VIP Polyketide Synthesis

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Synthesis of an Advanced C10–C32 Spiroacetal Fragment and Assignment of the Absolute Configuration of Spirangien A**

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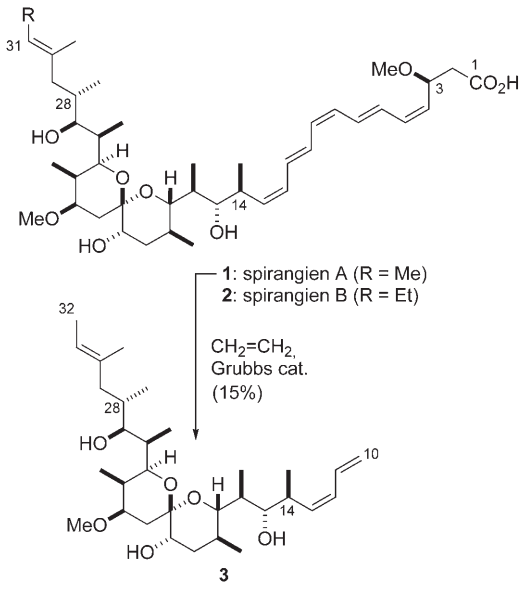
Spirangiens A (**1**, Scheme 1) and B (**2**),[1] isolated by the research group of Höfle from the epothilone-producing



Scheme 1. Spirangiens A (**1**) and B (**2**), and generation of the 1,3-diene degradation fragment **3**.

myxobacterium *Sorangium cellulosum* (strain So ce90), are polyketide metabolites[2] that possess potent antifungal and cytotoxic activity (IC_{50} 0.7 ng mL^{-1} against L929 mouse fibroblast cell line). From a structural perspective, the spirangiens contain 14 stereocenters, and include a densely functionalized spiroacetal core appended with a delicate pentaene side chain that bears a terminal carboxy group. Spirangiens A and B differ only with the presence of a methyl or ethyl substituent at C31.

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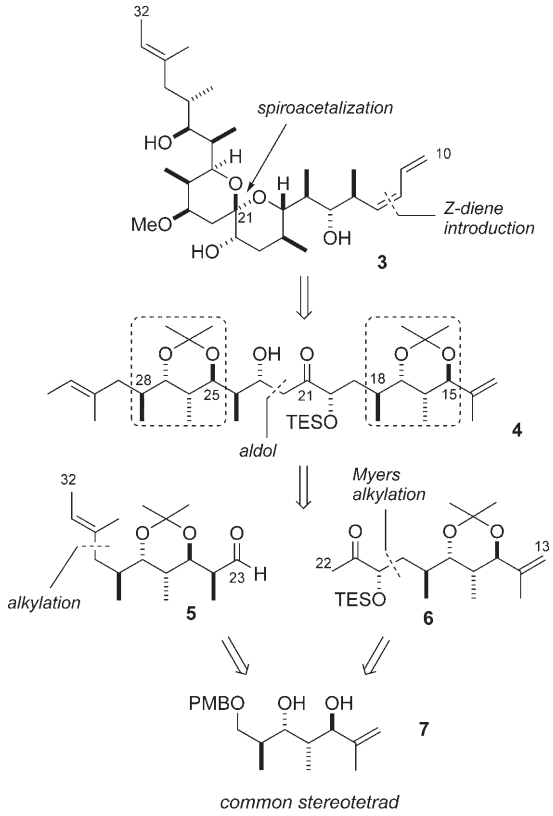
As an aid to stereochemical elucidation, their controlled chemical degradation was reported recently by Niggemann et al.[1a] The absolute configuration at the isolated C3 stereocenter was thus determined by GC analysis of an ozonolysis product on a chiral stationary phase. Cross-metathesis of the pentaene moiety in spirangien A with ethene generated the spiroacetal fragment **3**, which enabled X-ray crystal structure analysis. Whilst this led to the secure determination of the relative stereochemistry, the absolute configuration of **3**, and correspondingly the C14–C28 region of the spirangiens A and B, was unresolved. Notably, this 1,3-diene **3** retained one tenth of the cytotoxic activity of spirangien A (IC_{50} 7 ng mL^{-1} against L929), thus highlighting the importance of the C10–C32 core to the pharmacophore.

