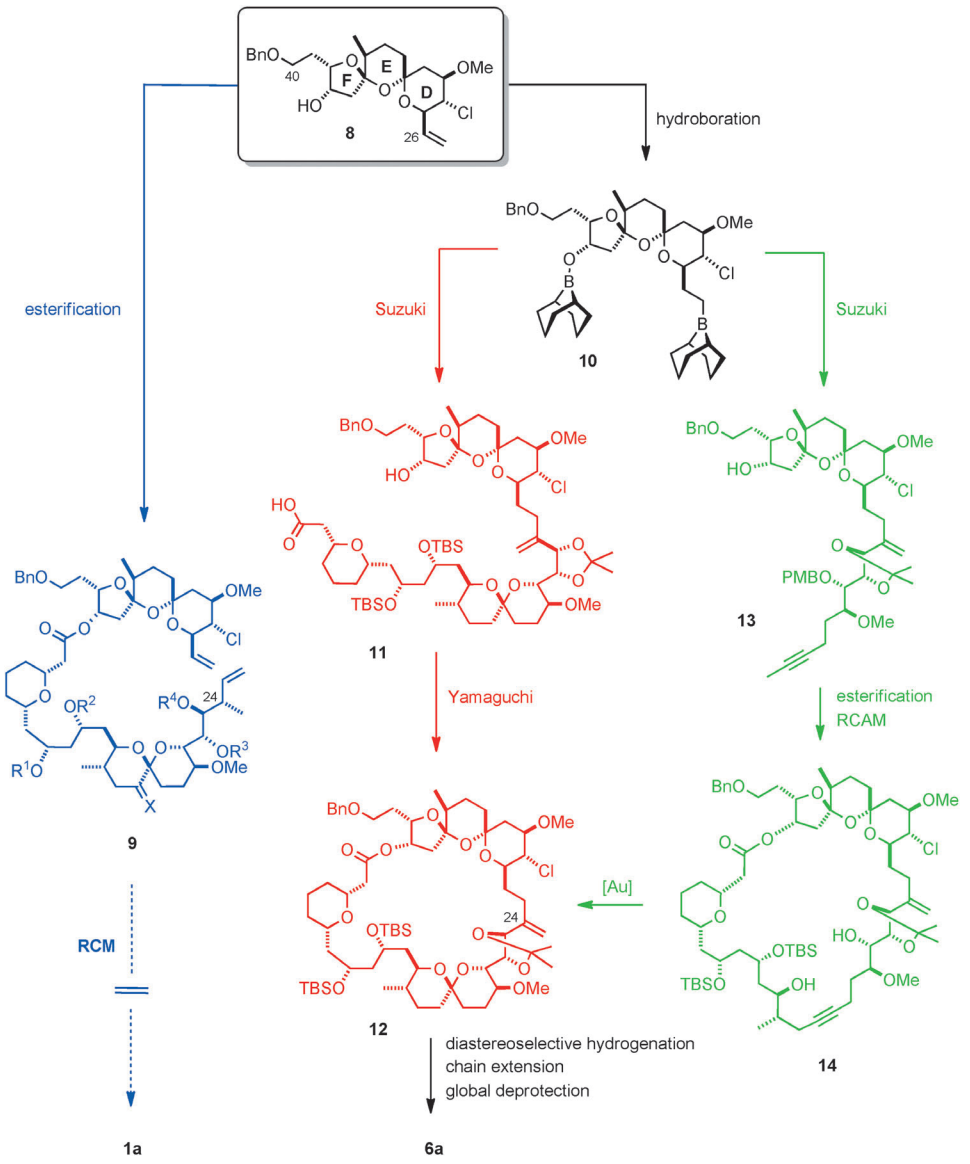
In the present publication we expand our investigations into this enticing family of marine natural products beyond spirastrellolide F. Although the total synthesis of spirastrellolide A methyl ester (**1a**) outlined below has certainly benefitted from our previous work (Scheme 2), care was taken to refine the preparation and assembly of the required building blocks while solving the additional selectivity problems posed by this exigent target.

Results and Discussion

Retrosynthetic analysis: As previously discussed in some detail, our original synthesis plan had hinged upon the formation of the macrocycle of the spirastrellolides at the nonstereogenic C25–C26 bond by olefin metathesis, which—unfortunately—was unsuccessful, despite considerable experimentation (Scheme 2, blue route).[18] Prompted by this failure, the approach toward spirastrellolide F was reprogrammed toward the use of an alkyl-Suzuki reaction.[19] This revised tactics allowed us to utilize the rather sensitive "Northern" sector **8** unchanged, while effecting the critical C–C-bond formation one carbon atom further away from the very bulky and rigid DEF-bisspiroketal unit (Scheme 2, red and green routes).[12,14]

The price to be paid for this amendment was the stereochemical uncertainty during the subsequent hydrogenation of the resulting C24 *exo*-methylene group in **12** to the methyl branch. Careful conformational analysis, however, had suggested that protection of the adjacent hydroxyl groups at C22 and C23 in the form of an isopropylidene acetal provides a handle to control the course of the reduction. This conjecture turned out to be correct: the properly configured compound was obtained as the only detectable product, when **12** was hydrogenated with the aid of a modified Crabtree catalyst. Furthermore, X-ray diffraction data confirmed our original design strategy by revealing the conformational features that account for the exquisite substrate-control over this transformation.[12] Therefore, the Suzuki reaction/hydrogenation sequence is considered a stronghold of our approaches to **6a**, which converge at this point (cf., Scheme 1).

If one were to retain this favorable strategic maneuver en route to spirastrellolide A (**1**), the timing of events becomes a critical issue: specifically, the $\Delta^{[15,16]}$ unsaturation within the B-ring of this target can only be revealed at a late stage of the synthesis after the *exo*-methylene group has been reduced (Scheme 2). Reasoning that a carbonyl group at C16 might serve as an adequate orthogonal double bond surrogate, we opted for a dithiane-based fragment coupling for



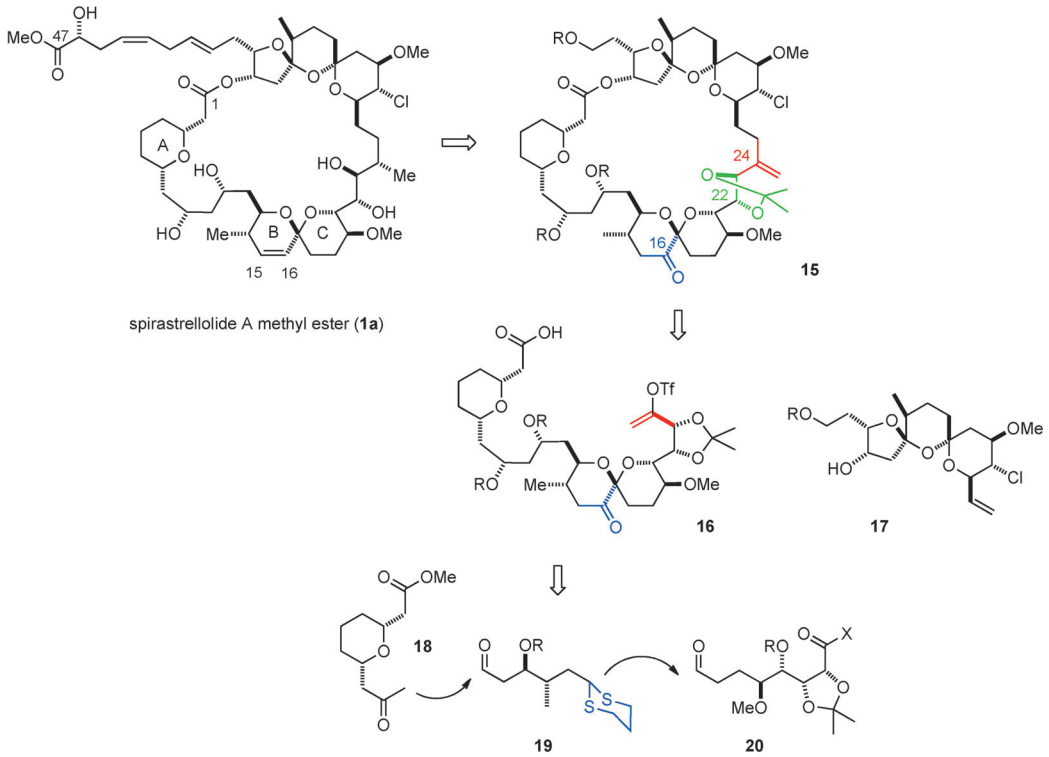
Scheme 1. Summary of the approaches to the spirastrellolides published by our group: original but unsuccessful RCM-based route toward spirastrellolide A methyl ester (**1a**, blue);[18] first successful total synthesis of spirastrellolide F methyl ester (**6a**, R^1 = Me) by a Suzuki/Yamaguchi route (red);[12] second generation synthesis of **6a** comprising a Suzuki coupling, an RCAM-based macrocyclization and a Au-catalyzed transannular spiroketalization (green), cf. text.[14]

the assembly of the target's "Southern" domain. While this rationale echoes our own exploratory studies in this field,[9] the preparation of the required fragments **16**–**20** would draw from the knowledge gained since then. Provided that this route brings the macrocyclic array **15** into reach, the lateral chain could then be attached via a modified Julia–Kocienski olefination[20] that had distinguished our second-generation synthesis of the sister compound **6a**.[14]

