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Total Synthesis of (−)-Spirangien A, an Antimitotic Polyketide Isolated from the Myxobacterium *Sorangium Cellulosum*

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Abstract: An expedient first total synthesis of (−)-spirangien A, a potent cytotoxic and antifungal polyketide of myxobacterial origin, is described. By using a common 1,3-diol intermediate obtained by an efficient aldol-reduction sequence for installation of the C15–C18 and C25–C28 stereotetrads and a reagent-controlled boron aldol coupling followed by spiroacetalization, a highly convergent strategy was developed for construction of the elaborate spiroacetal core. Conversion of this advanced spiroacetal intermediate into (+)-spirangien diene, obtained previously by controlled degradation of spirangien A, was then achieved by installation of the truncated side-chain using an allylboration–Peterson sequence. The total synthesis of (−)-spirangien A was then achieved by the controlled attachment of the unsaturated C1–C12 side-chain, avoiding exposure to light. A Stork–Wittig olefination and double Stille cross-coupling sequence was exploited to install the delicate conjugated pentaene chromophore featuring alternating (*Z*)- and (*E*)-olefins, leading initially to the methyl ester of spirangien A, which proved significantly more stable than the corresponding free acid. Subsequent careful hydrolysis afforded (−)-spirangien A, validating the relative and absolute configuration.

Keywords: aldol reaction · cytotoxicity · natural products · polyketides · spiro compounds

Introduction

Exploiting the wealth of novel natural products as both lead structures and scaffolds for further elaboration has proven highly successful in the quest for the discovery of efficacious therapeutic agents.[1] As such, there is considerable interest focused upon the identification of alternative sources of secondary metabolites.[2] Over the past two decades, myxobacteria have emerged as a prolific source of novel secondary metabolites with pronounced biological activities and therapeutic potential.[3] Within the class of myxobacteria, the genus *Sorangium* is the source of approximately half of all metabolites isolated thus far, the most important being the epothilone anticancer agents.[4,5]

Another interesting class of polyketide natural products produced by *Sorangium cellulosum* (strain So ce90) is that of the spirangiens, isolated initially by Höfle and co-workers in 1993,[6] and reported by Niggemann et al. in 2005.[7] In terms of biological activity, spirangien A (**1**, Figure 1) has been shown to possess both potent antifungal and cytotoxic activity, with an IC_{50} value of 0.7 ng mL^{-1} against an L929 mouse fibroblast cell line. To date, the mechanism of action associated with this promising anticancer activity has not been determined. The spirangiens have a unique structural motif, featuring a densely substituted spiroacetal core appended with a side-chain bearing a delicate pentaene chromophore, having alternating (*Z*)- and (*E*)-olefins, and a terminal carboxyl group. Spirangiens A and B (**2**) both possess 14 stereocenters and differ only in the presence of a methyl or an ethyl substituent at C31. The spiroacetal motif is a feature common to a large array of natural product structures, including those of marine, plant, and bacterial origin, which often display impressive biological profiles.[8,9] Within our

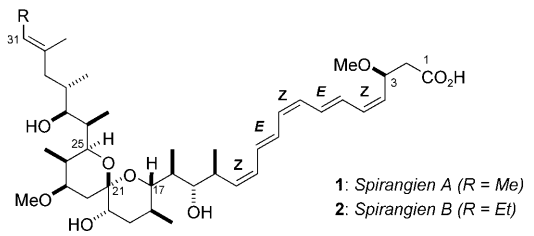

Figure 1. Structures of the spirangiens.

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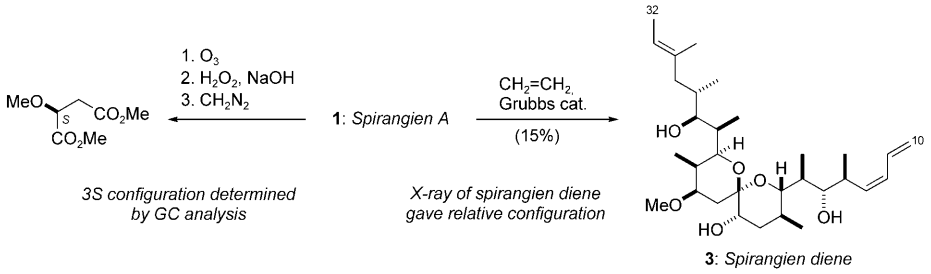
laboratory, synthetic endeavors directed towards accessing such spiroacetal-containing molecular frameworks have encompassed a number of challenging targets, as exemplified by spirastrellolide A[10] and spongistatin 1/altohyrtin A.[11] Recently, we[12] and the Kalesse group,[13] among others, have been attracted to the spirangiens as challenging bioactive polyketide[14] targets for chemical synthesis, particularly as the full stereostructure required rigorous assignment.

As an aid to stereochemical elucidation, Niggemann et al. first performed a series of chemical degradation experiments on spirangien A (Scheme 1).[7] The *S* configuration at the isolated C3 stereocenter was thus determined by GC analysis of an ozonolysis product. Moreover, a cross-metathesis reaction of the pentaene moiety with ethene generated the spiroacetal fragment **3** with a truncated side-chain, which enabled X-ray crystal structure analysis. Whilst this led to a secure determination of the relative stereochemistry, the absolute configuration of **3**, and correspondingly the C14–C28 spiroacetal-containing region of the spirangiens, remained unresolved. Notably, the resulting spirangien diene (**3**) also showed potent cytoxicity ($IC_{50} = 7\ ng\,mL^{-1}$ in the L929 mouse fibroblast line), retaining around one tenth of the activity of spirangien A itself, thus highlighting the importance of the C10–C32 spiroacetal core to the pharmacophore.

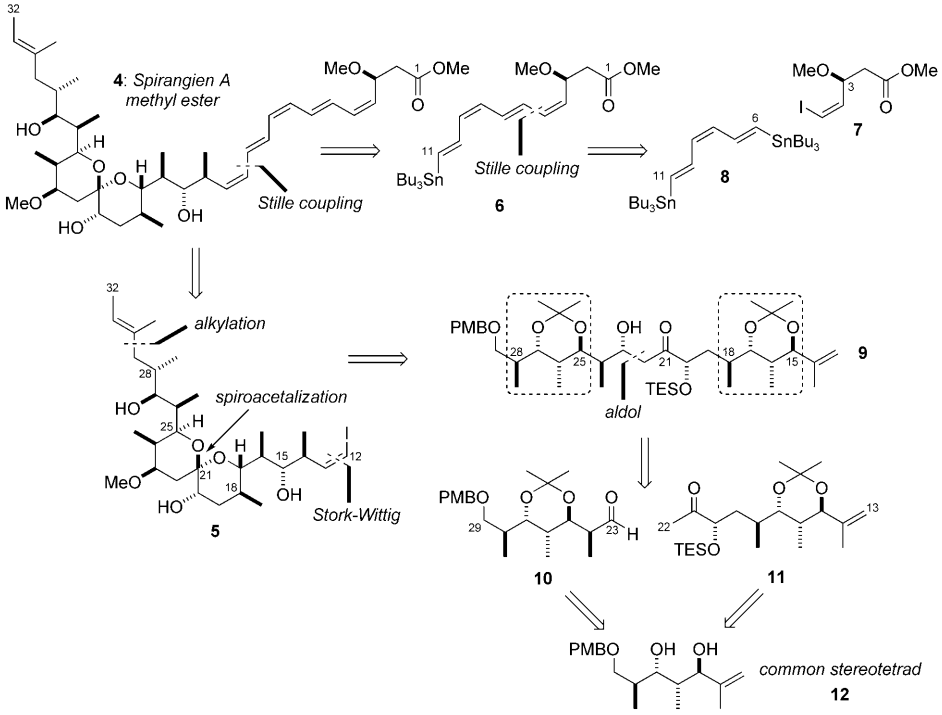


Scheme 1. Chemical degradation of spirangien A as an aid to structural elucidation.

As part of a program directed towards the synthesis of antimitotic polyketides, we recently embarked on a total synthesis of the spirangiens. Herein, we provide a full account of the development of an expedient aldol-based strategy for the controlled assembly of the spirangiens and relevant background material on the evolution of a highly convergent synthetic route to spirangien diene (**3**). This preliminary work then provided us with a secure platform from which to progress to the first total synthesis of (−)-spirangien A by the challenging introduction of the sensitive pentaene-containing side-chain.

Results and Discussion

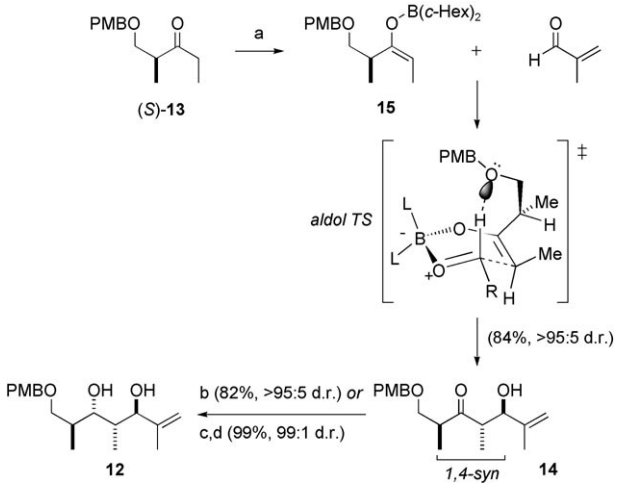
At the outset, concerns over the instability of the spirangiens, associated with facile isomerization of the pentaene chromophore, dictated a late-stage incorporation of the unsaturated side-chain onto a fully elaborated spiroacetal intermediate to initially produce spirangien A methyl ester (**4**). As outlined retrosynthetically in Scheme 2, we envisaged achieving this transformation by use of a mild metal-mediated coupling protocol, highly tolerant of other functional groups, such that a complex Stille cross-coupling[15] between vinyl iodide **5** and stannane **6** was proposed. In turn, it was envisaged that vinyl stannane **6** would be accessed by a Stille coupling of (*Z*)-vinyl iodide **7** and the bis-stannylated (1*E*, 3*Z*, 5*E*)-triene linker **8**. Following unravelling of the spiroacetal core in **5**, careful inspection of the proposed open-chain precursor **9** revealed a repeating pattern of four contiguous stereo-



Scheme 2. Retrosynthetic analysis of spirangien A leading to common precursor **12**.

centers at C15–C18 and C25–C28 that could potentially be exploited to develop a modular and step-economic strategy. Anticipating that this acyclic ketone **9** might arise from an aldol coupling of aldehyde **10** and ketone **11**, a parallel sequence of reactions could thus be developed to access both **10** and **11** from a common stereotetrad building block **12**. This plan was viewed as particularly attractive owing to the ready availability of **12** by a robust aldol-reduction sequence.