Inspired by both the pronounced biological activity and unique structural features associated with this novel spiroacetal scaffold, we embarked on a total synthesis of the spirangiens. Herein, we report an expedient strategy for assembling the elaborate spiroacetal core,[3] which culminated in the preparation of the C10–C32 fragment (+)-**3**, and thus led to the assignment of the absolute configuration of spirangiens A and B.

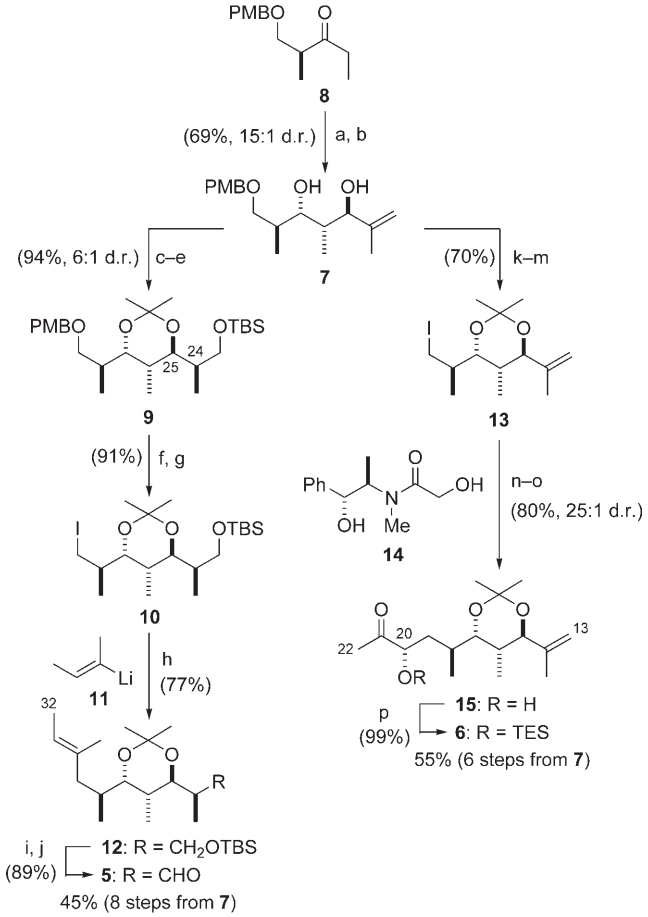
As outlined in Scheme 2, our retrosynthetic analysis of **3** envisaged a late-stage incorporation of the (*Z*)-dienyl side chain. Careful inspection of linear spiroacetalization precursor **4** reveals a repeating pattern of four contiguous stereocenters (C15–C18 and C25–C28) that we recognized could be exploited to develop a modular, step-economic synthetic strategy. In turn, this acyclic ketone **4** might arise from an aldol coupling of aldehyde **5** with ketone **6**, both of which should be accessible from the 1,3-diol **7** as a common stereotetrad building block.

As shown in Scheme 3, our synthesis began with the ethyl ketone (*S*)-**8**,[4] which was converted by an aldol-reduction sequence into the common precursor **7** with high diastereoselectivity (69%, > 15:1 d.r.). Multigram quantities of the 1,3-diol **7** were readily accessed, thereby enabling two parallel sequences of reactions to be performed to generate the requisite C23–C32 and C13–C22 subunits, **5** and **6**, respectively.

Focusing first on aldehyde **5**, previous studies[5] suggested that the hydroboration of the 1,1-disubstituted olefin of 1,3-diol **7** using BH_3 in THF should result in installation of the required stereocenter at C24. Following this hydration protocol, **7** generated the corresponding C24,C25-*syn* triol (94%, 6:1 d.r. by ^{1}H NMR analysis) which underwent selective silylation of the primary hydroxy group (TBSCl, imidazole), followed by formation of the *anti* acetonide (2,2-dimethoxypropane, PPTS), to give **9** (89%, 2 steps). At this stage, the PMB ether in **9** was cleaved by DDQ to reveal the primary



Scheme 2. Retrosynthetic analysis of **3** (spirangien numbering) leading to the common precursor **7**.