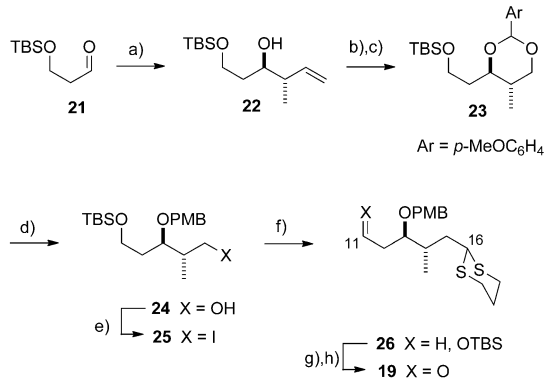
The C1–C16 dithiane fragment: For the construction of the short dithiane fragment **19** we adapted our previous synthesis of a similar fragment to the current needs (Scheme 3).[9a] Specifically, mono-TBS-protected 1,3-propanediol was oxidized and the resulting aldehyde **21** immediately subjected to a Brown crotylation[21] to yield compound **22** in high enantiomeric and diastereomeric excess. Cleavage of the double bond by ozonolysis followed by a reductive workup using sodium borohydride was effective but furnished a crude product that contained considerable amounts of boron impurities as determined by ^{11}B NMR spectroscopy. Gratifyingly, the desired diol was isolated in excellent purity without the need for column chromatography by simply stirring a solution of the material in THF with aqueous NaOH (15% w/w). Treatment with anisaldehyde dimethylacetal and catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) in the presence of molecular sieves yielded the *p*-methoxyphenyl acetal **23** as a 3:1 mixture of epimers at the benzylic position. For the sake of convenience of characterization, the mixture can be equilibrated to the more stabile isomer with an equatorially-disposed phenyl group upon treatment with camphorsulfonic acid (CSA).[22]

The acetal ring of **23** was then reductively opened on treatment with DIBAl-H[23] to give the secondary PMB-ether **24**; this reaction had to be performed at low temperature to avoid cleavage of the primary TBS group.[24] Alcohol **24** was transformed into the corresponding iodide **25**, which served to alkylate lithiated 1,3-dithiane. Recourse to the previously developed slow addition protocol furnished the desired product **26** in good yield while minimizing the competing elimination of HI.[9a] A standard desilylation using TBAF gave the corresponding primary alcohol, which was oxidized under Parikh–Doering conditions[25] to aldehyde **19** in readiness for chain elongation.

The required coupling partner **18** was best prepared by a modification of our original route (Scheme 4).[9] Specifically, Weiler-dianion alkylation of **27**[26] with bromide **28** followed by a Noyori-type reduction of the resulting β-ketoester **29** in the presence of catalytic amounts of HCl gave product **30** in



Scheme 2. Retrosynthetic analysis, accounting for the need to unravel the $\Delta^{[15,16]}$-bond of the target late in the synthesis, only after the chiral center at C24 has been properly set by substrate-controlled hydrogenation of the *exo*-methylene group formed in the projected cross coupling.

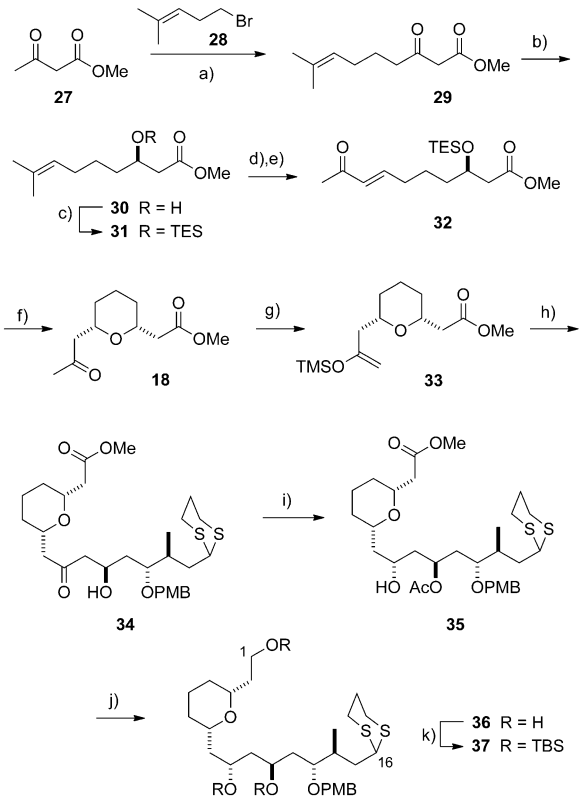


Scheme 3. a) (−)-[(*E*)-crotyl]B(ipc)$_2$, THF, −78 °C, 82 %, 94 % *ee*, 95 % *de*; b) i) O_3, MeOH, CH_2Cl_2, −78 °C; ii) $NaBH_4$, −78 °C → RT, then 15 % aq. NaOH, THF, 93 %; c) *p*MeOC_6H_4CH(OMe)$_2$, PPTS, CH_2Cl_2, MS 4 Å, 89 %, d.r. 3:1; d) DIBAl-H, CH_2Cl_2, −60 °C, 82 %; e) I_2, PPh_3, imidazole, THF, 0 °C, quant.; f) 1,3-dithiane, *n*BuLi, THF, DMPU, −78 °C→RT, 81 %; g) TBAF, THF, 0 °C → RT, 98 %; h) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C, 85 %; RT = room temperature, PPTS = pyridinium *p*-toluenesulfonate, ipc = isopinocampheyl, MS = molecular sieves, DIBAl-H = diisobutylaluminiumhydride, DMPU = *N*,*N*′-dimethylpropylenurea, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl; PMB = *p*-methoxybenzyl.

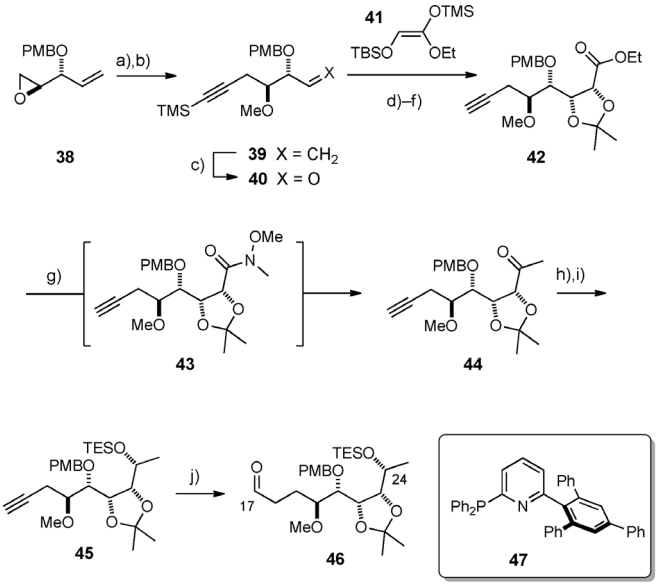
excellent optical purity, leaving the trisubstituted alkene untouched;[27,28] this compound was O-silylated to give the TES-ether **31** prior to ozonolytic cleavage of the double bond. The resulting aldehyde reacted cleanly with the stabilized ylide Ph_3P=CC(O)Me to give the corresponding enone **32**, which was treated with camphorsulfonic acid to cleave the silyl ether and cause a spontaneous oxa-Michael addition with formation of the desired pyrane derivative **18**. Although the same product can also be reached by processing the free alcohol **30** directly, the temporary TES protection was found beneficial in terms of yield, selectivity and material throughput.[29]

Under soft enolization conditions, ketone **18** was cleanly transformed into silyl enol ether **33**, which underwent a productive Mukaiyama aldol reaction with aldehyde **19** in the presence of BF_3·Et_2O as promoter.[30] In line with our previous experiences, the subsequent 1,3-*anti* reduction of the carbonyl group in the resulting product **34** was best effected by the Evans–Tishchenko protocol,[31] without the dithioacetal interfering.[32] Cleavage of the concomitantly installed acetate moiety and simultaneous reduction of the methyl ester terminus of **35** was accomplished with DIBAl-H in preparation for the upcoming lithiation of the dithiane during the envisaged fragment coupling. Prior to this critical event, the three hydroxyl groups in **36** had to be protected upon exposure of the crude material from the DIBAl-step to TBSOTf/lutidine under standard conditions.