Synthetic endeavors towards spirangien A began with the preparation of the planned common intermediate **12**, which we had first prepared in the context of our discodermolide total synthesis.[16] Starting from the ethyl ketone (*S*)-**13**,[17] a 1,4-*syn*-selective aldol reaction mediated by dicyclohexylboron chloride with methacrolein afforded the corresponding 3,4-*anti* adduct **14** in good yield (84%) and with the usual excellent diastereoselectivity (Scheme 3). This boron aldol

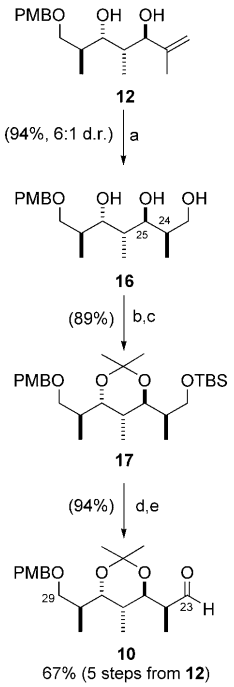


Scheme 3. Preparation of common precursor **12**. a) 1. *c*-Hex_2BCl, Et_3N, Et_2O, 0°C, 1 h; $H_2C{=}C(Me)CHO$, −78→−27°C, 16 h; 2. MeOH, pH 7 buffer, H_2O_2; b) $Me_4NBH(OAc)_3$, AcOH, MeCN, −30°C, 48 h; c) EtCHO, SmI_2, THF, −20→−10°C, 2 h; d) K_2CO_3, MeOH/H_2O (10:1), 20°C, 5 h.

reaction[18] proceeds through the (*E*)-enolate **15** and the favored bicyclic transition state (TS) shown, which is stabilized by a formyl hydrogen bond involving the PMB ether oxygen.[19] Next, an Evans–Saksena[20] hydroxyl-directed reduction protocol was employed, as it provided direct access to the required diol **12**. However, it was found to be more scaleable to perform a two-step procedure, involving an Evans–Tischenko[21] 1,3-*anti* reduction of **14** followed by K_2CO_3-mediated hydrolysis of the resultant crude ester. This generated the required diol **12** in 99% yield with essentially complete stereocontrol (99:1 d.r.).

With expedient access to multigram quantities of the common building block **12**, our attention turned to preparation of the two key fragments required for the complex aldol coupling to assemble the spiroacetal core of spirangien. In our initial work, we targeted the aldehyde **10** (Scheme 4) retaining a PMB ether at C29, with a view to introducing the required trisubstituted alkene after spirocyclization. Thus, elaboration of the common precursor **12** would require a controlled installation of the C24 stereocenter.

Focussing on the preparation of the C23–C29 aldehyde **10**, previous work[22] suggested that hydroboration of the 1,1-disubstituted olefin of 1,3-diol **12** using borane in THF should result in installation of the required *R*-configured stereocenter at C24. Pleasingly, when allylic alcohol **12** was treated with $BH_3{\cdot}SMe_2$ complex followed by oxidative workup, the corresponding C24,C25-*syn* triol **16** was obtained in high yield (94%) and with a good level of diastereoselectivity (6:1 d.r. by ^1H NMR analysis of the crude reaction mixture; Scheme 4).[23] These epimeric triol products proved readily separable by column chromatography. Differentiation of the hydroxyl groups of **16** was then achieved by selective silylation of the primary hydroxyl (TBSCl, imidazole). An appropriate choice of protecting group for the remaining two hydroxyls (C25 and C27) was deemed crucial, as it would be destined for removal under mild acidic conditions designed to induce concurrent spiroacetalization. As such, an acetonide was selected and treatment of the diol with 2,2-dimethoxypropane and catalytic PPTS in CH_2Cl_2 gave **17** (89%, two steps). Cleavage of the TBS ether in **17** and Dess–Martin oxidation[24] of the resulting alcohol completed the efficient preparation of the C23–C29 aldehyde **10** (five steps from **12**, 67% overall).



Scheme 4. Synthesis of C23–C29 aldehyde **10**. a) 1. $BH_3{\cdot}SMe_2$, THF, 0→20°C, 3 h; 2. MeOH, NaOH, H_2O_2; b) TBSCl, imidazole, CH_2Cl_2, 20°C, 2 h; c) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 20°C, 16 h; d) TBAF, THF, 0→20°C, 1 h; e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 20°C, 1 h. 9-BBN = 9-borobicyclo[3.3.1]nonane; TBSCl = *tert*-butyldimethylsilyl chloride; TBAF = tetrabutyl ammonium fluoride; PMB = *para*-methoxybenzyl.

We then turned our attention to preparation of the requisite C13–C22 aldol coupling partner **11** (Scheme 5). With a view towards the planned spiroacetalization step, and the required facile liberation of the C17 alcohol, an acetonide seemed a natural choice as the 1,3-diol protecting group, in accordance with that present in aldehyde **10**. Thus, treatment of **12** with 2,2-dimethoxypropane and catalytic PPTS was performed and was followed by cleavage of the PMB ether and conversion of the resulting alcohol into the iodide **18** (93%, three steps). A Myers asymmetric alkylation[25] was selected for chain extension and concomitant introduction of the C20 oxygen-bearing stereocenter, where the aux-

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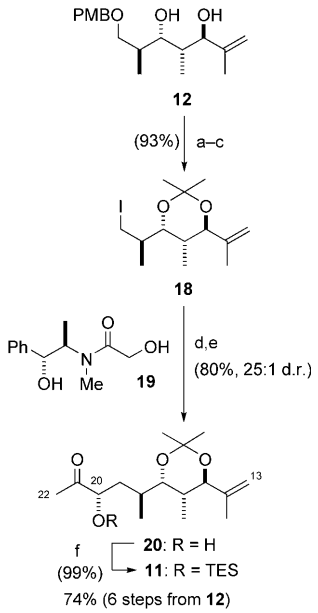
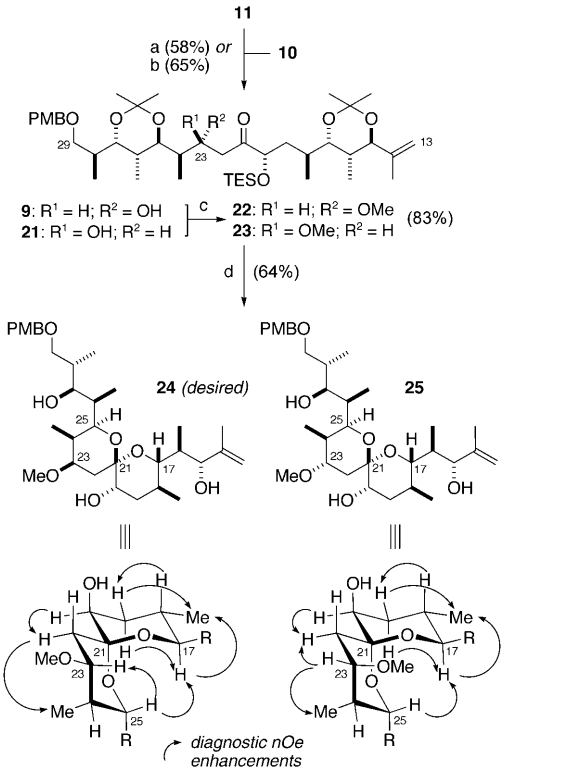


Scheme 5. Synthesis of C13–C22 ketone **11**. a) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 20 °C, 16 h; b) DDQ, CH_2Cl_2/pH 7 buffer (10:1), 0→20 °C, 2 h; c) I_2, PPh_3, Et_3N, imidazole, PhMe, 0→20 °C, 3 h; d) **19**, LDA, THF, −78→20 °C, 1 h; **18**, 0→20 °C, 16 h; e) MeLi, THF, −78→0 °C, 1 h; f) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; LDA = lithium diisopropylamide; TESOTf = triethylsilyl trifluoromethanesulfonate.



Scheme 6. Aldol coupling and spiroacetalization. a) LDA, THF, −78 °C, 1 h; **10**, −78 °C, 1 h; b) 1. (−)-Ipc_2BCl, Et_3N, Et_2O, 0 °C, 1 h; **10**, −78→−30 °C, 16 h; 2. MeOH, pH 7 buffer, H_2O_2; c) $Me_3O{\cdot}BF_4$, Proton Sponge, CH_2Cl_2, 0→20 °C, 2 h; d) CSA, MeOH, 20 °C, 16 h. CSA = camphorsulfonic acid.

iliary might subsequently be cleaved directly to generate the required methyl ketone. However, it is recognized[25b] that use of hydroxyacetamide **19** (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. Furthermore, reactions with β-branched electrophiles are usually slow, leading to diminished yields. In spite of these concerns, we were gratified to find that, after suitable optimization studies, alkylation of the lithium enolate derived from **19** with iodide **18**, followed by treatment with MeLi, generated the desired methyl ketone **20** in high yield and selectivity (80%, 25:1 d.r.). That the alkylation had proceeded with the desired sense of stereoinduction at C20 was confirmed by preparation of the corresponding (*R*)- and (*S*)-MTPA ester derivatives and application of the advanced Mosher method.[26] TES ether formation then completed the efficient preparation of the C13–C22 ketone **11** (six steps from **12**, 74% overall).

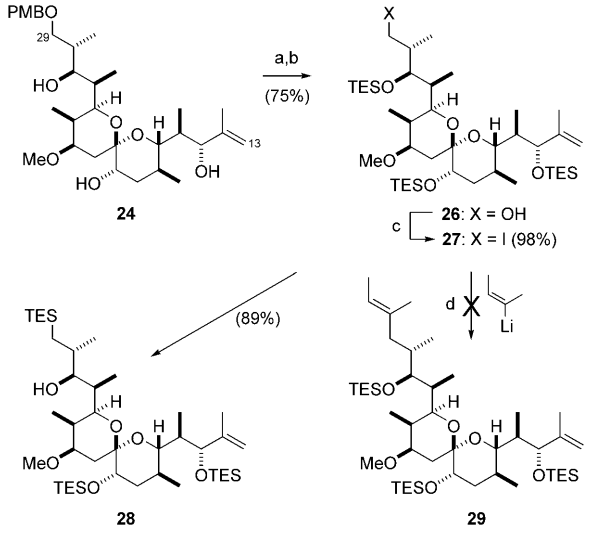
With aldehyde **10** and methyl ketone **11** in hand, our attention turned to their proposed union by aldol coupling (Scheme 6). Preliminary studies using the lithium enolate of **11** (LDA) generated a 2.8:1 mixture (ascertained by ^{1}H NMR analysis of the crude reaction mixture) of epimeric adducts **9** and **21**, which proved inseparable by flash chromatography. To assign the stereochemistry, Mosher ester analysis was performed on this mixture. Treatment of aldol adducts **9** and **21**, in turn, with (*R*)- and (*S*)-MTPA chlorides and pyridine generated the MTPA esters (each as a mixture of diastereoisomers). Careful ^{1}H NMR analysis of these derivatives, again using the advanced Mosher method,[26] revealed the major isomer of the aldol reaction to be **21**, bearing the undesired *S* configuration at the newly installed C23 stereocenter. The use of the dicyclohexylboron enolate (*c*-Hex_2BCl/Et_3N) enhanced selectivity for the undesired product (5:1 d.r.). Pleasingly, this inherent diastereoselectivity in the undesired Felkin–Anh direction could be overturned by reagent control, employing the appropriate Ipc ligand on the boron enolate.[16,27] Thus, enolization of ketone **11** with (−)-Ipc_2BCl/Et_3N, followed by addition of aldehyde **10**, generated the two aldol adducts in 65% combined yield and 2.5:1 d.r. in favor of the desired diastereomer **9**. The so formed epimeric mixture of β-hydroxy ketones was progressed to the corresponding methyl ethers using mild (non-anionic) conditions to prevent retro-aldol cleavage. Treatment of **9** and **21** with Meerwein's salt and Proton Sponge[28] generated the corresponding methyl ethers **22** and **23** in a combined yield of 83%.