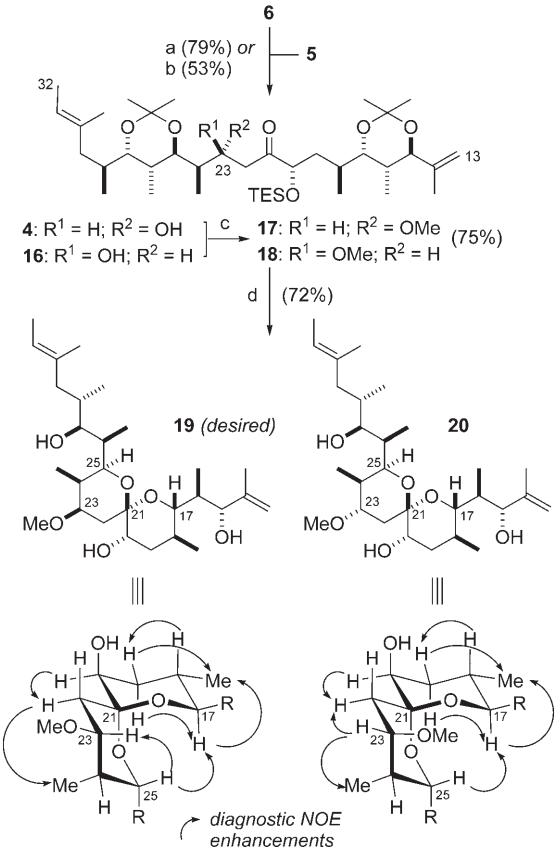


Scheme 3. Synthesis of C23–C32 aldehyde **5** and C13–C22 ketone **6**. a) 1. *c*Hex$_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 1 h; H$_2$C=C(Me)CHO, −78→−27 °C, 16 h; 2. MeOH, pH 7 buffer, H$_2$O$_2$; b) Me$_4$NHB(OAc)$_3$, AcOH, MeCN, −30 °C, 16 h; c) 1. BH$_3$·SMe$_2$, THF, 0→20 °C, 3 h; 2. MeOH, NaOH, H$_2$O$_2$; d) TBSCl, imidazole, CH$_2$Cl$_2$, 20 °C, 2 h; e) 2,2-dimethoxypropane, PPTS, CH$_2$Cl$_2$, 20 °C, 16 h; f) DDQ, CH$_2$Cl$_2$/pH 7 buffer (10:1), CH$_2$Cl$_2$, 0→20 °C, 2 h; g) I$_2$, PPh$_3$, Et$_3$N, imidazole, toluene, 0→20 °C, 3 h; h) 1. (*E*)-2-bromobut-2-ene, *t*BuLi, −78 °C; **10**, THF, −78→0 °C, 1 h; 2. 9-BBN, THF, 0→20 °C, 3 h; MeOH, NaOH, H$_2$O$_2$; i) TBAF, THF, 0→20 °C, 1 h; j) Dess–Martin periodinane, NaHCO$_3$, CH$_2$Cl$_2$, 20 °C, 1 h; k) 2,2-dimethoxypropane, PPTS, CH$_2$Cl$_2$, 20 °C, 16 h; l) DDQ, CH$_2$Cl$_2$/pH 7 buffer (10:1), CH$_2$Cl$_2$, 0→20 °C, 2 h; m) I$_2$, PPh$_3$, Et$_3$N, imidazole, toluene, 0→20 °C, 3 h; n) **14**, LDA, THF, −78→20 °C, 1 h; **13**, 0→20 °C, 16 h; o) MeLi, THF, −78→0 °C, 1 h; p) TESOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 1 h. 9-BBN = 9-borobicyclo[3.3.1]nonane, *c*Hex = cyclohexyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, LDA = lithium diisopropylamide, OTf = triflate = trifluoromethanesulfonate, PPTS = pyridinium *para*-toluenesulfonate, PMB = *para*-methoxybenzyl, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