The C17–C24 fragment: The challenging stereotetrad comprised within the C17–C24 sector of the target was built-up starting from epoxide **38**, which in turn derives from divinylcarbinol via Sharpless asymmetric epoxidation and O-protection as previously described.[33] BF_3·Et_2O-mediated opening of the oxirane ring by lithiated TMS-acetylene followed by methylation of the resulting hydroxyl group with *n*BuLi/



Scheme 4. a) NaH, *n*BuLi, then **28**, THF, 0 °C→RT, 55 %; b) $[Ru_2Cl_5((R)\text{-binap})_2][Et_2NH_2]$, HCl cat., H_2 (5 bar), MeOH, 45 °C, 93 % (>98 % *ee*); c) TESCl, imidazole, CH_2Cl_2, 0 °C→RT, quant.; d) i) O_3, CH_2Cl_2/MeOH/pyridine 5:5:1, −78 °C; ii) Me_2S, 78 °C→RT, 83 %; e) $Ph_3P{=}C(O)Me$, toluene, 110 °C, 79 %; f) CSA, CH_2Cl_2/MeOH 4:1, −30 °C, 85 % (>99 % *ee*); g) TMSOTf, *i*Pr_2NEt, CH_2Cl_2, −78 °C; h) **19**, $BF_3{\cdot}OEt_2$, −78 °C, 88 %, d.r. 93:Σ7; i) SmI_2, MeCHO, THF, −11 °C, 95 %, d.r. 90/Σ10; j) DIBAL-H, toluene, −78 °C→RT, quant.; k) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT, 90 %; TES = triethylsilyl; Tf = trifluoromethanesulfonyl.



Scheme 5. a) TMSC≡CH, *n*BuLi, THF, −78 °C, then **38**, $BF_3{\cdot}OEt_2$, −78 °C, 94 %; b) *n*BuLi, MeOTf, THF, −78→0 °C, 95 %; c) i) O_3, MeOH, CH_2Cl_2, −78 °C; ii) Me_2S, −78 °C→RT, 80 %, see text; d) **41**, $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, −78 °C→RT, d.r. ≥16:1; e) TBAF, THF, 0 °C, 73 % (2 steps); f) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 0 °C→RT, 82 %; g) HN(OMe)Me·HCl, MeMgBr, THF, −8 °C→RT, 91 %; h) L-selectride, $NaOH/H_2O_2$, THF, −78 °C, 89 %; i) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95 %; j) $[CpRu(MeCN)_3]PF_6$ (2 mol %), **47** (4 mol %), MeCN, 60 °C; ii) **45**, H_2O, acetone, 50 °C, 95 %; L-selectride = lithium tri-*sec*-butyl(hydrido)-borate; CSA = camphorsulfonic acid, Cp = cyclopentadienyl.

MeOTf afforded product **39** in good yield, which displays an alkyne and an alkene terminus meant to serve as orthogonal aldehyde surrogates (Scheme 5). First, the olefinic site had to be oxidatively cleaved as prelude for a subsequent glycolate aldol reaction. In our previous campaign, a similar transformation had been accomplished by dihydroxylation under Sharpless conditions followed by cleavage of the resulting diol with $Pb(OAc)_4$.[12] Despite some optimization, however, the overall yield remained moderate and the use of expensive and/or hardly benign reagents was deemed suboptimal, particularly on a larger scale.

We therefore sought to replace this two-step procedure by ozonolysis, even though we were apprehensive that the electron-rich *p*-methoxybenzyl ether as well as the TMS-protected alkyne present in **39** might be prone to overoxidation. Although the reactions were closely monitored by using different dies as indicators (Sudan red 7B, Sudan III),[34] the results remained erratic and the yields rather disappointing.[35] In all runs, a methyl ester derivative formed by cleavage of the alkyne moiety was isolated as a major byproduct, suggesting that the dosing of the oxidant was a significant problem when passing a stream of ozone through the reaction mixture. We reasoned that the use of a saturated stock solution of ozone in dichloromethane might solve the selectivity problem.[36] In fact, this change in the experimental setup allowed the olefin site of **39** to be selectively cleaved to give the desired aldehyde **40** in high yield. The ozone solution was slowly added via a jacketed addition funnel cooled to −78 °C to a solution of the substrate at the same temperature and the conversion closely monitored by thin-layer chromatography. Under these conditions, well reproducible results were obtained even upon scale up of the reaction.

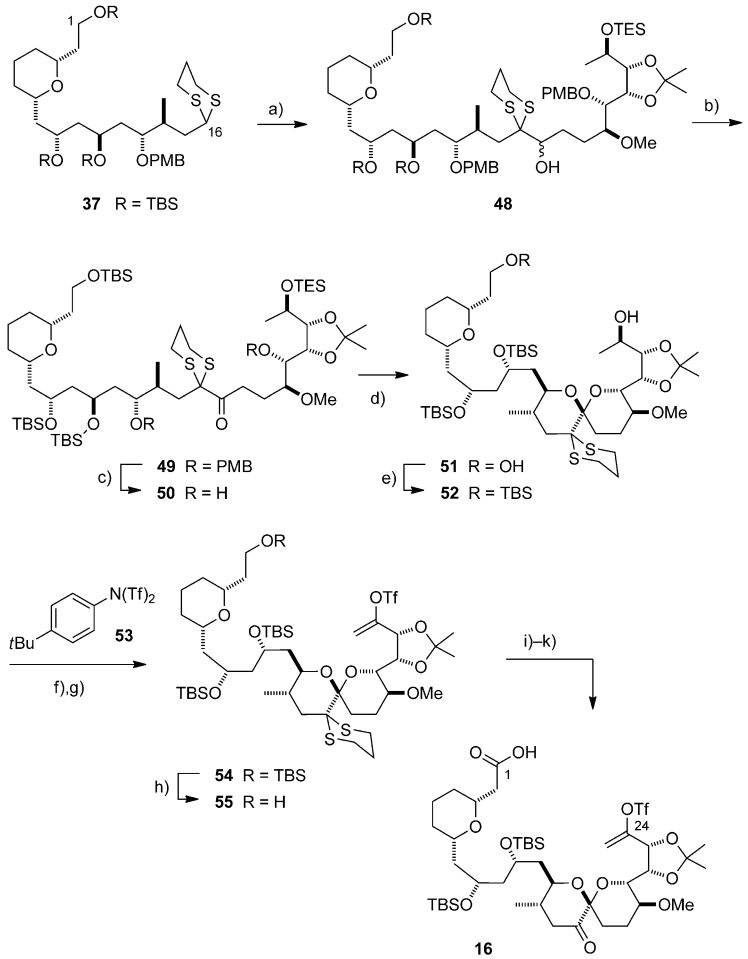
Delighted with the efficiency of this transformation, we went on to set the yet missing two stereocenters by a $MgBr_2{\cdot}OEt_2$-mediated glycolate aldol reaction of aldehyde **40** with the known silyl ketene acetal **41**.[37,38] Changing the solvent from toluene to dichloromethane increased the diastereoselectivity from 3:1 to ≥16:1 (determined by HPLC after global desilylation of the product), while retaining the excellent productivity of this transformation.

In preparation for the fragment coupling by addition of the lithiated dithiane **37**, it was originally planned to convert the ester site of **42** into the corresponding Weinreb amide[39] and the alkyne terminus into the required aldehyde. In so doing, however, it was observed that treatment of **42** with HN(OMe)Me·HCl and *i*PrMgCl furnished substantial amounts of the corresponding isopropyl ketone. Taking advantage of this unexpected course, *i*PrMgCl was replaced by an excess of MeMgBr;[40] in fact, its use furnished the

methyl ketone **44** directly and in good yield without the need for the isolation of the Weinreb amide **43** that must have been transiently formed. This smooth conversion completed the carbon backbone of the C17–C24 synthon. To avoid any selectivity issue during the dithiane addition, however, we opted to reduce the ketone group in **44** with L-selectride in THF. The *syn*-configured secondary alcohol was exclusively formed under these conditions in line with a Felkin–Anh transition state model.[41] In accord with this rationale, a substantially lower selectivity (76:24) was observed when the reaction was carried out in dichloromethane, presumably because α-chelation becomes competitive in the non-coordinating solvent. The relative configuration of the alcohol product could be proven by X-ray analysis of a derivative (see the Supporting Information).[42]

After protection as a TES-ether, the stage was set for a ruthenium-catalyzed *anti*-Markovnikov hydration of the terminal alkyne **45** thus obtained.[43] The reaction required only 2 mol% of the catalyst, which was prepared from commercial $[CpRu(MeCN)_3PF_6]$ and the bulky ARPYPhos-ligand **47** in MeCN. This convenient procedure afforded the desired product **46** in excellent yields, without any cleavage of the TES-ether interfering when the amount of water was limited to five equivalents. The effective use of the alkyne as an aldehyde equivalent epitomized by this conversion completed the second building block required for the preparation of the southern sector of spirastrellolide A methyl ester (**1a**). The described route was found high yielding and readily scalable.