The stage was now set to investigate the pivotal spiroacetalization reaction, where we anticipated that the configuration of the C21 acetal center would be controlled under equilibrating conditions, as a result of double anomeric stabilization. A range of acidic conditions, designed to induce removal of the two acetonide protecting groups and concurrent formation of the requisite spiroacetal core of the spi-

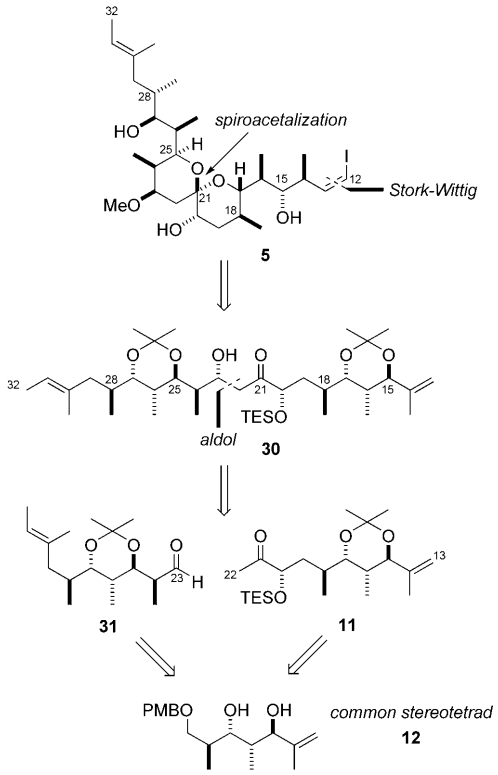
rangiens, were evaluated. In the event, optimal results were achieved using CSA in MeOH at ambient temperature. This led to clean conversion of the C23-epimeric bis-acetonides **22** and **23** into the two spiroacetals **24** and **25** in 64% yield in a ca. 2.5:1 ratio, in accordance with the aldol diastereoselectivity. Following chromatographic separation, unequivocal assignment of their stereochemistry, including the configuration of the C21 acetal carbon atom, was made by nOe analysis and comparison with the ^{1}H NMR data reported for the corresponding region of the spirangiens.[7] Both **24** and **25** were found to benefit from double anomeric stabilization, with the observed coupling constants for H17 and H25 (in both **24** and **25**) showing close agreement with the values reported. Assignment of the C23 configuration was made on the basis of the diagnostic nOe enhancements indicated for both epimers, with the anticipated major isomer **24** bearing the correct configuration. The measured ^{1}H–^{1}H coupling constants were also in agreement, with H23 (dt, J=12.0, 4.5 Hz) in **24** showing close agreement to the corresponding spirangien value (dt, J=12.0, 4.7 Hz). In contrast, H23 in the epimeric spiroacetal **25** appeared as a multiplet. By inference, the previously performed Mosher ester analysis of the aldol reaction outcome was also corroborated, as the ratio of spiroacetal products favored **24**.

With the full spiroacetal core in place, together with 12 of the 14 stereocenters now introduced, suitable elaboration of the C13 and C29 termini was necessary. For the introduction of the C30–C31 trisubstituted double bond, it was envisaged that displacement of a suitable leaving group at C29 with a vinylic organometallic species would constitute a viable strategy. To this end (Scheme 7), protection of the hydroxyl groups of **24** as the corresponding TES ethers was followed by cleavage of the PMB ether at C29 with DDQ to reveal the primary alcohol **26**, which was then smoothly transformed into iodide **27** (74%, three steps). Attempted displacement of this leaving group with the organolithium species generated from (2*E*)-2-bromobutene (*t*BuLi, THF) was next performed. Disappointingly, the sole product of this reaction was identified as **28**, whereby unanticipated migration of the ethereal C27 TES group to the C29 carbon atom had occurred.

While related examples of such oxygen to carbon silyl migrations (retro-Brook-type rearrangements) have been reported previously,[29] which may sometimes be circumvented by a solvent switch from THF to diethyl ether,[30] this and other modifications to the experimental conditions proved unproductive and the desired transformation of **27** into **29** could not be achieved satisfactorily. At the time, the unanticipated difficulties encountered prompted a refinement of our proposed synthetic strategy towards spirangien A, as outlined in Scheme 8. We reasoned that a more streamlined approach would be to introduce the C30–C31 trisubstituted alkene moiety prior to spiroacetalization, leading to the revised acyclic precursor **30**.



Scheme 7. Attempted introduction of C30–C31 trisubstituted double bond. a) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h; b) DDQ, CH_2Cl_2/pH 7 buffer (10:1), 0→20 °C, 1 h; c) I_2, PPh_3, Et_3N, imidazole, PhMe, 0→20 °C, 3 h; d) (2*E*)-2-bromobutene, *t*BuLi, −78 °C; **27**, THF, −78→0 °C, 1 h; DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone



Scheme 8. Revised retrosynthetic analysis involving acyclic precursor **30**.

With this strategy evolution in mind, an efficient preparation of the new C23–C32 aldehyde fragment **31** for the aldol coupling with ketone **11** was required. As shown in Scheme 9, this started with oxidative cleavage of the PMB ether of **17** with DDQ and conversion of the ensuing alcohol into the corresponding primary iodide **32**. Displacement of

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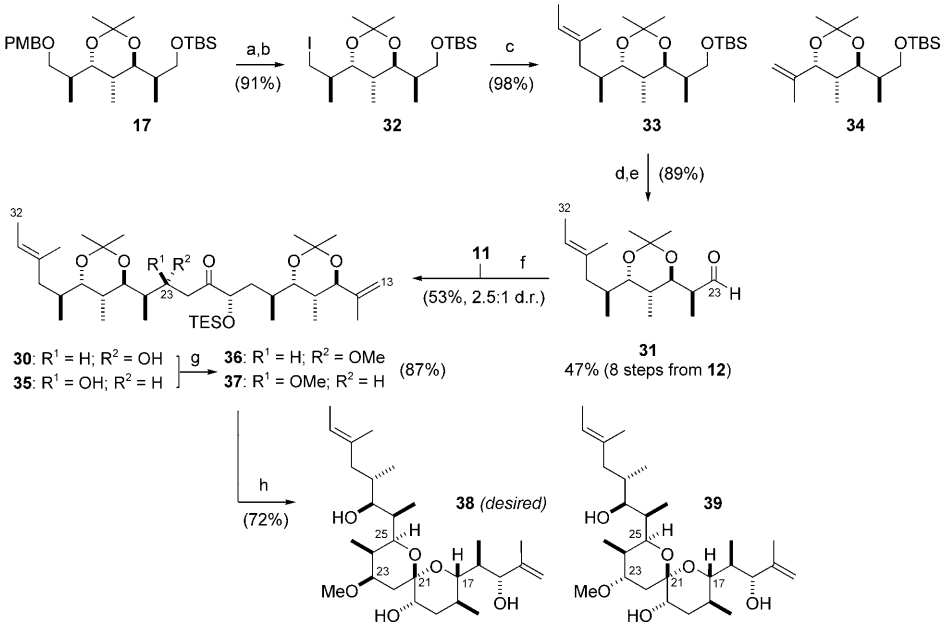


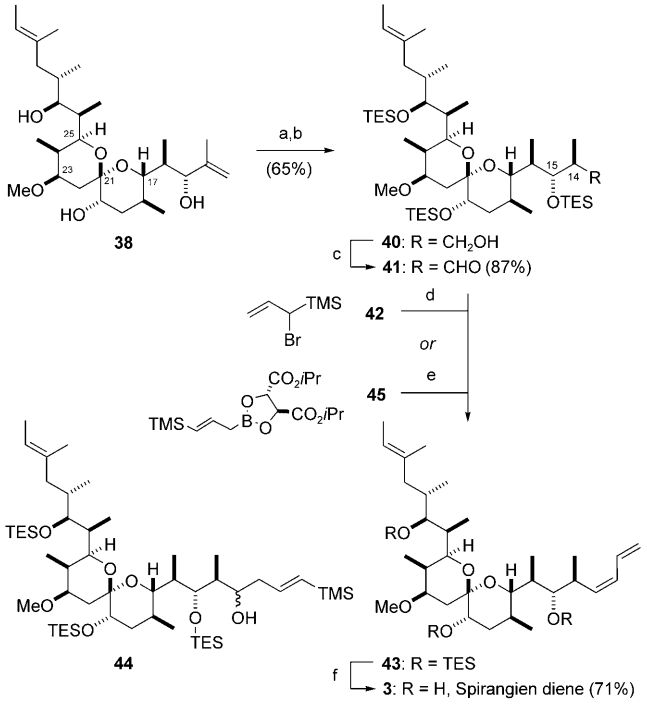
Scheme 9. Revised C23–C29 aldehyde preparation, aldol coupling, and spiroacetalization. a) DDQ, CH_2Cl_2/pH 7 buffer (10:1), 0→20 °C, 2 h; b) I_2, PPh_3, Et_3N, imidazole, PhMe, 0→20 °C, 3 h; c) (2*E*)-2-bromobutene, *t*BuLi, −100 °C, 15 min; CuCN, Et_2O, −78→−50 °C, 20 min; **32**, Et_2O, −50→20 °C, 6 h; d) TBAF, THF, 0→20 °C, 1 h; e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 20 °C, 1 h; f) (−)-Ipc_2BCl, Et_3N, Et_2O, 0 °C, 1 h; **31**, −78→−30 °C, 2 h; 2. MeOH, pH 7 buffer, H_2O_2; g) $Me_3O{\cdot}BF_4$, Proton Sponge, CH_2Cl_2, 0→20 °C, 2 h; h) CSA, MeOH, 20 °C, 16 h.

this leaving group with the organolithium species generated from (2*E*)-2-bromobutene (*t*BuLi, THF) was next performed to afford the required alkene **33**. In the absence of a neighboring silyl ether, any competition from a retro-Brook-type pathway was now negated, and the displacement reaction proceeded as planned. While a small amount (ca. 20%) of olefin side-product **34** corresponding to E2 elimination of the iodide was observed in this reaction, this was conveniently removed by selective hydroboration of the product mixture using 9-BBN, enabling the isolation of pure coupled product **33**. Whilst this two-step procedure proved convenient and reliable on a small scale, an alternative procedure that avoided any competing E2 elimination was clearly desirable. In the event, the use of a CuCN-mediated displacement reaction,[31] involving treatment of a solution of (2*E*)-2-bromobutene with *tert*-butyllithium followed by transmetalation to copper, was found to be superior. The desired coupled product **33** was now formed exclusively, in a greatly improved 98% yield, even when performed on a gram scale. Cleavage of the TBS ether in **33** and Dess–Martin[24] periodinane-mediated oxidation then completed the efficient preparation of the C23–C32 aldehyde **31** (eight steps from **12**, 47% overall, representing an improvement over our initial report[12a]).

Attention now turned to the union of fragments **31** and **11** by aldol coupling. Building upon previous experience,[27] enolization of **11** with (−)-Ipc_2BCl/Et_3N in Et_2O at 0 °C, followed by addition of aldehyde **31**, successfully generated the corresponding epimeric aldol adducts **30** and **35**, isolated as an inseparable mixture (53%, ca. 2.5:1 d.r.). Given the complexity of this aldol coupling, it was gratifying to have formed the desired product; however, both the yield and selectivity proved consistently moderate. It therefore seemed appropriate to investigate alternative reaction conditons. Replacement of the C20 TES ether of the ketone coupling partner with a more robust TBS ether was evaluated, as were alternative chiral boron enolates and Mukaiyama-type aldol unions (using a range of Lewis acids). Unfortunately, in all cases examined poor yields or inferior selectivities were obtained.