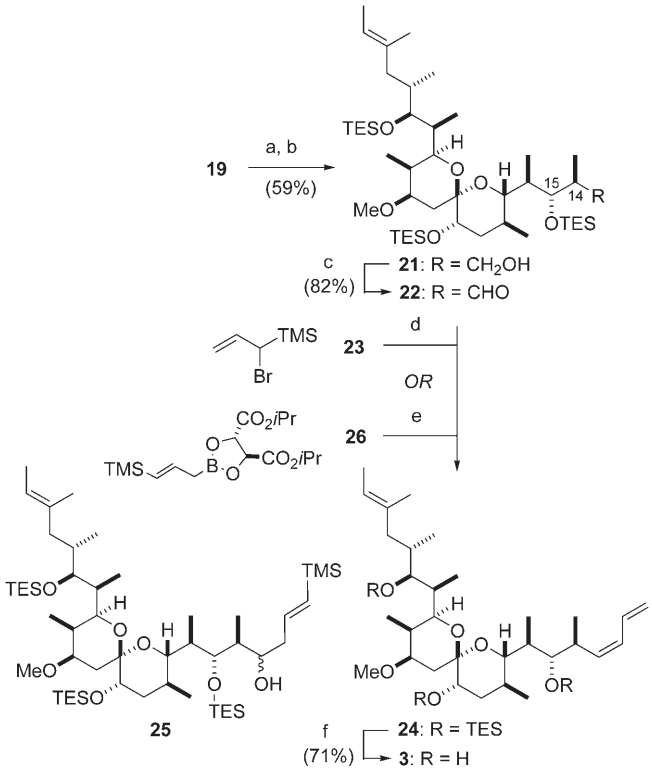
alcohol which was then smoothly transformed into iodide **10** (91%, 2 steps). Displacement of this leaving group with the organolithium species **11** generated from (*E*)-2-bromobut-2-ene (*t*BuLi, THF) was performed next. While a small amount (around 20%) of olefin side product corresponding to E2 elimination of the iodide was observed, this was conveniently removed by selective hydroboration of the product mixture using 9-BBN, enabling the isolation of pure coupled product **12** in 77% yield. Cleavage of the TBS ether in **12** and Dess–Martin oxidation[6] completed the efficient preparation of the C23–C32 aldehyde **5** (8 steps from **7**, 45% overall).

Attention was now directed to preparation of the requisite C13–C22 aldol coupling partner **6**. From the common intermediate **7**, this commenced with formation of the *anti* acetonide. The PMB ether was then converted into primary iodide **13** (70%, 3 steps). A Myers asymmetric alkylation[7] was selected for introduction of the oxygenation at the C20-stereocenter, where the auxiliary might then be subsequently cleaved directly to generate the required methyl ketone. It is recognized that the use of hydroxyacetamide **14** (prepared from (−)-pseudoephedrine and methyl glycolate) tends to result in lower diastereoselectivities in alkylation reactions, possibly as a consequence of the trianion that is generated upon enolization.[7] Furthermore, reactions with β-branched electrophiles are usually slow, thus leading to diminished yields. In spite of these concerns, we were gratified to find that the alkylation of the lithium enolate derived from **14** with iodide **13**, followed by treatment with MeLi, generated the desired methyl ketone **15** in high yield and selectivity (80%, 25:1 d.r.).[8] Formation of the TES ether then completed the efficient preparation of the C13–C22 ketone **6** (6 steps from **7**, 55% overall).

With aldehyde **5** and methyl ketone **6** in hand, our attention turned to their proposed aldol coupling and introduction of the C23-stereocenter. Preliminary studies using LDA generated a 3.5:1 mixture of adducts **16** and **4** (Scheme 4), while the use of *c*Hex$_2$BCl/Et$_3$N gave similar results (5:1 d.r.). Pleasingly, this inherent diastereoselectivity



Scheme 4. Aldol coupling and spiroacetalization. a) LDA, THF, −78 °C, 1 h; **5**, −78 °C, 1 h; b) 1. (−)-Ipc_2BCl, Et_3N, Et_2O, 0 °C, 1 h; **5**, −78 °C, 2 h; 2. MeOH, pH 7 buffer, H_2O_2; c) Me_3OBF_4, proton sponge, CH_2Cl_2, 0→20 °C, 2 h; d) CSA, MeOH, 20 °C, 16 h. CSA = camphorsulfonic acid; Ipc = isopinocampheyl.