Elaboration of the "Southern" domain: The decisive formation of the [6,6]-spiroketal motif began with the addition of dithiane **37** to aldehyde **46** (Scheme 6). A number of bases and conditions[44,45] were screened but a protocol using a mixed metallic reagent ultimately gave the best results. In the event, **37** was deprotonated with a mixture of Bu_2Mg and *n*BuLi in a 1:4 ratio[46] and the solution of the resulting metalated species cooled to −78 °C prior to the addition of the aldehyde component. The desired secondary alcohol **48** (mixture of diastereomers at C17) was isolated in 75% yield, together with 19% of the product formed by butyl addition. Although the yield of **48** obtained with *n*BuLi alone was definitely lower (62%), the loss of advanced material by a competing carbonyl addition process was not ideal. The subsequent optimization showed that an increased amount of Bu_2Mg favored the parasitic butyl addition, whereas a ratio of *n*BuLi/Bu_2Mg 8.4:1 allowed the desired product **48** to be obtained in 83% yield and the side reaction to be suppressed. Even higher Li/Mg ratios, however, turned out to be less productive, presumably due to the fading positive effect of the magnesium additive. It was suggested in the literature that the Bu_2Mg increases the stability of the deprotonated dithiane by forming a magnesium ate-complex.[46] We have reasons to believe that it also reduces the basicity of the anion and hence favors nucleophilic addition over deprotonation of the aldehyde partner.



Scheme 6. a) *n*BuLi/Bu_2Mg, THF, 0 °C→RT then RT→−78 °C, **46** in THF, 83%; b) DMP, CH_2Cl_2, 0 °C, 93%; c) DDQ, CH_2Cl_2, H_2O, 0 °C; d) PPTS, CH_2Cl_2, MeOH, 26% (**51**) + 43% (**52**); e) TBSCl, imidazole, CH_2Cl_2, 93%; f) TPAP, NMO, MeCN, CH_2Cl_2, MS 4 Å, 82%; g) **53**, KHMDS, THF, −78 °C, 89%; h) HF·pyridine, THF, −11 °C, 75% (87% brsm); i) NCS, $AgNO_3$, 2,6-lutidine, MeCN, H_2O, 77%; j) DMP, CH_2Cl_2; k) $NaClO_2$, NaH_2PO_4, isopentene, *t*BuOH, H_2O, 94% (over two steps); DMP = Dess–Martin periodinane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TPAP = tetra-*n*-propylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide, KHMDS = potassium bis(trimethylsilyl)amide, NCS = *N*-chloro succinimide, PPTS = pyridinium *p*-toluenesulfonate.

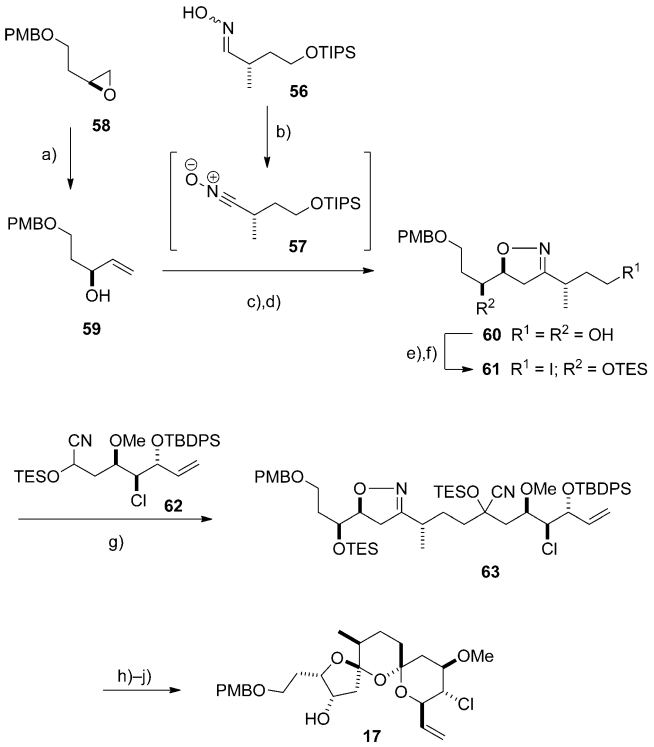
Next, the diastereomeric alcohols **48** were oxidized to ketone **49** using Dess–Martin periodinane[47] without affecting the oxidation-prone dithiane. The cleavage of the *p*-methoxybenzyl ethers with DDQ in a biphasic medium delivered a mixture of two compounds of distinctly different polarity, which are believed to be the open chain diol-ketone **50** and a hemiacetal form thereof; in any case, the more polar component converted into the less polar product upon separation by flash chromatography on silica. A spontaneous spiroketalization, as previously noticed for related compounds in the spirastrellolide F series, was not observed, most likely because of the steric hindrance about the ketone exerted by the "neopentylic" dithiane neighborhood. Gratifyingly though, treatment of this difficult-to-characterize product with PPTS in CH_2Cl_2/MeOH resulted in the cleavage of the secondary TES-ether followed by clean spirocyclization.[48] Despite the only mildly acidic conditions, some concomitant deprotection of the primary TBS-ether was also noticed; this side reaction, however, was inconsequential as the primary alcohol **51** could be selectively re-protected. The desired spirocyclic product **52** was thus obtained in respectable yield as a single isomer.

In preparation for the upcoming Suzuki fragment coupling, the remaining free OH group in **52** had to be oxidized to the corresponding ketone without affecting the dithiane moiety. Of the different reagents screened, tetra-*n*-propylammonium perruthenate (TPAP) in combination with N-methylmorpholine-*N*-oxide (NMO) gave by far the best result, when the reaction was performed at high concentration; to reach full conversion, however, acetonitrile had to be added as a co-solvent.[49] Subsequent deprotonation with the aid of KHMDS and trapping of the resulting enolate with triflimide **53** afforded the required alkenyl triflate **54** without incident. In line with our expectations,[12] this product was stable enough to allow for the selective deprotection of the primary TBS-ether on exposure to HF·pyridine to give **55**, although it was best to quench the reaction before full conversion had been reached and to recycle the remaining starting material.

At this stage, the dithiane had fulfilled its double role as a handle for the fragment coupling and an orthogonal protecting group for a carbonyl moiety at C16. Taking the sensitivity of dithioacetals towards oxidative cleavage into account, it was originally hoped that the oxidation of the primary alcohol in **55** to the required carboxylic acid and the deprotection of the dithiane could be accomplished in one operation.[50] Although a variety of reagents were screened, the yields of the desired product **16** remained impractically low. For the sake of material throughput, we therefore pursued a stepwise approach, commencing with the well reproducible cleavage of the dithioacetal with $NCS/AgNO_3$.[51] The resulting product was then effectively transformed by a sequence of Dess–Martin- and Pinnick oxidation[52] into acid **16**, which represents a properly functionalized surrogate of the "Southern" sector of spirastrellolide A (**1**).

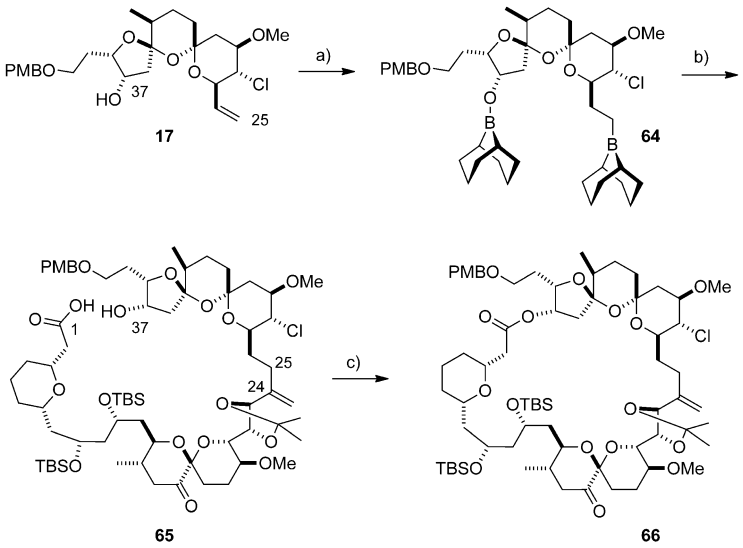
The Northern fragment: The preparation of the required Northern fragment closely followed the sequence previously described by our group,[9b] except that the benzyl ether at the primary hydroxyl group was replaced by a PMB group. This change was deemed necessary to ensure selective deprotection at this site in the final stages of the synthesis, once the signature C15–C16 double bond embedded in the B-ring of the target has been unveiled.