At this stage, with several options for C22−C23 bond formation having been investigated, it was decided that the result offered by the (−)-Ipc_2BCl-mediated aldol coupling presented the most workable solution. Consequently, the epimeric mixture obtained by (−)-Ipc_2BCl-mediated aldol coupling was transformed to the corresponding methyl ethers **36** and **37** by treatment with Meerwein's salt and Proton Sponge[28] (87%). From here, exposure of this mixture to CSA in MeOH at room temperature generated the fully functionalized spiroacetals **38** and **39** in good yield (72%). Following chromatographic separation, strong evidence for the assigned stereochemistry was provided by comparison with the NMR data for the previously synthesized spiroacetal core **24** of the spirangiens, and with the natural product itself.[7]

Now, with the highly advanced spiroacetal **38** in hand, completion of the diene degradation fragment **3** required installation of the C14 stereocenter and the truncated spirangien side-chain (Scheme 10). Silylation of the hydroxyl groups of **38** (TESOTf, 93%), followed by selective hydroboration of the disubstituted over the trisubstituted alkene using 9-BBN, then generated the expected C14,C15-*anti* alcohol **40** cleanly (70%, >20:1 d.r.).[22,32] Subsequent Dess–Martin periodinane-mediated oxidation gave aldehyde **41**, in readiness for installation of the (*Z*)-dienyl side-chain. Previous work on discodermolide[33] prompted initial examination of a Nozaki–Hiyama/Peterson sequence using allyl silane **42**. However, complications pertaining to steric factors owing to the conformational rigidity of **41** led to a low yield (25%) of the targeted diene **43** and isolation of the undesired regioisomeric side-product **44** (53%). An alternative procedure was therefore sought and accordingly allyl boronate **45** was employed,[34] which was obtained by modification of a Roush protocol.[35] Treatment of aldehyde **41** with **45** (3 M, PhMe), followed by in situ KOH-mediated Peterson elimi-



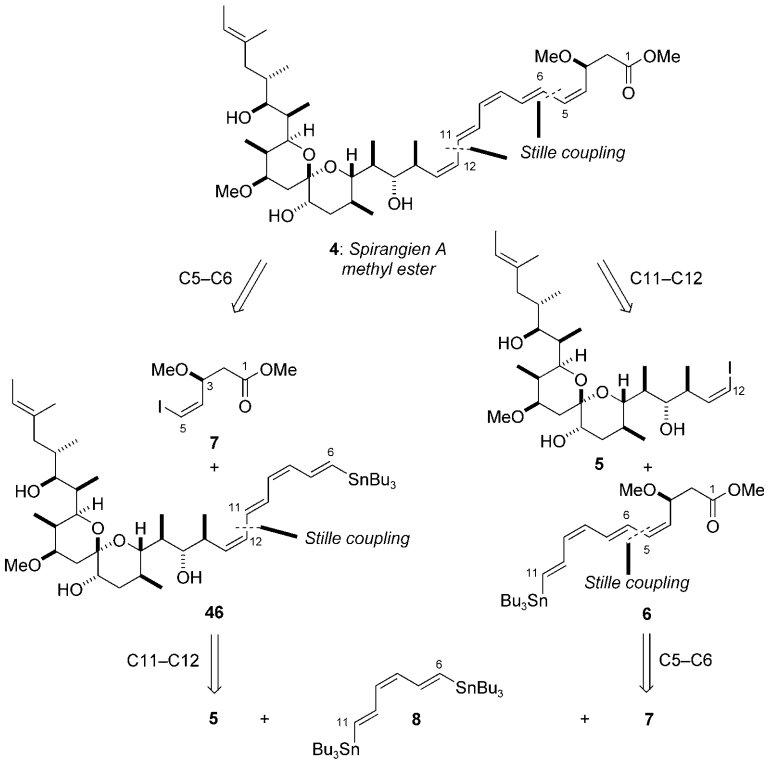
Scheme 10. Elaboration to spirangien diene (**3**). a) TESOTf, 2,6-lutidine, CH_2Cl_2, −78→0 °C, 2 h; b) 1. 9-BBN, THF, 0→20 °C, 3 h; 2. MeOH, NaOH, H_2O_2; c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 20 °C, 1 h; d) 1. **42**, $CrCl_2$, THF, 0→20 °C, 1 h; 2. KOH, MeOH, 0→20 °C, 16 h; e) 1. **45**, 4 Å mol. sieves; 2. KOH, MeOH, 0→20 °C, 16 h; f) TBAF, THF, 0→20 °C, 3 h. TMS = trimethylsilyl.

nation of the ensuing *anti*-β-hydroxy silanes, now produced only **43** (50%). Finally, global deprotection of **43** with TBAF completed the preparation of the target C10–C32 diene degradation fragment **3** (71%). Gratifyingly, the spectroscopic data (^1H, ^{13}C NMR and MS) obtained for 1,3-diene **3** were in complete accordance with that reported for the corresponding spirangien diene degradation fragment.[7] Moreover, the measured specific rotation, $[\alpha]_D^{20} = +34$ ($c = 0.04$, MeOH), compared to +33.1 ($c = 1.0$, MeOH), was also in agreement, 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 Figure 1.

With the unambiguous assignment of the full configuration now achieved, completion of the total synthesis of spirangien A became our next objective. As mentioned previously, concerns over the instability and facile isomerization of the pentaene chromophore of the spirangiens dictated the late-stage incorporation of the side-chain onto a fully elaborated spiroacetal core.

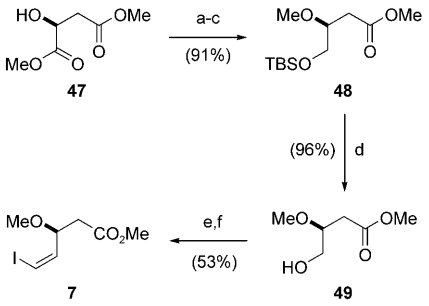
As outlined in Scheme 11, we envisaged the rapid and efficient construction of the requisite pentaene moiety by sequential Stille[15] cross-coupling reactions at C11–C12 and C5–C6, thus requiring the preparation of spiroacetal-containing intermediate **5**, bearing a truncated (*Z*)-vinyl iodide side-chain, and a suitable stannyl tetraene partner **6**. Further disconnection of this tetraene revealed (*Z*)-vinyl iodide **7** and the bis-stannylated (1*E*, 3*Z*, 5*E*)-triene linker **8**. Strategically, it was recognized that the use of such a linker species would offer welcome flexibility with regards to the order of assembly of the full (4*Z*, 6*E*, 8*Z*, 10*E*, 12*Z*)-pentaene. A Stille cross-coupling reaction between **7** and **8** to form tetraene **6** appeared to be the more straightforward and convergent option, followed by a second Stille coupling to attach the spiroacetal core of spirangien A. However, initial formation of the spiroacetal-containing tetraene **46**, followed by attachment of the remaining C1–C5 unit **7** was recognized as a potentially viable alternative scenario. Owing to the advanced nature of the spiroacetal-containing fragment **5**, we considered it prudent to prepare and employ a suitable model system to gauge the relative merits of the two proposed reaction sequences and enable the optimization of the coupling conditions.

In the degradation studies performed by Niggemann et al. on spirangien A, the isolated C3 methoxy-bearing stereocenter was assigned as having an *S* configuration.[7] Hence, it



Scheme 11. Retrosynthetic analysis of pentaene side-chain of spirangien A.

was decided that the (*Z*)-vinyl iodide **7** required for construction of the side chain should originate from dimethyl (*S*)-malate (**47**), as shown in Scheme 12. Following a chemo-

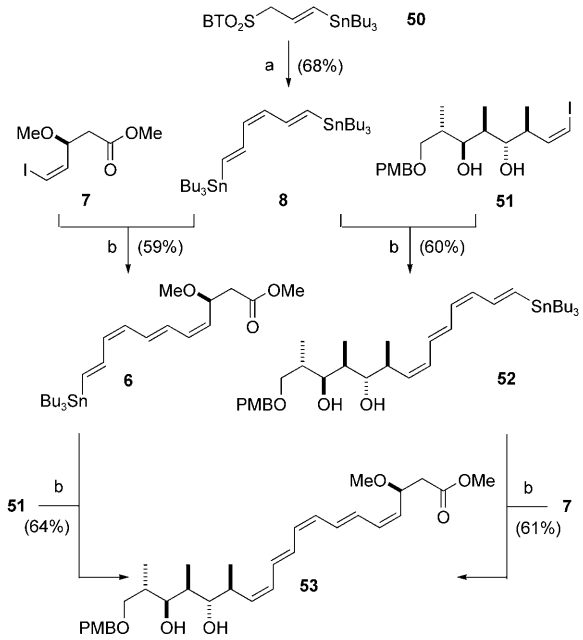


Scheme 12. Preparation of (*Z*)-vinyl iodide **7** from dimethyl (*S*)-malate. a) $BH_3{\cdot}SMe_2$, THF, 0→20 °C; $NaBH_4$, 0→20 °C, 1 h; b) TBSCl, imid., 0→20 °C, 12 h; c) $Me_3O{\cdot}BF_4$, Proton Sponge, CH_2Cl_2, 0→20 °C, 1 h; d) TBAF, AcOH, THF, 0→20 °C; 16 h; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78→20 °C, 1 h; f) $(Ph_3PCH_2I)^+I^-$, NaHMDS, HMPA, THF, −100→20 °C, 1 h.

selective reduction of **47** ($BH_3{\cdot}SMe_2$, cat. $NaBH_4$),[36] the 1,2-diol product was sequentially selectively silylated (TBSCl, imidazole) and methylated with Meerwein's reagent to afford **48**. Cleavage of the TBS ether provided alcohol **49** (88% from **47**), where Swern oxidation led to the corresponding aldehyde which was subjected to a Stork–Wittig[37] olefination to generate the required (*Z*)-vinyl iodide **7** selectively (53%, *Z*/*E* 19:1).

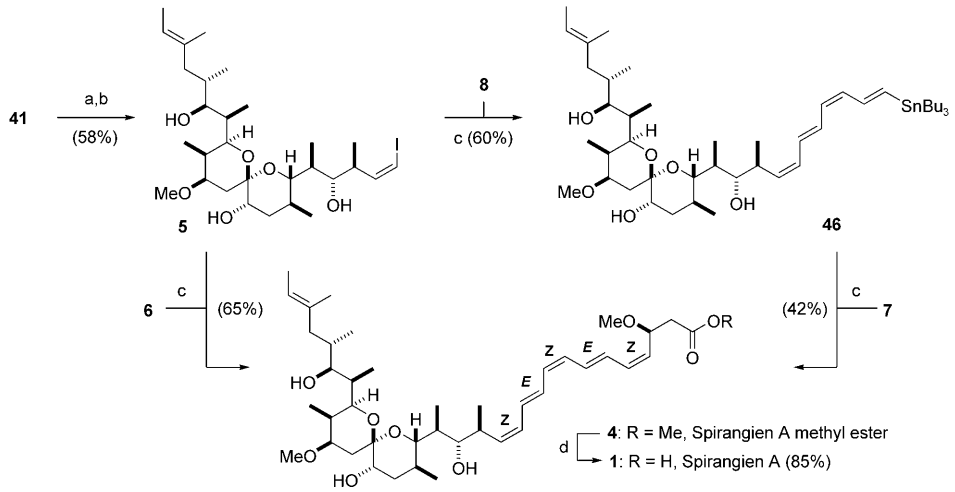
With the targeted iodide **7** now in hand, access to the bis-stannylated triene linker **8** was required. This was obtained in high geometric purity (>20:1, 68%) as the (1*E*, 3*Z*, 5*E*)-isomer, according to the procedure of Brückner and coworkers[38] by a *Z*-selective, modified Julia olefination[39] between the benzothiazolylsulfone **50** and (*E*)-Bu_3SnCH=CHCHO (Scheme 13).