Scheme 5. Completion of the synthesis of 1,3-diene **3**. a) TESOTf, 2,6-lutidine, CH_2Cl_2, −78→0 °C, 2 h; b) 1. 9-BBN, THF, 0→20 °C, 3 h; 2. MeOH, NaOH, H_2O_2; c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 20 °C, 1 h; d) 1. **23**, $CrCl_2$, THF, 0→20 °C, 1 h; 2. KOH, MeOH, 0→20 °C, 16 h; e) 1. **26**, 4-Å molecular sieves, 20 °C, 16 h; 2. KOH, MeOH, 0→20 °C, 16 h; f) TBAF, THF, 0→20 °C, 3 h. TMS = trimethylsilyl.

in the undesired Felkin–Anh direction could be overturned by employing chiral Ipc ligands on the boron enolate.[4,9] Thus, enolization of ketone **6** with (−)-Ipc_2BCl/Et_3N, followed by addition of aldehyde **5**, generated the aldol adducts in 53% yield and 2.5:1 d.r. in favor of the desired diastereomer **4**. The latter epimeric mixture was progressed to the corresponding methyl ethers **17** and **18** using the Meerwein salt reagent (75%).[10]

The stage was now set to investigate the pivotal spiroacetalization reaction, where we anticipated that the acetal center at C21 would be controlled under equilibrating conditions as a result of double anomeric stabilization. A range of acidic conditions were evaluated, with the best results achieved using CSA in MeOH at ambient temperature. This led to clean conversion of the C23-epimeric bis(acetonide) **17** and **18** into the two spiroacetals **19** and **20** in 72% yield in a 2.5:1 ratio in accordance with the aldol diastereoselectivity. Following chromatographic separation, unequivocal assignment of their stereochemistry, including that of the acetal center at C21, was made by NOE analysis (Scheme 4) and comparison with the ^{1}H NMR data of the spirangiens.[1a]

It now remained to install the C14-stereocenter and the truncated spirangien side chain (Scheme 5). Silylation of the hydroxy groups in **19** (TESOTf, 84%), followed by selective hydroboration of the disubstituted over the trisubstituted alkene using 9-BBN, then generated the expected C14,C15-*anti* alcohol **21** cleanly (70%, >20:1 d.r.).[5,11] Subsequent Dess–Martin oxidation gave aldehyde **22**, in readiness for installation of the (*Z*)-dienyl side chain. Previous studies[12] prompted the initial examination of a Nozaki–Hiyama/Peterson sequence using allyl silane **23**. However, complications pertaining to steric factors as a result of the conformational rigidity of **22** led to a low yield (25%) of the targeted diene **24** and isolation of the undesired regioisomeric side product **25** (53%). An alternative procedure was therefore sought and allyl boronate **26** was employed,[13] which was obtained by modification of a Roush protocol.[14] Treatment of aldehyde **22** with **26** (3 M, toluene), followed by in situ KOH-mediated Peterson elimination of the ensuing *anti* β-hydroxy silanes, now produced only **24** (50%). Finally, global deprotection of **24** with TBAF completed the synthesis of **3** (71%).

Gratifyingly, the spectroscopic data (^{1}H, ^{13}C NMR and MS) obtained for 1,3-diene **3** were in complete accordance with that reported for the corresponding spirangien degradation fragment.[1a,15] In addition, the measured specific rotation, $[\alpha]_D^{20} = +34$ ($c = 0.04$, MeOH) agreed with the +33.1 ($c = 1.0$, MeOH) reported, both in terms of magnitude and sign, thereby leading to the confident assignment of the

absolute configuration of the spirangiens as shown in structures **1** and **2** in Scheme 1.

In summary, a highly convergent and flexible synthetic strategy has been developed for spirangien A and B, which makes use of a common stereotetrad building block to lead to the advanced C10–C32 fragment (+)-**3**, thus enabling the unambiguous assignment of the full configuration of these bioactive polyketide metabolites. Based on the pronounced cytotoxicity associated with this novel spiroacetal scaffold, including that for truncated analogue **3**, this synthesis opens further SAR studies into the anticancer activity of the spirangiens. The present work also provides a secure foundation for the future completion of the total synthesis of spirangien A.

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