To this end, the known epoxide **58**[53] was chosen as the point of departure, which is accessible in excellent optical purity by hydrolytic kinetic resolution.[54] On treatment with dimethylsulfonium methylide,[55] this compound was transformed into the allylic alcohol **59** as the substrate for a diastereoselective 1,3-dipolar cycloaddition[56] with nitrile oxide **57** derived from oxime **56** (Scheme 7).[9b] The reaction was highly diastereoselective, affording diol **60** as the only product in high yield after complete desilylation. Selective transformation of the primary alcohol into the corresponding iodide followed by TES protection of the secondary alcohol gave fragment **61** in readiness for alkylation of the lithium enolate derived from the known cyanohydrin **62**.[9b] The desired product **63** was obtained in excellent yield as an inconsequential mixture of diastereomers (d.r. 87:13).



Scheme 7. a) $[Me_3S]I$, *n*BuLi, THF, −10 °C→RT, 88 %; b) *t*BuOCl, CH_2Cl_2, −78 °C; c) *i*PrOH, EtMgBr, CH_2Cl_2, 0 °C, then add **57**, d) TBAF, THF, 76 % (over two steps); e) I_2, imidazole, PPh_3, THF, 67 %; f) TESOTf, 2,6-lutidine, THF, 93 %; g) **62**, LDA, THF, −78 °C, then **61**, 95 % (d.r. 87:13); h) $[Mo(MeCN)_3(CO)_3]$, MeCN, H_2O, 50 °C, then Me_3NO; i) TASF, DMF, H_2O; j) PPTS, CH_2Cl_2/MeOH, 48 % (after one recycle, over three steps); LDA = lithium diisopropylamide, TASF = $[(Me_2N)_3S][F_2Si(Me)_3]$.

The procedure for the subsequent N–O bond cleavage was subject to optimization. Rather than relying on $[Mo(CO)_6]$ as previously described,[9b,57] we found the use of $[Mo(MeCN)_3(CO)_3]$ beneficial, as it allows the reaction to be run more cleanly at lower temperature.[58] To facilitate the work-up, trimethylamine-*N*-oxide was added to the crude mixture. This simple means improved the mass balance and delivered the product virtually free of metal contaminants. Since the removal of metal residues is a known issue in the cleavage of isoxazolines with zero-valent molybdenum complexes,[58,59] this simple modification should be of wider relevance. The product was isolated as a mixture of partially desilylated compounds, which was of no concern as global desilylation with concomitant break-down of the cyanohydrin was to follow. Treatment with TASF followed by exposure of the resulting sensitive material to PPTS in a mixture of CH_2Cl_2/MeOH gave the desired thermodynamically favored [5,6,6]-bis-spiroketal **17** as the major compound, together with three diastereomers that could be separated and re-equilibrated to further the material supply.[9] Overall, this sequence afforded the northern fragment in a respectable yield, ready for coupling with the Southern sector.



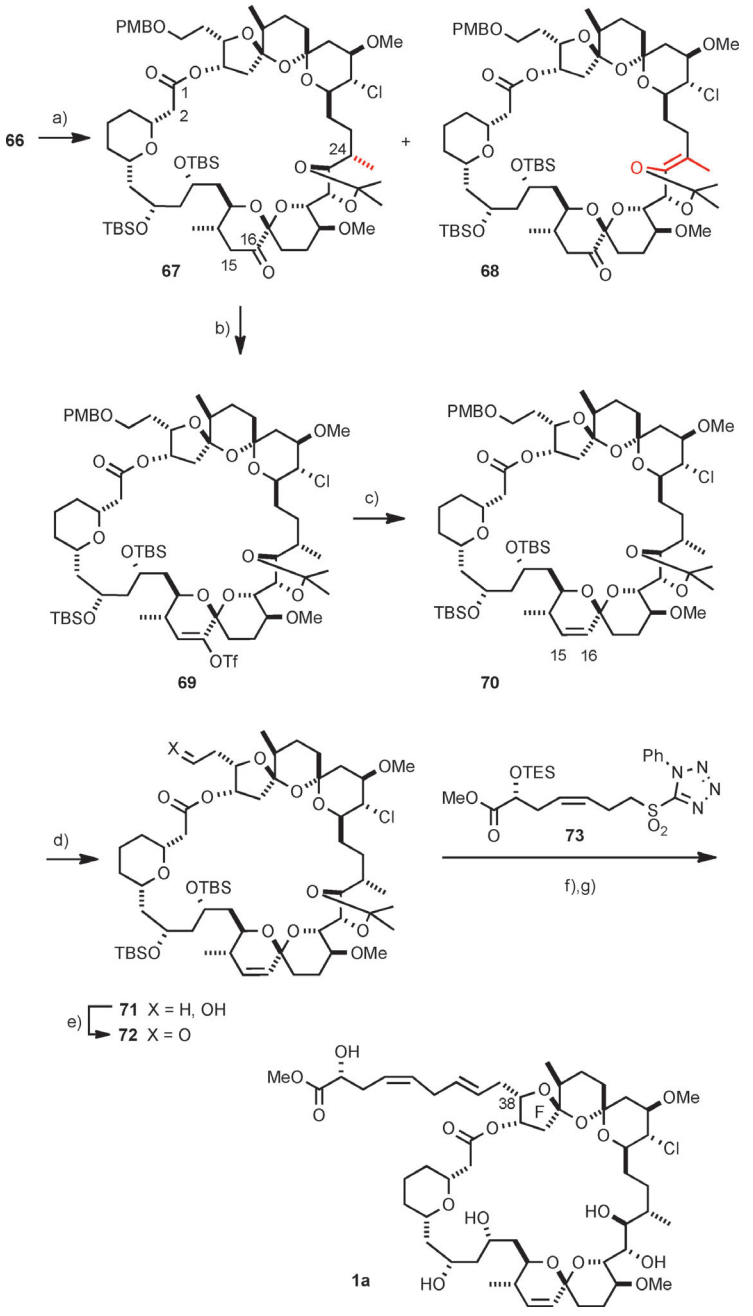
Scheme 8. a) 9-*H*-9-BBN dimer, THF; b) i) aq. NaOH; ii) **16**, $[PdCl_2(dppf)\cdot CH_2Cl_2]$ (20 mol%), Ph_3As (20 mol%), 65%; c) i) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene; ii) DMAP, toluene, reflux, 88%; DMAP = 4-dimethylaminopyridine, 9-H-9-BBN = 9-borabicyclo[3.3.1]nonane, dppf = 1,1′-bis(diphenylphosphino)ferrocene.

Formation of the macrolactone and completion of the total synthesis: With all required building blocks in hand, the project entered the critical phase of macrocycle formation followed by elaboration of the final target.

In concord with our previous experiences, the Northern and the Southern sectors could be stitched together by an alkyl-Suzuki coupling[19] followed by a Yamaguchi macrolactonization (Scheme 8).[60] To this end, the terminal alkene of **17** was hydroborated with 9-*H*-9-BBN dimer to give the alkylborane **64** bearing a borinate ester at the C37 position. Reaction of this compound with the polyfunctionalized alkenyl triflate **16** under the aegis of $[(dppf)PdCl_2]$ as precatalyst and aqueous sodium hydroxide as promoter delivered the desired product **65** in respectable 65% yield after an oxidative work up to cleave the C37-borinate moiety off. This *seco*-acid was equally cleanly converted to the macrolactone **66** by a Yamaguchi reaction,[60] provided that the preformed mixed anhydride was slowly added to a refluxing solution of DMAP in toluene. The need for such harsh conditions is ascribed to an unfavorable conformation imposed on the *seco*-acid by the isopropylidene group at C22–C23 and/or to repulsive transannular interactions within the incipient macrocycle.