With triene **8** in hand, it was now time to address the preparation of the requisite tetraenes. Thus, a Stille cross-coupling coupling between (*Z*)-vinyl iodide **7** and triene **8**, using catalytic [$Pd_2(dba)_3$] (5 mol%) and Ph_3As (13 mol%) in DMF/THF,[40] afforded the desired product **6** in 59% yield. At this point, we elected to make use of (*Z*)-vinyl iodide **51**[41] as an appropriate model for the spiroacetal-containing coupling fragment. Tetraene **52** was thus prepared in 60% yield under the same Pd-catalysis conditions, using **51** in combination with triene **8**. With the targeted tetraenes **6** and **52** now in hand, the stage was set for the second Stille reaction to afford the characteristic (4*Z*, 6*E*, 8*Z*, 10*E*, 12*Z*)-pentaene moiety of the spirangiens. Under the same reaction conditions ([$Pd_2(dba)_3$], Ph_3As), coupling of tetraene **6** and (*Z*)-vinyl iodide **51** generated the desired pentaene **53** in 64% yield. In comparison, coupling between tetraene **52** and vinyl iodide **7** gave a 61% yield of **53**. Necessarily, all of these Stille coupling reactions were performed with the strict exclusion of light to avoid undesired isomerization. In this way, only minor traces (≤10%) of geometric isomers were evident by ^1H and ^{13}C NMR analysis.



Scheme 13. Preparation of tetraene **6**, model tetraene **52**, and model pentaene **53**. a) (*E*)-Bu_3SnCH=CHCHO, KHMDS, THF, −78→20 °C, 16 h; b) [$Pd_2(dba)_3$], Ph_3As, DMF/THF (4:1), 20 °C, 16 h.

Encouraged by the positive results obtained thus far, we returned our attention to the real system (Scheme 14). It was clear that aldehyde **41**, which had previously been efficiently converted into degradation fragment **3**, could equally well serve as a precursor for the preparation of the required coupling partner **5** for the assembly of spirangien A itself. Hence, a Stork–Wittig[37] olefination of **41** using iodomethylenetriphenyl phosphorane (generated using NaHMDS) in THF/HMPA, followed by cleavage of the TES ethers using CSA/MeOH, enabled the isolation of configurationally pure iodide **5**, in readiness for attachment of the C1–C11 side-chain. Under analogous Pd-catalysis conditions to those employed previously, with strict exclusion of light and employing base-washed amberized glassware, bis-stannyl triene **8** was coupled with **5** to afford the desired tetraene **46** in 60% yield. We were now poised to incorporate the remainder of the side-chain, thus generating the corresponding methyl ester **4** of spirangien A. Crucially, the Pd-catalyzed Stille reaction of stannyl tetraene **6** with the corresponding (*Z*)-vinyl iodide **5** afforded the desired product **4** in 65% yield. The alternative coupling sequence between iodide **7** and stannane **46** performed less well, leading to the formation of **4** in 42% yield. At this stage, spirangien A methyl ester was isolated and submitted to careful HPLC purification. Detailed ^1H and ^{13}C NMR analysis of the so-obtained product and comparison with available literature data[7] for spirangien A itself were then possible. Gratifyingly, other than having the additional methyl signal, the NMR data for the synthetic spirangien A methyl ester[42] was in good agreement (see the Supporting Information for details), providing a tantalizing glimpse of an eventual successful completion of the total synthesis.



Scheme 14. Completion of the total synthesis of spirangien A (**1**). a) $(Ph_3PCH_2I)^+I^-$, NaHMDS, HMPA, THF, −78→20 °C, 1 h; b) CSA, MeOH, 20 °C, 16 h; c) $[Pd_2(dba)_3]$, Ph_3As, DMF/THF (4:1), 20 °C, 16 h; d) KOH, EtOH/H_2O (2:1), 20 °C, 16 h.

Having secured the synthesis of spirangien A methyl ester, the task still remained to identify suitable conditions to hydrolyze to the corresponding acid, mindful of the need to avoid isomerization of the delicate pentaene moiety. After extensive experimentation,[43] optimal results were achieved by treatment of ester **4** with KOH in aqueous EtOH, which delivered the unstable[44] carboxylic acid **1** (85%). Notably, the spectroscopic data obtained for synthetic **1** were in complete accordance with that reported for natural spirangien A.[7] Moreover, the measured specific rotation, $[\alpha]_D^{20} = -17.5$ ($c = 0.04$, MeOH), compared to −19.4 ($c =$ 1.0, MeOH), was also in agreement, both in terms of magnitude and sign, thereby validating the full configurational assignment of the spirangiens. Importantly, the methyl ester **4** was found to display much improved stability compared to the natural product itself.

Conclusions

In conclusion, we have completed the first total synthesis of (−)-spirangien A, which proceeds in 18 steps and 2.0% overall yield (via **6**) from the readily available 1,3-diol **12**. This convergent and expedient strategy relies upon the use of our boron aldol methodology and a common stereotetrad building block, to rapidly assemble the spiroacetal core of the spirangiens. Initially, efforts focussed on the preparation of the advanced C10–C32 diene degradation fragement **3**, thereby enabling the assignment of the full configuration of the spirangiens. With a confident assignment of stereochemistry achieved, the developed synthetic route served as a secure platform from which to advance to the total synthesis of spirangien A itself. Attachment of the delicate pentaene side-chain was achieved by making use of Stork–Wittig olefination and sequential Stille cross-coupling reactions with the bis-stannyltriene linking unit **8**, and subsequent hydrolysis of the initially formed (and more stable) spirangien methyl ester. It is envisaged that this completed total synthesis will serve as an excellent point from which to progress SAR studies of the spirangiens, and enable the determination of the mechanism of action. Notably, by suitable editing of the pendant side-chain, potentially more stable analogues may be designed that retain the associated potent antimitotic activity.

Experimental Section

General procedures: See the Supporting Information for details of instrumentation, purification of reagents and solvents, and chromatography. All non-aqueous reactions were performed under an atmosphere of argon using oven-dried apparatus and employing standard techniques for handling air-sensitive materials.

Aldol adduct 14: To a solution of dicyclohexylboron chloride (20.0 mL, 91.4 mmol) in dry Et_2O (80 mL) at 0 °C was added triethylamine (14.4 mL, 104 mmol). Ketone **(*S*)-13** (14.4 g, 60.9 mmol) in Et_2O (40 mL) was added by cannula and the reaction mixture was stirred at 0 °C for 1 h before cooling to −78 °C. A solution of freshly distilled methacrolein (10.1 mL, 122 mmol) in Et_2O (40 mL) was added by cannula and stirring was continued for 1 h before placing in the freezer overnight. The reaction mixture was partitioned between Et_2O (3×100 mL) and pH 7 buffer (200 mL) and the organic extracts were concentrated in vacuo to give an oil, which was then taken up in methanol (300 mL) and pH 7 buffer (300 mL) and stirred at 0 °C. H_2O_2 (30% aqueous, 90 mL) was added dropwise, and after stirring at room temperature for 2 h the mixture was diluted with water and extracted with CH_2Cl_2 (3×200 mL). The combined organics were washed with saturated aqueous $Na_2S_2O_3$ (300 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting crude aldol product was subjected to high-vacuum distillation (0.1 mm Hg/40 °C) to remove excess cyclohexanol. Flash column chromatography (10→20% EtOAc/hexanes) yielded aldol adduct **14** (15.7 g, 84%) as a colorless oil. The characterization data for this compound was in agreement with that reported.[16a]

***Anti*-diol 12**: To a solution of aldol adduct **14** (9.40 g, 30.7 mmol) and propionaldehyde (8.84 mL, 123 mmol) in THF (75 mL) at −10 °C was added a solution of freshly prepared SmI_2 (0.1 M in THF, 61.4 mL, 6.14 mmol) dropwise. A color change of the SmI_2 from deep blue to pale yellow was observed. After 1.5 h at −10 °C the reaction was partitioned between $NaHCO_3$ (75 mL) and Et_2O (3×100 mL). The combined organics were dried ($MgSO_4$) and evaporated in vacuo to give crude ester. To a solution of crude ester (11.2 g, 30.7 mmol) in MeOH (132 mL) and H_2O (13 mL) at room temperature was added K_2CO_3 (9.68 g, 61.4 mmol). After stirring at room temperature for 5 h, the reaction was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo to give diol **12** (9.46 g, quantitative). The characterization data for this compound was in agreement with that reported.[16a]

Triol 16: To a solution of diol **12** (750 mg, 2.43 mmol) in THF (25 mL) at 0 °C was added $BH_3{\cdot}SMe_2$ (2 M in THF, 3.65 mL, 7.30 mmol). The resulting solution was allowed to warm to room temperature and stirred at this temperature for 3 h, before recooling to 0 °C. The reaction was quenched by the addition of EtOH (19 mL), NaOH (10% aqueous, 21 mL), and H_2O_2 (30% aqueous, 17 mL) and then stirred for 1 h. The phases were separated and the aqueous phase was extracted with EtOAc (3×40 mL).

The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (1→2% MeOH/CH_2Cl_2) to yield desired *syn*-triol **16** (635 mg, 80%) and undesired *anti*-triol **16a** (111 mg, 14%) as colorless oils. *Syn*-triol **16**: R_f 0.26 (100% EtOAc); $[\alpha]_D^{20}=+22.3$ ($c=5.47$, $CHCl_3$); IR (neat): $\tilde{\nu}=3361$, 2965, 2934, 1613, 1513, 1248 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H=7.23$ (2H, d, $J=8.5$ Hz, ArH), 6.87 (2H, d, $J=8.6$ Hz, ArH), 4.45 (2H, AB quartet, $J=2.5$ Hz, OCH_2Ar), 4.15 (1H, brs, OH27), 3.87 (1H, d, $J=9.4$ Hz, H27), 3.79 (3H, s, ArOCH_3), 3.79–3.76 (1H, obs, H25), 3.72–3.63 (2H, m, H23a and H23b), 3.41 (1H, dd, $J=9.1$, 4.0 Hz, H29a), 3.48 (1H, dd, $J=9.1$, 9.1 Hz, H29b), 3.33 (1H, brs, OH25), 2.66 (1H, brs, OH23), 2.03–1.96 (1H, m, H28), 1.86–1.79 (1H, m, H24), 1.76–1.69 (1H, m, H26), 0.97 (3H, d, $J=7.2$ Hz, Me24), 0.85 (3H, d, $J=7.0$ Hz, Me26), 0.77 ppm (3H, d, $J=6.8$ Hz, Me28); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C=159.4$, 129.6, 129.4, 113.9, 76.7, 76.2, 75.8, 73.2, 67.7, 55.3, 35.7, 36.8, 35.7, 13.1, 9.8, 9.7 ppm; HRMS (ES+) calculated for $C_{18}H_{31}O_5$ [M+H^+]: 327.2166, found: 327.2163. *Anti*-triol **16a**: R_f 0.38 (100% EtOAc); $[\alpha]_D^{20}=+38.2$ ($c=3.13$, $CHCl_3$); IR (neat): $\tilde{\nu}=3364$, 2964, 2933, 1612, 1513, 1246 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H=7.24$ (2H, d, $J=8.4$ Hz, ArH), 6.90 (2H, d, $J=8.6$ Hz, ArH), 4.52 (1H, s, OH25), 4.45 (2H, AB quartet, $J=8.3$ Hz, OCH_2Ar), 4.46 (1H, s, OH27), 3.99–3.94 (1H, m, OH23), 3.91 (1H, d, $J=9.0$ Hz, H27), 3.81 (3H, s, ArOCH_3), 3.70–3.66 (2H, m, H23a and H23b), 3.59 (1H, dd, $J=9.3$, 4.0 Hz, H29a), 3.48–3.42 (2H, m, H29b and H25), 2.09–1.97 (2H, m, H24 and H28), 1.84–1.76 (1H, m, H26), 1.08 (3H, d, $J=7.1$ Hz, Me26), 0.85 (3H, d, $J=6.8$ Hz, Me24 or Me28), 0.74 ppm (3H, d, $J=6.9$ Hz, Me24 or Me28); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C=159.5$, 129.5, 129.3, 114.0, 84.1, 76.7, 76.6, 73.4, 69.6, 55.3, 38.0, 35.5, 34.5, 13.7, 12.7, 10.5 ppm; HRMS (ES+) calculated for $C_{18}H_{31}O_5$ [M+H^+]: 327.2166, found: 327.2168.

TBS ether 16b: To a solution of triol **16** (881 mg, 2.70 mmol) in CH_2Cl_2 (17 mL) at room temperature was added imidazole (239 mg, 3.51 mmol), followed by *tert*-butyldimethylsilyl chloride (448 mg, 2.97 mmol). The resulting solution was stirred at room temperature for 1 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/hexanes) to yield TBS ether **16b** (1.11 g, 93%) as a colorless oil. The data for this compound was in agreement with that reported.[45]

Acetonide 17: To a solution of diol **16b** (741 mg, 1.68 mmol) in CH_2Cl_2 (12 mL) at room temperature was added dimethoxypropane (4.14 mL, 33.7 mmol) followed by PPTS (42 mg, 0.17 mmol). The resulting solution was stirred at room temperature overnight before quenching by the addition of saturated aqueous $NaHCO_3$ (15 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/hexanes) to yield acetonide **17** (771 mg, 96%) as a colorless oil. The data for this compound was in agreement with that reported.[45]

Alcohol 17a: To a solution of TBS ether **17** (674 mg, 1.40 mmol) in THF (20 mL) at 0°C was added TBAF (1M in THF, 2.81 mL, 2.81 mmol). The resulting solution was allowed to warm to room temperature, stirred for 2 h, and then quenched by the addition of saturated aqueous NH_4Cl (20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (30→40% EtOAc/hexanes) to yield alcohol **17a** (500 mg, 98%) as a pale yellow oil. R_f 0.29 (20% EtOAc/hexanes); $[\alpha]_D^{20}=+1.2$ ($c=1.40$, $CHCl_3$); IR (neat): $\tilde{\nu}=3419$, 1613, 1514, 1379, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H=7.27$ (2H, d, $J=8.9$ Hz, ArH), 6.89 (2H, d, $J=8.7$ Hz, ArH), 4.43 (2H, s, OCH_2Ar), 3.82 (3H, s, ArOCH_3), 3.72–3.62 (2H, m, H29a and H29b), 3.62 (1H, dd, $J=11.0$, 4.2 Hz, H27), 3.55 (1H, dd, $J=8.7$, 3.0 Hz, H23a), 3.51 (1H, dd, $J=7.3$, 3.0 Hz, H25), 3.41 (1H, dd, $J=8.7$, 6.3 Hz, H23b), 2.46 (1H, brs, OH), 1.96–1.89 (1H, m, H26), 1.88–1.80 (2H, m, H24 and H28), 1.35 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.29 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 0.99 (3H, d, $J=7.0$ Hz, Me28), 0.97 (3H, d, $J=7.0$ Hz, Me24), 0.89 ppm (3H, d, $J=6.6$ Hz, Me26); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C=159.0$, 131.0, 129.1, 113.4, 100.7, 77.9, 72.9, 72.1 70.3, 67.1, 55.3, 37.7, 34.1, 33.7, 25.0, 23.7, 13.4, 12.2, 10.7 ppm; HRMS (ES+) calculated for $C_{21}H_{34}O_5Na$ [M+Na^+]: 389.2298, found: 389.2301.

Aldehyde 10: To a solution of alcohol **17a** (25 mg, 68.2 μmol) in CH_2Cl_2 (1 mL) at room temperature was added $NaHCO_3$ (46 mg, 0.54 mmol) followed by Dess–Martin periodinane (116 mg, 0.27 mmol). The resulting solution was stirred at room temperature for 1 h and then quenched by the addition of hexanes (1.5 mL). The resulting suspension was filtered through a silica plug (20% EtOAc/hexanes) to provide aldehyde **10** (24 mg, 96%), which was used directly. R_f 0.61 (20% EtOAc/hexanes); $[\alpha]_D^{20}=+15.7$ ($c=2.67$, $CHCl_3$); IR (neat): $\tilde{\nu}=1726$, 1613, 1513, 1380, 1223 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H=9.70$ (1H, d, $J=1.1$ Hz, CHO), 7.25 (2H, d, $J=8.7$ Hz, ArH), 6.87 (2H, d, $J=8.7$ Hz, ArH), 4.41 (2H, s, OCH_2Ar), 3.80 (3H, s, ArOCH_3), 3.75 (1H, dd, $J=7.5$, 3.3 Hz, H25), 3.61 (1H, dd, $J=10.8$, 4.2 Hz, H27), 3.52 (1H, dd, $J=8.7$, 3.0 Hz, H29a), 3.40 (1H, dd, $J=8.7$, 6.1 Hz, H29b), 2.41 (1H, qdd, $J=7.5$, 3.5, 1.2 Hz, H24), 1.96–1.88 (1H, m, H26), 1.88–1.78 (1H, m, H28), 1.31 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.25 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.15 (3H, d, $J=7.0$ Hz, Me24), 0.94 (3H, d, $J=6.8$ Hz, Me28), 0.91 ppm (3H, d, $J=6.8$ Hz, Me26); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C=204.3$, 159.0, 130.9, 129.1, 113.7, 100.9, 74.1, 72.9 72.0, 70.1, 55.2, 49.0, 34.5, 33.7, 24.6, 23.5, 13.4, 11.9, 7.9 ppm; HRMS (ES+) calculated for $C_{21}H_{32}O_5Na$ [M+Na^+]: 387.2142, found: 387.2136.

Acetonide 12a: To a solution of diol **12** (2.00 g, 6.49 mmol) in CH_2Cl_2 (16 mL) at room temperature was added dimethoxypropane (14.1 mL, 115 mmol) followed by PPTS (163 mg, 0.06 mmol). The resulting solution was stirred at room temperature overnight before quenching by addition of saturated aqueous $NaHCO_3$ (20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/40-60 petroleum ether) to yield acetonide **12a** (2.24 g, 99%) as a colorless oil. R_f 0.76 (30% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20}=+24.0$ ($c=1.67$, $CHCl_3$); IR (neat): $\tilde{\nu}=1614$, 1512, 1378, 1246 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H=7.26$ (2H, d, $J=8.7$ Hz, ArH), 6.88 (2H, d, $J=8.8$ Hz, ArH), 4.94 (1H, s, H13a), 4.84 (1H, s, H13b), 4.42 (2H, s, OCH_2Ar), 3.81 (3H, s, ArOCH_3), 3.72–3.67 (2H, m, H17 and H15), 3.55 (1H, dd, $J=8.5$, 3.2 Hz, H19a), 3.41 (1H, dd, $J=8.4$, 5.8 Hz, H19b), 1.92–1.82 (2H, m, H16 and H18), 1.77 (3H, s, Me14), 1.36 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.31 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 0.95 (3H, d, $J=6.7$ Hz, Me16 or Me18), 0.90 ppm (3H, d, $J=6.8$ Hz, Me16 or Me18); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C=159.0$, 144.5, 131.1, 129.1, 113.1, 111.7, 100.8, 79.4, 72.9, 72.2, 70.1, 55.3, 35.9, 33.9, 24.9, 23.8, 18.0, 13.5, 11.7 ppm; HRMS (ES+) calculated for $C_{21}H_{33}O_4$ [M+H^+]: 349.2373, found: 349.2378.

Alcohol 12b: To a solution of PMB ether **12a** (670 mg, 1.92 mmol) in CH_2Cl_2 (60 mL) and pH 7 buffer (8 mL) at 0°C was added DDQ (524 mg, 2.31 mmol). The resulting solution was allowed to warm to room temperature and stirred for 30 min before being quenched by the addition of saturated aqueous $NaHCO_3$ (80 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organics were washed (H_2O), dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/toluene) to yield alcohol **12b** (437 mg, 99%) as a colorless oil. R_f 0.28 (30% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20}=+58.8$ ($c=1.20$, $CHCl_3$); IR (neat): $\tilde{\nu}=3486$, 1381, 1216, 1018 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H=4.94$ (1H, s, H13a), 4.84 (1H, s, H13b), 3.73 (1H, d, $J=6.8$ Hz, H15), 3.71 (1H, dd, $J=9.4$, 4.2 Hz, H17), 3.62–3.57 (1H, m, H19a), 3.56–3.50 (1H, m, H19b), 3.14 (1H, dd, $J=9.8$, 1.6 Hz, OH), 1.96–1.86 (2H, m, H16 and H18), 1.77 (3H, s, Me14), 1.41 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.37 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 0.92 (3H, d, $J=6.8$ Hz, Me18), 0.78 ppm (3H, d, $J=6.9$ Hz, Me16); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C=144.0$, 112.1, 100.9, 79.0, 75.8, 68.9, 36.0, 35.2, 25.1, 23.8, 17.9, 12.7, 11.8 ppm; HRMS (ES+) calculated for $C_{13}H_{25}O_3$ [M+H^+]: 229.1798, found: 229.1796.

Iodide 18: To a solution of alcohol **12b** (983 mg, 4.31 mmol) in toluene (25 mL) at room temperature was added triphenylphosphine (1.36 g, 5.17 mmol), followed by triethylamine (0.72 mL, 5.17 mmol). The resulting solution was cooled to 0°C and a solution of iodine (1.31 g, 5.17 mmol) in toluene (25 mL) was added slowly by cannula. After 5 min, imidazole (ca. 20 mg, catalytic) was added and the solution was al-

lowed to warm to room temperature. After stirring at this temperature for 2 h the reaction was quenched by partitioning between Et_2O and H_2O. The phases were separated and the aqueous phase was extracted with Et_2O (3×80 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/40-60 petroleum ether) to yield iodide **18** (1.33 g, 95%) as a colorless oil. R_f 0.68 (30% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20}=+15.8$ ($c=3.50$, $CHCl_3$); IR (neat): $\tilde{\nu}=2984$, 1456, 1377, 1223 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H=4.94$ (1H, s, H13a), 4.85 (1H, s, H13b), 3.70 (1H, d, $J=7.3$ Hz, H15), 3.49 (1H, dd, $J=10.3$, 4.3 Hz, H17), 3.43 (1H, dd, $J=9.5$, 3.2 Hz, H19a), 3.38 (1H, dd, $J=9.6$, 5.4 Hz, H19b), 1.93–1.86 (1H, m, H16), 1.78 (3H, s, Me14), 1.47–1.43 (1H, m, H18), 1.42 (3H, s, OC-(CH_3)$_a$(CH_3)$_b$), 1.36 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 0.94 (3H, d, $J=4.3$ Hz, Me16 or Me18), 0.92 ppm (3H, d, $J=4.6$ Hz, Me16 or Me18); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C=144.0$, 112.1, 100.9, 79.0, 75.8, 68.9, 36.0, 35.2, 25.1, 23.8, 17.9, 12.7, 11.8 ppm; HRMS (ES+) calculated for $C_{13}H_{24}IO_2$ [M+H^+]: 339.0815, found: 339.0817.