As expected, the hydrogenation of the C24 *exo*-methylene group on the macrocyclic frame of **66** was challenging but exquisitely selective in favor of the desired stereoisomer (Scheme 9). This outcome is ascribed to the rigid BC-ring system that effectively shields one of the π-faces of the olefin, allowing hydrogen to be delivered only from the open *Re*-face.[12b] However, considerable transannular strain has to be overcome during the concurrent rehybridization of the carbon atom from sp^2 to sp^3, during which the methyl branch clashes into the congested 6,6-spirobicyclic rear as long as the adjacent isopropylidene acetal is in place. In line with our previous observations, only a highly active Crabtree catalyst escorted by the non-coordinating BARF counteranion was able to affect this transformation (for the structure of this complex in the solid state, see the Supporting Information).[42,61,62] Moreover, high hydrogen pressure was mandatory, although no significant difference was noticed between 80 and 200 bar. As catalyst decomposition is fast under such forcing conditions, it was better not to insist on complete conversion but rather recycle the remaining substrate. This allowed the desired product **67** to be obtained in 58% yield (73% brsm). Small amounts (ca. 5%) of a by-product could be separated, which turned out to be the enolether **68** that originates from an iridium-catalyzed isomerization of the double bond into the ring.[63]

At this stage, the C16-ketone group of **67** had to be transformed into the characteristic $\Delta^{[15,16]}$-alkene of spirastrellolide A. Amongst the different choices, we opted for an adventurous selective enolization of the carbonyl in the presence of the equally enolizable lactone group, since the protons at C15 seemed sterically more accessible and, at the same time, also more acidic than the protons of the methylene



Scheme 9. a) [Ir(cod)(PCy_3)(pyridine)][BARF], H_2 (80 bar), 1,2-dichloroethane, 58% (73% brsm); b) **53**, KHMDS, THF, −100 °C, 73%; c) [$Pd(OAc)_2(PPh_3)_2$] (35 mol%), HCO_2H, nBu_3N, DMF, 60 °C, 97%; d) DDQ, CH_2Cl_2, H_2O, 0 °C, 89%; e) DMP, CH_2Cl_2, 0 °C→RT, 88%; f) **72**, KHMDS, THF, −78 °C, then **71**, THF, −78→−65 °C, 69%; g) PPTS, MeOH/Et_2O/H_2O 7:2:1, 50 °C, 51%; cod = cycloocta-1,5-diene, BARF = tetrakis(3,5-bis-trifluoromethylphenyl)borate, brsm = based on recovered starting material.

group at C2 (Scheme 9). A test reaction, in which KHMDS was added to a mixture of the substrate and triflimide **53** in THF at −78 °C, afforded an encouraging 55% of the desired alkenyl triflate **69** together with several minor byproducts. Pleasingly, the yield could be improved to 73% upon further lowering of the temperature to −100 °C. Reduction of this compound to the required olefin was achieved with the aid of [$Pd(OAc)_2(PPh_3)_2$] and tributylammonium formate,[64,65] which afforded the fully functional macrolactone core **70** of spirastrellolide A in almost quantitative yield.

The now missing side chain was readily installed by cleavage of the PMB group with DDQ followed by oxidation of the resulting primary alcohol **71** to the corresponding aldehyde **72** on exposure to Dess–Martin periodinane. A subsequent Julia–Kocienski olefination[20] with the known sulfone **73**[14] delivered fully protected spirastrellolide A as single geometric isomer at the newly formed double bond. Global deprotection with PPTS in a mixed solvent system completed our total synthesis of spirastrellolide A methyl ester (**1a**). In line with our own observations made with the sister compound spirastrellolide F methyl ester (**6a**)[12] as well as with the later report of Paterson and co-workers,[11d] the NMR spectra of our samples of **1a**, especially the ^1H NMR spectra, showed a significant and characteristic time- and solvent dependent behavior. They prove the integrity of our synthetic samples and their identity with the natural product (see the Supporting Information).

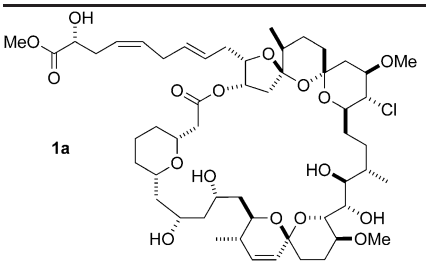
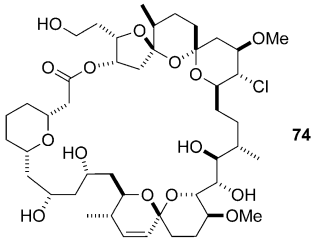
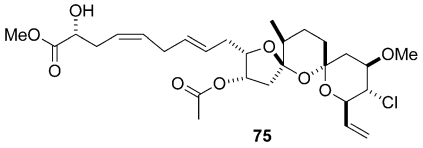
Surprisingly, however, a careful inspection showed that **1a** seems to be in equilibrium with a minor diastereomer. After separation by HPLC, the pure components convert back to the same equilibrium composition during the time needed for a complete NMR characterization. The same unusual phenomenon was also observed for some other macrocyclic derivatives passed through en route to **1**. Whereas the primary alcohol **71** and the corresponding aldehyde **72** were single components each (within the limits of detection), a second isomer built up in case of **67** (d.r. ≈87:13), **70** (d.r. ≈94:6) and the fully protected spirastrellolide A (d.r. ≈90:10). We gather from the literature that a similar observation was made by Matsunaga and coworkers during the re-isolation of the spirastrellolides from a sponge of the *Epipolasis* genus collected in the East China Sea.[66]

Due to the complexity and time-dependence of the spectra, the small concentration of the second component, and the signal overlap with the major constituent, the identity of the respective second isomer in the equilibrium could not be fully established. Yet, for compound **67**, the spectral dispersion was sufficiently large, allowing us to deduce that the constitution of the minor component is unaltered, but the stereochemistry about the F-ring seems to be affected. For example, the ^{13}C signals assigned to this region show distinctive shift differences relative to those of the major isomer, which are particularly substantial for C36 ($\Delta\delta$ = 8.1 ppm) and C38 ($\Delta\delta$ = 4.1 ppm). We tentatively ascribe these observations to a reversible epimerization of the

C35-spiroacetal center: although the DEF-ring subunit features a double anomeric effect, all large substituents on the five-membered F-ring are *cis*-oriented, thus rendering its α-side very crowded.[67] Any bulky group at C38—as present in **1a**, **67** and **70**—may well destabilize the [5,6,6]-bisspiroketal to the extent that it can equilibrate with an acetal epimer even under very mild conditions.[68,69]

Preliminary biological assessment: As a very first foray into a more detailed biological assessment of the spirastrellolides, compound **70** representing the entire macrocyclic perimeter was globally deprotected to give the pentaol **74** as a truncated analogue of **1**. Likewise, we ventured to attach the correct side chain to compound **17** in order to obtain compound **75** representing the "Northern half" of the natural product. Together with the synthetic samples of spirastrellolide A methyl ester (**1a**), these compounds were screened for their cytotoxicity against the human MDA-MB-231 breast cancer cell line, the human LoVo colon carcinoma cell line, and the 4T1 mouse carcinoma cell line.

Table 2. Assessment of the cytotoxicity (IC_{50}) of **1a** and two truncated variants against three different cancer cell lines after incubation for 4 d.[a]

Compound	MDA-MB-231 [nM]	LoVo [nM]	4T1 [nM]
 **1a**	9.6	14.2	<0.051
 **74**	>1000	974	>1000
 **75**	>1000	1000	>1000

[a] MDA-MB-231 breast cancer cell line; human LoVo colon carcinoma cell line; 4T1 mouse carcinoma cell line; the data refer to the standard MTS endpoint assay; MTS = 5-(3-carboxymethoxyphenyl)-2-(4,5-dimethylthiazolyl)-3-(4-sulfophenyl)tetrazolium, inner salt.

As can be seen from the data compiled in Table 2, **1a** itself was found very cytotoxic, with the 50 picomolar (!) level of activity against the 4T1 cell line being particularly impressive. In contrast, however, neither compound **74** with a truncated side chain nor compound **75** as the upper half of the natural product exerted any noticeable activity in the tested concentration range. Although we are certainly apprehensive that no final conclusions can be drawn from such a limited set of compounds, these data suggest that the entire carbon framework might be necessary to reach meaningful levels of cytotoxicity. This notion will be subject to further scrutiny in the future, together with studies into the phosphatase inhibition properties of these and related compounds.[70]

Conclusion

The work outlined above is the latest chapter of our group's long engagement with the spirastrellolides, a family of highly unusual marine natural products with enticing structures and promising biological properties. Because of serious stereochemical uncertainties surrounding these target molecules at the outset of our project, it was clear then that only a flexible synthesis plan could possibly be successful. The chemical suppleness inherent to our blueprint paid first important dividends after the originally projected ring-closing metathesis reaction had failed to forge the core region of these targets. The projected assembly process could be amended without the need to redesign all individual fragments and hence spirastrellolide F methyl ester (**6a**) be reached by two different routes that converge in their late stages.[12,14]

The work presented herein illustrates yet another facet of the flexible design: the project could be redirected, without undue effort, toward the total synthesis of the parent compound spirastrellolide A methyl ester (**1a**). The additional selectivity issue posed by the signature C15–C16 double bond of this specific target was addressed by masking this olefinic site in the form of a carbonyl group until after the methyl branch at C24 had been properly set by a substrate-controlled hydrogenation reaction. This tactics, in turn, inspired an assembly process based on dithiane chemistry, which is necessarily different in its details from the routes leading to **6a**, yet shares with them a common fuzzy chemical logic. Therefore we believe that this venture, in its totality, meets Woodward's verdict, that chemical synthesis always has to have some element of planning, but this element should never be too rigid.[71]

Experimental Section

All experimental details can be found in the Supporting Information. The material includes compound characterization, the crystal structures of a *p*-bromobenzoate ester proving the stereochemistry of **45** and of [Ir(cod)(PCy_3)(pyridine)][BARF] used for the hydrogenation of compound **66**, and copies of spectra for all new compounds.