Ketone 20: To a suspension of LiCl (1.97 g, 46.5 mmol, weighed in glove box and flame dried prior to use) in THF (30 mL) at room temperature was added diisopropylamine (6.95 mL, 49.6 mmol). The resulting suspension was cooled to −78°C and *n*-butyllithium (1.6 M in hexanes, 29.1 mL, 46.5 mmol) was added. The solution was allowed to warm to 0°C briefly and then recooled to −78°C. An ice-cooled solution of amide **19** (3.46 g, 15.5 mmol) in THF (15 mL) was added by cannula and the mixture was stirred at −78°C for 1 h, at 0°C for 15 min, and at room temperature for 5 min before recooling to 0°C. A solution of iodide **18** (1.31 g, 3.87 mmol) in THF (11 mL) was added by cannula and the resulting solution was allowed to warm to room temperature and was stirred at this temperature for 16 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (4×50 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (1% Et_3N in EtOAc) to yield amide **18a** (1.55 g, 93%) as a colorless oil. To a solution of amide **18a** (azeotroped from toluene twice before use) (100 mg, 0.23 mmol) in THF (3 mL) at −78°C was added methyllithium (1.6 M in hexanes, 0.43 mL, 0.70 mmol). The mixture was allowed to warm to 0°C and held at this temperature for 10 min. Excess methyllithium was quenched at 0°C by the addition of diisopropylamine (32 μL, 0.23 mmol). After 15 min, a solution of acetic acid in Et_2O (10% v/v, 3 mL) was added. The mixture was partitioned between EtOAc (4 mL) and saturated aqueous $NaHCO_3$ (4 mL) and the organic phase was separated and extracted with saturated aqueous $NaHCO_3$ (4 mL) and H_2O (4 mL). The organic phase was dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (30% EtOAc/40-60 petroleum ether) to yield ketone **20** (56 mg, 86%) as a colorless oil. R_f 0.23 (20% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20}=+80.0$ ($c=1.10$, $CHCl_3$); IR (neat): $\tilde{\nu}=3470$, 1714, 1458, 1378, 1223, 1082 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H=4.94$ (1H, s, H13a), 4.85 (1H, s, H13b), 4.22–4.17 (1H, m, H20), 3.80 (1H, d, $J=4.5$ Hz, OH20), 3.71 (1H, d, $J=7.5$ Hz, H15), 3.44 (1H, dd, $J=10.6$, 4.4 Hz, H17), 2.22 (3H, s, Me22), 1.96–1.90 (1H, m, H16), 1.91–1.87 (1H, m, H19a), 1.85 (1H, dd, $J=11.1$, 3.2 Hz, H18), 1.78 (3H, s, Me14), 1.51–1.45 (1H, m, H19b), 1.37 (3H, s, O(CH_3)$_a$-(CH_3)$_b$), 1.34 (3H, s, O(CH_3)$_a$(CH_3)$_b$), 0.97 (3H, d, $J=6.7$ Hz, Me18), 0.90 ppm (3H, d, $J=6.9$ Hz, Me16); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C=$ 211.0, 144.2, 111.9, 100.9, 79.2, 75.9, 73.5, 37.4, 36.1, 30.4, 25.3, 24.9, 23.8, 18.0, 16.0, 11.8 ppm; HRMS (ES+) calculated for $C_{16}H_{29}O_4$ [M+H^+]: 285.2060, found: 285.2063.

Ketone 11: To a solution of alcohol **20** (389 mg, 1.37 mmol) in CH_2Cl_2 (25 mL) at −78°C was added 2,6-lutidine (0.64 mL, 5.47 mmol). The reaction mixture was stirred at −78°C for 10 min before triethylsilyl trifluoromethanesulfonate (0.93 mL, 4.10 mmol) was added. The reaction mixture was stirred at −78°C for 30 min and then quenched by the addition of saturated aqueous NH_4Cl (30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were dried ($MgSO_4$), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/40-60 petroleum ether) to yield ketone **11** (546 mg, 99%) as a colorless oil. R_f 0.63 (20% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20}=+4.5$ ($c=1.75$, $CHCl_3$); IR (neat): $\tilde{\nu}=1717$, 1458, 1377, 1223, 1083 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H=$ 4.92 (1H, s H13a), 4.83 (1H, s, H13b), 4.10 (1H, dd, $J=9.5$, 4.0 Hz, H20), 3.68 (1H, d, $J=7.2$ Hz, H15), 3.36 (1H, dd, $J=10.6$, 4.4 Hz, H17), 2.16 (3H, s, Me22), 2.07 (1H, ddd, $J=12.9$, 9.4, 2.8 Hz, H19a), 1.92–1.85 (1H, m, H16), 1.79–1.72 (1H, obs, H18), 1.76 (3H, s, Me14), 1.34 (3H, s, OC-(CH_3)$_a$(CH_3)$_b$), 1.29 (1H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.10 (1H, ddd, $J=13.6$, 9.5, 4.1 Hz, H19b), 0.96 (9H, t, $J=8.1$ Hz, Si(CH_2CH_3)$_3$), 0.87 (3H, d, $J=$ 6.8 Hz, Me16), 0.84 (3H, $J=6.5$ Hz, Me18), 0.61 ppm (6H, q, $J=8.0$ Hz, Si(CH_2CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C=212.4$, 144.4, 111.7, 100.7, 79.1, 73.2, 37.9, 36.1, 28.9, 24.9, 24.7, 23.8, 18.0, 15.4, 11.7, 6.7, 4.9, 4.8 ppm; HRMS (ES+) calculated for $C_{22}H_{46}O_4SiN$ [M+NH_4]$^+$: 416.3191, found: 416.3189.

Aldol adducts 9 and 21: To a solution of (−)-Ipc_2BCl (202 mg, 0.63 mmol) [dried by stirring under vacuum (1 mm Hg) at room temperature for 1.5 h] in Et_2O (3 mL) at 0°C was added triethylamine (110 μL, 0.79 mmol), followed by ketone **11** (157 mg, 0.39 mmol) in Et_2O (3 mL) by cannula. The reaction mixture was stirred for 1 h, cooled to −78°C, and a solution of aldehyde **10** (110 mg, 0.30 mmol) in Et_2O (3 mL) was then added by cannula. After 1 h at −78°C and 16 h at −27°C, the reaction mixture was quenched by the addition of pH 7 buffer (4 mL), MeOH (4 mL), and H_2O_2 (30% aqueous, 2 mL). After allowing to warm to room temperature and stirring for 1 h, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (20% EtOAc/hexanes) to yield aldol adducts **9** and **21** (148 mg 65%, ca. 2.5:1 d.r. by ^1H NMR analysis) as an inseparable mixture. Major diastereomer **9**: R_f 0.16 (10% EtOAc/40-60 petroleum ether); IR (neat): $\tilde{\nu}=3504$, 1713, 1614, 1514, 1378, 1224, 1018 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H=7.25$ (2H, d, $J=8.6$ ArH), 6.87 (2H, d, $J=8.6$ Hz, ArH), 4.93 (1H, s, H13a), 4.84 (1H, s, H13b), 4.41 (2H, s, OCH_2Ar), 4.19–4.10 (1H, m, H20), 4.06–3.99 (1H, m, H23), 3.80 (3H, s, ArOCH_3), 3.69 (1H, d, $J=7.3$ Hz, H15), 3.66 (1H, dd, $J=7.6$, 1.6 Hz, H25), 3.60–3.56 (1H, m, H27), 3.54–3.49 (1H, m, H29a), 3.42–3.34 (2H, m, H17 and H29b), 3.29 (1H, brs, OH), 2.75 (2H, d, $J=6.4$ Hz, H22a and H22b), 2.11–2.02 (1H, m, H19a), 1.94–1.79 (4H, m, H16, H18, H26, and H28), 1.76 (3H, s, Me14), 1.67–1.60 (1H, m, H24), 1.34 (6H, s, 2×OC(CH_3)$_a$(CH_3)$_b$), 1.29 (3H, s, OC(CH_3)$_a$-(CH_3)$_b$), 1.25 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.19–1.14 (1H, m, H19b), 0.99–0.92 (15H, m, Me24, Me28, and Si(CH_2CH_3)$_3$), 0.87 (3H, d, $J=6.9$ Hz, Me16), 0.86 (3H, d, $J=7.1$ Hz, Me18), 0.85 (3H, d, $J=6.5$ Hz, Me26), 0.62 ppm (6H, q, $J=7.9$ Hz, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta_C=214.7$, 159.0, 144.4, 131.0, 129.2, 113.7, 111.8, 100.7, 100.7, 79.2, 78.3, 74.3, 73.2, 72.9, 70.3, 70.0, 55.3, 42.3, 41.7, 40.4, 39.5, 37.9, 36.1, 35.1, 34.8, 33.8, 33.7, 29.1, 23.8, 18.0, 15.5, 15.3, 13.5, 13.4, 11.8, 10.3, 6.8, 4.9 ppm; HRMS (ES+) calculated for $C_{43}H_{74}O_6SiNa$ [M+Na^+]: 785.4994, found: 785.4983. Minor diastereomer **21**: R_f 0.16 (10% EtOAc/40-60 petroleum ether); ^1H NMR (500 MHz, $CDCl_3$): $\delta_H=7.25$ (2H, d, $J=8.7$ ArH), 6.87 (2H, d, $J=8.7$ Hz, ArH), 4.93 (1H, s, H13a), 4.84 (1H, s, H13b), 4.41 (2H, s, OCH_2Ar), 4.22 (1H, td, $J=6.4$, 2.8 Hz, H23), 4.14 (1H, dd, $J=$ 9.4, 3.7 Hz, H20), 3.80 (3H, s, ArOCH_3), 3.69 (1H, d, $J=7.3$ Hz, H15), 3.58 (1H, dd, $J=10.8$, 4.3 Hz, H27), 3.54–3.49 (2H, m, H25 and H29a), 3.43–3.35 (2H, m, H17 and H29b), 3.28 (1H, brs, OH), 2.75 (2H, d, $J=$ 6.5 Hz, H22a and H22b), 2.10–2.03 (1H, m, H19a), 1.92–1.79 (3H, m, H16, H26, and H28), 1.76 (3H, s, Me14), 1.67–1.60 (1H, m, H18), 1.60–1.52 (1H, m, H24), 1.35 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.34 (3H, s, OC-(CH_3)$_a$(CH_3)$_b$), 1.29 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.26 (3H, s, OC(CH_3)$_a$-(CH_3)$_b$), 1.18–1.12 (1H, m, H19b), 0.99–0.95 (12H, m, Me24 and Si-(CH_2CH_3)$_3$), 0.94 (3H, d, $J=6.9$ Hz, Me28), 0.87 (3H, d, $J=6.8$ Hz, Me16), 0.87 (3H, d, $J=7.1$ Hz, Me18), 0.85 (3H, d, $J=6.8$ Hz, Me26), 0.62 ppm (6H, q, $J=7.9$ Hz, Si(CH_2CH_3)$_3$).