Acknowledgements

Generous financial support by the MPG and the Fonds der Chemischen Industrie (Kekulé stipends to A.A. and S.B.) is gratefully acknowledged. We express our sincere gratitude to all co-workers who helped initiate the spirastrellolide project and laid a solid basis for the current success by developing the general strategic and methodological framework for our studies; their names appear in references [9], [12], [14], [18], and [29]. Furthermore, we thank the analytical departments of our Institute for excellent support and Dr. Andreas Maderna and Dr. Frank Loganzo, Pfizer Inc., for the cytotoxicity data.

[1] M. Roberge, B. Cinel, H. J. Anderson, L. Lim, X. Jiang, L. Xu, C. M. Bigg, M. T. Kelly, R. J. Andersen, *Cancer Res.* **2000**, *60*, 5052–5058.

[2] D. E. Williams, M. Roberge, R. Van Soest, R. J. Andersen, *J. Am. Chem. Soc.* **2003**, *125*, 5296–5297.

[3] K. Warabi, D. E. Williams, B. O. Patrick, M. Roberge, R. J. Andersen, *J. Am. Chem. Soc.* **2007**, *129*, 508–509.

[4] 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.

[5] 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.

[6] M. Suzuki, R. Ueoka, K. Takada, S. Okada, S. Ohtsuka, Y. Ise, S. Matsunaga, *J. Nat. Prod.* **2012**, *75*, 1192–1195.

[7] For the correction of the originally proposed constitution (ref. [2]) and the elucidation of the relative stereochemistry of the color coded stereoclusters of **1a**, see: D. E. Williams, M. Lapawa, X. Feng, T. Tarling, M. Roberge, R. J. Andersen, *Org. Lett.* **2004**, *6*, 2607–2610.

[8] For studies toward the spirastrellolides, see: 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; q) J. L.-Y. Chen, M. A. Brimble, *J. Org. Chem.* **2011**, *76*, 9417–9428; r) X. Wang, T. J. Paxton, N. Li, A. B. Smith, *Org. Lett.* **2012**, *14*, 3998–4001.

[9] 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.

[10] Reviews: a) I. Paterson, S. M. Dalby, *Nat. Prod. Rep.* **2009**, *26*, 865–873; b) I. Paterson, S. M. Dalby, P. Maltas, *Isr. J. Chem.* **2011**, *51*, 406–419; c) M. V. Perkins, *Angew. Chem.* **2008**, *120*, 2963–2967; *Angew. Chem. Int. Ed.* **2008**, *47*, 2921–2925.

[11] 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, E. A. Anderson, S. M. Dalby, J. H. Lim, P. Maltas, O. Loiseleur, J. Genovino, C. Moessner, *Org. Biomol. Chem.* **2012**, *10*, 5861–5872; d) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, P. Maltas, *Org. Biomol. Chem.* **2012**, *10*, 5873–5886.

[12] 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.

[13] I. Paterson, P. Maltas, S. M. Dalby, J. H. Lim, E. A. Anderson, *Angew. Chem.* **2012**, *124*, 2803–2807; *Angew. Chem. Int. Ed.* **2012**, *51*, 2749–2753.

[14] S. Benson, M.-P. Collin, A. Arlt, B. Gabor, R. Goddard, A. Fürstner, *Angew. Chem.* **2011**, *123*, 8898–8903; *Angew. Chem. Int. Ed.* **2011**, *50*, 8739–8744.

[15] a) J. Heppekausen, R. Stade, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 11045–11057; b) J. Heppekausen, R. Stade, A. Kondoh, G. Seidel, R. Goddard, A. Fürstner, *Chem. Eur. J.* **2012**, *18*, 10281–10299; c) A. Fürstner, G. Seidel, *Angew. Chem.* **1998**, *110*, 1758–1760; *Angew. Chem. Int. Ed.* **1998**, *37*, 1734–1736.

[16] A. Fürstner, P. W. Davies, *Chem. Commun.* **2005**, 2307–2320.

[17] A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449.

[18] A. Fürstner, B. Fasching, G. W. O'Neil, M. D. B. Fenster, C. Godbout, J. Ceccon, *Chem. Commun.* **2007**, 3045–3047.

[19] a) N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314–321; b) reviews: S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676–4701; *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568; c) G. Seidel, A. Fürstner, *Chem. Commun.* **2012**, *48*, 2055–2070; for early applications in total synthesis from this laboratory, see: d) A. Fürstner, I. Konetzki, *Tetrahedron* **1996**, *52*, 15071–15078; e) A. Fürstner, G. Seidel, *J. Org. Chem.* **1997**, *62*, 2332–2336; f) A. Fürstner, I. Konetzki, *J. Org. Chem.* **1998**, *63*, 3072–3080.

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

[21] H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 293–294.

[22] It should be noted that the direct use of CSA in the acetalization reaction resulted in significantly lower yields of **23**.

[23] S. Takano, M. Akiyama, S. Sato, K. Ogasawara, *Chem. Lett.* **1983**, *12*, 1593–1596.

[24] E. J. Corey, G. B. Jones, *J. Org. Chem.* **1992**, *57*, 1028–1029.

[25] J. R. Parikh, W. v. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

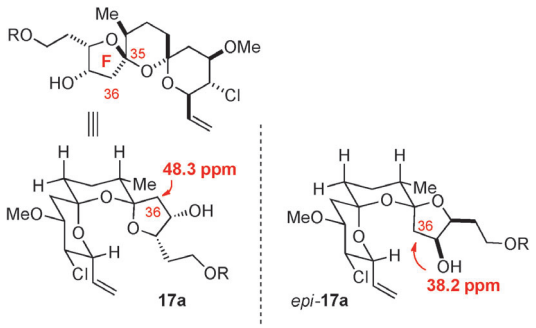
[26] a) L. Weiler, *J. Am. Chem. Soc.* **1970**, *92*, 6702–6704; b) S. N. Huckin, L. Weiler, *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087.

[27] T. Ohkuma, R. Noyori in *Comprehensive Asymmetric Catalysis, Vol. 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 199–246.

[28] a) S. A. King, A. S. Thompson, A. O. King, T. R. Verhoeven, *J. Org. Chem.* **1992**, *57*, 6689–6691; see also: b) A. Fürstner, T. Dierkes, O. R. Thiel, G. Blanda, *Chem. Eur. J.* **2001**, *7*, 5286–5298.

[29] See also: G. W. O'Neil, A. Fürstner, *Chem. Commun.* **2008**, 4294–4296.

[30] a) D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343; b) review: T. Mukaiyama, *Org. React.* **1982**, *28*, 203–331.
[31] a) D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449; b) review: K. J. Ralston, A. N. Hulme, *Synthesis* **2012**, 2310–2324.
[32] A. B. Smith, D. Lee, C. M. Adams, M. C. Kozlowski, *Org. Lett.* **2002**, *4*, 4539–4541.
[33] a) M. Nakatsuka, J. A. Ragan, T. Sammakia, D. B. Smith, D. E. Uehling, S. L. Schreiber, *J. Am. Chem. Soc.* **1990**, *112*, 5583–5601; b) for a use in this laboratory, see: A. Fürstner, O. R. Thiel, *J. Org. Chem.* **2000**, *65*, 1738–1742.
[34] a) T. Veysoglu, L. A. Mitscher, J. K. Swayze, *Synthesis* **1980**, 807–810; b) see also: 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 and references therein.
[35] The same outcome was recorded when **39** was replaced by the analogous substrate bearing a sterically more hindered TIPS moiety.
[36] a) M. B. Rubin, *J. Chem. Educ.* **1964**, *41*, 388; for applications in synthesis, see: b) P. A. Wender, B. A. DeChristopher, A. J. Schrier, *J. Am. Chem. Soc.* **2008**, *130*, 6658–6659; c) F. Li, S. S. Tartakoff, S. L. Castle, *J. Org. Chem.* **2009**, *74*, 9082–9093; d) D. L. J. Clive, X. He, M. H. D. Postema, M. J. Mashimbye, *J. Org. Chem.* **1999**, *64*, 4397–4410.
[37] K. Hattori, H. Yamamoto, *J. Org. Chem.* **1993**, *58*, 5301–5303.
[38] M. S. M. Timmer, A. Adibekian, P. H. Seeberger, *Angew. Chem.* **2005**, *117*, 7777–7780; *Angew. Chem. Int. Ed.* **2005**, *44*, 7605–7607.
[39] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
[40] J. M. Williams, R. B. Jobson, N. Yasuda, G. Marchesini, U.-H. Dolling, E. J. J. Grabowski, *Tetrahedron Lett.* **1995**, *36*, 5461–5464.
[41] H. Chikashita, T. Nikaya, H. Uemura, K. Itoh, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2121–2123.
[42] CCDC 907987 and 908599 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.
[43] 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) L. Hintermann in *C-X Bond Formation, Top. Organomet. Chem., Vol. 31* (Ed.: A. Vigalok), Springer, Berlin, **2010**, pp. 123–155.
[44] a) B. H. Lipshutz, E. Garcia, *Tetrahedron Lett.* **1990**, *31*, 7261–7264; b) D. Seebach, E. J. Corey, *J. Org. Chem.* **1975**, *40*, 231–237.
[45] a) D. Seebach, *Synthesis* **1969**, 17–36; b) M. Yus, C. Nájera, F. Foubelo, *Tetrahedron* **2003**, *59*, 6147–6212; c) A. B. Smith, S. M. Condon, J. A. McCauley, *Acc. Chem. Res.* **1998**, *31*, 35–46.
[46] M. Ide, M. Nakata, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491–2499.
[47] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; b) S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549–7552.
[48] Spirocyclization did not take place as long as the TES-ether was in place. This observation is ascribed to the steric hindrance imposed by this group, which is forced by the flanking *cis*-configured dioxolane at C22-C23 into close proximity to the alcohol at C21 which has to attack the ketone.
[49] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639–666.
[50] J. S. Yadav, C. S. Reddy, *Org. Lett.* **2009**, *11*, 1705–1708.
[51] E. J. Corey, B. W. Erickson, *J. Org. Chem.* **1971**, *36*, 3553–3560.
[52] a) B. S. Bal, W. E. Childers, Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091–2096; b) G. A. Kraus, M. J. Taschner, *J. Org. Chem.* **1980**, *45*, 1175–1176; c) B. O. Lindgren, T. Nilsson, *Acta Chem. Scand.* **1973**, *27*, 888–890.
[53] A. Fürstner, M. Albert, J. Mlynarski, M. Matheu, E. DeClercq, *J. Am. Chem. Soc.* **2003**, *125*, 13132–13142.
[54] a) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315; b) L. P. C. Nielsen, C. P. Stevenson, D. G. Blackmond, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 1360–1362.
[55] L. Alcaraz, J. J. Harnett, C. Mioskowski, J. P. Martel, T. Le Gall, D.-S. Shin, J. R. Falck, *Tetrahedron Lett.* **1994**, *35*, 5449–5452.
[56] a) S. Kanemasa, M. Nishiuchi, A. Kamimura, K. Hori, *J. Am. Chem. Soc.* **1994**, *116*, 2324–2339; b) see also: J. W. Bode, N. Fraefel, D. Muri, E. M. Carreira, *Angew. Chem.* **2001**, *113*, 2128–2131; *Angew. Chem. Int. Ed.* **2001**, *40*, 2082–2085.
[57] P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, D. Simoni, *Synthesis* **1987**, 276–278.
[58] a) A. Guarna, A. Guidi, A. Goti, A. Brandi, F. De Sarlo, *Synthesis* **1989**, 175–178; b) J. A. Bull, E. P. Balskus, R. A. J. Horan, M. Langner, S. V. Ley, *Chem. Eur. J.* **2007**, *13*, 5515–5538.
[59] J. W. Bode, E. M. Carreira, *J. Org. Chem.* **2001**, *66*, 6410–6424.
[60] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993; b) review: A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.* **2006**, *106*, 911–939.
[61] R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331–337.
[62] a) B. Wüstenberg, A. Pfaltz, *Adv. Synth. Catal.* **2008**, *350*, 174–178; b) S. P. Smidt, A. Pfaltz, E. Martínez-Viviente, P. S. Pregosin, A. Albinati, *Organometallics* **2003**, *22*, 1000–1009.
[63] a) J. M. Bueno, J. M. Coterón, J. L. Chiara, A. Fernández-Mayoralas, J. M. Fiandor, N. Valle, *Tetrahedron Lett.* **2000**, *41*, 4379–4382; b) D. Solé, X. Urbaneja, J. Bonjoch, *Org. Lett.* **2005**, *7*, 5461–5464; c) E. M. Phillips, J. M. Roberts, K. A. Scheidt, *Org. Lett.* **2010**, *12*, 2830–2833; d) M. Krel, J.-Y. Lallemand, C. Guillou, *Synlett* **2005**, 2043–2046.
[64] S. Cacchi, E. Morera, G. Ortar, *Tetrahedron Lett.* **1984**, *25*, 4821–4824.
[65] Investigations of this key reaction on a model substrate had shown this combination to be superior to the use of Et_3SiH and Bu_3SnH as the hydride sources under a variety of experimental conditions.
[66] Matsunaga et al. mentioned that an "unidentified equilibrium" visible in the signals of the C12–C34 region of spirastrellolide B (**2**) was observed upon treatment of the free acid **2** with [D_5]pyridine, cf. ref. [6].
[67] The crowed α-face of the F-ring is also the likely reason why the acid-catalyzed spiroketalization of the dihydroxyketone derived from **63** affords bisspiroketal **17** featuring a double anomeric effect as the major but not as the only isomer, cf. Scheme 8. Furthermore, the C36 signals of the resulting major isomer **17a** (R = Bn) and of the minor isomer *epi*-**17a** with an inverted C35 acetal center show the same pronounced shift difference ($\Delta\delta = 10.1$ ppm), which is likely caused by the lone pairs of the other ketal oxygen atoms.



[68] For a relevant discussion of another natural product containing a [5,6]-spiroketal, in which destabilization caused by two eclipsing substituents on the five membered ring overrides a stabilizing anomeric effect, see: a) P. Buchgraber, T. N. Snaddon, C. Wirtz, R. Mynott, R. Goddard, A. Fürstner, *Angew. Chem.* **2008**, *120*, 8578–8582; *Angew. Chem. Int. Ed.* **2008**, *47*, 8450–8454; b) T. N. Snaddon, P. Buchgraber, S. Schulthoff, C. Wirtz, R. Mynott, A. Fürstner, *Chem. Eur. J.* **2010**, *16*, 12133–12140.
[69] A similar epimerization process accompanied by large chemical shift differences in the ^{13}C NMR spectra of the equilibrating isomers,

was described for the spiroketal center in the pectenotoxins, see: K. Sasaki, J. L. C. Wright, T. Yasumoto, *J. Org. Chem.* **1998**, *63*, 2475–2480.

[70] For studies from this laboratory on the preparation and evaluation of natural-product-based phosphatase inhibitors, see: a) A. Fürstner, F. Feyen, H, Prinz, H. Waldmann, *Angew. Chem.* **2003**, *115*, 5519–5522; *Angew. Chem. Int. Ed.* **2003**, *42*, 5361–5364; b) A. Fürstner, F. Feyen, H. Prinz, H. Waldmann, *Tetrahedron* **2004**, *60*, 9543–9558; c) A. Fürstner, J. Ruiz-Caro, H. Prinz, H. Waldmann, *J. Org. Chem.* **2004**, *69*, 459–467; d) A. Fürstner, K. Reinecke, H. Prinz, H. Waldmann, *ChemBioChem* **2004**, *5*, 1575–1579; e) M. Manger, M. Scheck, H. Prinz, J. P. von Kries, T. Langer, K. Saxena, H. Schwalbe, A. Fürstner, J. Rademann, H. Waldmann, *ChemBioChem* **2005**, *6*, 1749–1753.

[71] R. B. Woodward in *Proceedings of The Robert A. Welch Foundation Conferences on Chemical Research. XII. Organic Synthesis* (Ed.: W. O. Milligan), The Robert A. Welch Foundation, Houston, **1968**, pp. 3–6.

Received: November 6, 2012
Published online: February 18, 2013