Methyl ethers 22 and 23: To a solution of alcohols **9** and **21** (148 mg, 0.19 mmol) in CH_2Cl_2 (18 mL) at 0°C was added Proton Sponge (250 mg, 1.16 mmol) followed by trimethyloxonium tetrafluoroborate (114 mg, 0.78 mmol). The resulting solution was stirrred at room temperature for 1 h and quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with citric acid (10% weight solution, 40 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (15% EtOAc/hexanes) to yield methyl ethers **22** and **23** (125 mg, 83%, ca. 2:1

d.r. by ^{1}H NMR analysis) as an inseparable mixture. Major diastereomer **22**: R_f 0.30 (10% EtOAc/40-60 petroleum ether); IR (neat): $\tilde{\nu}$ = 1718, 1513, 1458, 1378, 1223, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.25 (2H, d, J = 8.4 Hz, ArH), 6.87 (2H, d, J = 8.7 Hz, ArH), 4.93 (1H, s, H13a), 4.84 (1H, s, H13b), 4.41 (2H, s, OCH_2Ar), 4.20–4.13 (1H, m, H20), 3.80 (3H, s, ArOCH_3), 3.77–3.71 (1H, m, H23), 3.69 (1H, d, J = 7.5 Hz, H15), 3.59–3.49 (2H, m, H25 and H29a), 3.43–3.33 (3H, m, H17, H27, and H29b), 3.28 (3H, s, OMe), 2.84 (1H, dd, J = 17.5, 9.3 Hz, H22a), 2.67 (1H, dd, J = 17.6, 4.0 Hz, H22b), 2.13–2.00 (1H, m, H19a), 1.93–1.86 (1H, m, H16), 1.85–1.78 (4H, m, H18, H24, H26, and H28), 1.77 (3H, s, Me14), 1.35 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.29 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.25 (3H, s, OC(CH_3)$_a$(CH_3)$_b$), 1.23 (3H, s, OC(CH_3)$_a$-(CH_3)$_b$), 1.17–1.10 (1H, m, H19b), 0.96 (9H, t, J = 7.8 Hz, Si(CH_2CH_3)$_3$), 0.91 (3H, d, J = 7.0 Hz, Me24), 0.89–0.83 (12H, m, Me16, Me18, Me26, and Me28), 0.61 ppm (6H, q, J = 7.9 Hz, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 212.4, 159.0, 144.4, 131.0, 129.2, 113.6, 111.8, 100.7, 100.7, 79.5, 79.2, 75.0, 73.2, 73.1, 72.2, 70.2, 57.7, 55.3, 40.1, 39.1, 38.7, 38.6, 37.6, 37.4, 36.1, 35.7, 33.8, 29.1, 24.7, 23.8, 23.5, 18.0, 15.2, 13.4, 11.7, 10.0, 8.4, 6.8, 4.9 ppm; HRMS (ES+) calculated for $C_{44}H_{76}O_9SiNa$ [M+Na$^+$]: 799.5151, found: 799.5114.

Spiroacetals 24 and 25: To a solution of ketones **22** and **23** (126 mg, 162 μmol) in MeOH (5 mL) at room temperature was added CSA (3.9 mg, 16.2 μmol). After stirring at room temperature for 16 h the reaction was quenched by addition of saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10→40% EtOAc/hexanes) to yield spiroacetals **24** (47 mg, 51%) and **25** (12 mg, 13%). Spiroacetal **24**: R_f 0.11 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +10.0 (c = 0.69, MeOH); IR (neat): $\tilde{\nu}$ = 3407, 1614, 1514, 1456, 1247 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.30 (2H, d, J = 8.7 Hz, ArH), 6.92 (2H, d, J = 8.7 Hz, ArH), 4.93 (1H, s, H13a), 4.91 (1H, s, H13b), 4.49 (2H, s, OCH_2Ar), 4.14 (1H, d, J = 9.5 Hz, H15), 4.06 (1H, d, J = 9.9 Hz, H27), 3.82 (3H, s, ArOCH_3), 3.76 (1H, dd, J = 10.4, 2.0 Hz, H25), 3.72 (1H, app. dt, J = 12.0, 4.5 Hz, H23), 3.66 (1H, dd, J = 8.9, 4.0 Hz, H29a), 3.60 (1H, dd, J = 10.4, 1.9 Hz, H17), 3.56 (1H, dd, J = 9.2, 5.9 Hz, H29b), 3.44 (1H, t, J = 2.9 Hz, H20), 3.38 (3H, s, OMe), 2.19 (1H, m, H24), 2.08 (1H, dd, J = 13.0, 4.8 Hz, H22a), 1.97 (1H, m, H18), 1.88 (1H, m, H28), 1.83 (1H, m, H26), 1.81 (1H, m, H16), 1.79 (1H, dd, J = 6.4, 2.5 Hz, H19a), 1.74 (3H, s, Me14), 1.65 (1H, dt, J = 13.3, 3.6, 3.6 Hz. H19b), 1.40 (1H, dd, J = 12.5, 12.5 Hz, H22b), 0.94 (3H, d, J = 7.0 Hz, Me28), 0.83 (3H, d, J = 7.2 Hz, Me26), 0.81 (3H, d, J = 7.0 Hz, Me24), 0.77 (3H, d, J = 7.0 Hz, Me16), 0.74 (3H, d, J = 6.5 Hz, Me18); ^{13}C NMR (125 MHz, CD_3OD): δ_C = 160.7, 147.7, 132.0, 130.2, 114.7, 114.3, 99.5, 78.9, 78.4, 74.9, 74.0, 73.8, 72.8, 71.9, 70.9, 55.7, 55.5, 37.8, 37.8, 37.4, 37.2, 33.8, 32.9, 25.9, 17.6, 16.2, 14.7, 9.6, 7.7, 4.0 ppm; HRMS (ES+) calculated for $C_{32}H_{52}O_8Na$ [M+Na$^+$]: 587.3554, found: 587.3552. Spiroacetal **25**: R_f 0.07 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +34.6 (c = 0.46, MeOH); IR (neat): $\tilde{\nu}$ = 3415, 1613, 1513, 1456, 1246 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.30 (2H, d, J = 8.7 Hz, ArH), 6.92 (2H, d, J = 8.7 Hz, ArH), 4.95 (1H, s, H13a), 4.90 (1H, s, H13b), 4.49 (2H, s, OCH_2Ar), 4.29 (1H, d, J = 9.3 Hz, H15), 4.09 (1H, dd, J = 10.6, 2.1 Hz, H25), 4.05 (1H, d, J = 9.8 Hz, H27), 3.82 (3H, s, ArOCH_3), 3.67 (1H, dd, J = 8.9, 4.0 Hz, H29a), 3.63 (1H, dd, J = 10.4, 1.7 Hz, H17), 3.55 (1H, dd, J = 9.1, 6.1 Hz, H29b), 3.51–3.48 (1H, m, H23), 3.40 (3H, s, OMe), 3.40 (1H, app. t, J = 3.1 Hz, H20), 2.25 (1H, dd, J = 15.4, 1.5 Hz, H22a), 2.01–1.93 (1H, m, H18), 1.93–1.85 (2H, m, H26 and H28), 1.85–1.77 (2H, m, H16 and H19a), 1.76–1.75 (1H, obs, H24), 1.74 (3H, s, Me14), 1.64 (1H, dt, J = 13.2, 3.7 Hz, H19b), 1.48 (1H, dd, J = 15.4, 3.8 Hz, H22b), 0.94 (3H, d, J = 6.7 Hz, Me26), 0.93 (3H, d, J = 7.1 Hz, Me28), 0.81 (3H, d, J = 7.0 Hz, Me16), 0.80 (3H, d, J = 7.0 Hz, Me24), 0.74 ppm (3H, d, J = 6.7 Hz, Me18); ^{13}C NMR (125 MHz, CD_3OD): δ_C = 160.7, 148.0, 132.0, 130.2, 114.7, 113.9, 98.2, 80.4, 78.2, 75.1, 74.0, 74.0 72.7, 71.6, 67.3, 55.9, 55.7, 37.9, 37.8, 37.3, 37.0, 34.3, 28.9, 25.6, 17.7, 16.6, 14.7, 10.4, 10.0, 7.7 ppm; HRMS (ES+) calculated for $C_{32}H_{52}O_8$ [M+Na$^+$]: 587.3554, found: 587.3553.

TES ether 24a: To a solution of triol **24** (12 mg, 21 μmol) in CH_2Cl_2 (2 mL) at −78 °C was added 2,6-lutidine (49 μL, 0.42 mmol). The reaction mixture was stirred at −78 °C for 10 min before triethylsilyl trifluoromethanesulfonate (48 μL, 0.21 mmol) was added. The reaction mixture was stirred at −78 °C for 1 h and then quenched by the addition of saturated aqueous NH_4Cl (4 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (5% EtOAc/hexanes) to yield TES-protected spiroacetal **24a** (18 mg, 94%). R_f 0.71 (10% EtOAc/hexanes); $[\alpha]_D^{20}$ = +22.6 (c = 0.25, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1514, 1458, 1246, 1087, 1002 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.27 (2H, d, J = 8.8 Hz, ArH), 6.91 (2H, d, J = 8.6 Hz, ArH), 4.98 (1H, s, H13a), 4.79 (1H, s, H13b), 4.45 (2H, AB quartet, J = 3.6 Hz, OCH_2Ar), 4.20 (1H, d, J = 4.8 Hz, H15), 3.99 (1H, m, H27), 3.82 (3H, s, ArOCH_3), 3.68 (1H, m, H23), 3.59 (2H, m, H25 and H29a), 3.48 (1H, m, H20), 3.35 (3H, s, OMe), 3.32 (1H, obs, H17), 3.20 (1H, dd, J = 9.2, 7.7 Hz, H29b), 2.29 (1H, m, H28), 2.07 (3H, m, H16, H18, and H24), 2.02 (1H, dd, J = 12.5, 4.4 Hz, H22a), 1.91 (1H, m, H26), 1.83 (3H, s, Me14), 1.80 (1H, obs, H19a), 1.41 (1H, ddd, J = 13.9, 3.7, 3.6 Hz, H19b), 1.40 (1H, dd, J = 12.5, 12.2 Hz, H22b), 1.10 (3H, d, J = 7.1 Hz, Me28), 1.02 (27H, t, J = 8.2 Hz, 3×Si(CH_2CH_3)$_3$), 0.85 (3H, d, J = 7.0 Hz, Me26), 0.80 (3H, d, J = 6.6 Hz, Me18), 0.73 (6H, m, Me16 and Me24), 0.65 ppm (18H, q, J = 7.6 Hz, 3×Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, CD_3OD): δ_C = 160.7, 149.5, 131.9, 130.1, 114.7, 113.8, 99.7, 81.5, 77.7, 76.8, 76.8, 76.2, 73.5, 73.0, 71.7, 55.7, 55.4, 43.0, 41.9, 38.3, 36.5, 34.3, 33.5, 25.8, 20.1, 18.6, 15.9, 13.2, 9.3, 7.7, 7.4, 7.3, 7.0, 6.0, 5.9, 4.4 ppm; HRMS (ES+) calculated for $C_{50}H_{94}O_8Si_3$ [M+Na$^+$]: 929.6149, found: 929.6176.

Alcohol 26: To a solution of PMB ether **24a** (5 mg, 5.5 μmol) in CH_2Cl_2 (400 μL) and pH 7 buffer (40 μL) at 0 °C was added DDQ (1.5 mg, 6.6 μmol). The resulting solution was stirred at room temperature for 2 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organics were washed (H_2O), dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (5% EtOAc/hexanes) to yield alcohol **26** (3.5 mg, 80%) as a colorless oil. R_f 0.53 (10% EtOAc/hexanes); $[\alpha]_D^{20}$ = +23.4 (c = 0.35, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3482, 1459, 1381, 1232 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H = 4.90 (2H, obs, H13a and H13b), 4.23 (1H, d, J = 5.0 Hz, H27), 4.00 (1H, dd, J = 4.9, 2.3 Hz, H15), 3.73 (1H, dd, J = 10.8, 2.3 Hz, H29a), 3.71–3.67 (1H, m, H23), 3.62 (1H, dd, J = 10.3, 2.2 Hz, H17), 3.52 (1H, t, J = 2.8 Hz, H20), 3.42–3.33 (2H, obs, H25 and H29b), 3.37 (3H, s, OMe), 2.19–2.08 (4H, m, H18, H24, H26, and H28), 2.04 (1H, dd, J = 13.2, 4.9 Hz, H22a), 1.99–1.92 (1H, m, H16), 1.90 (1H, dd, J = 13.2, 2.9 Hz, H19a), 1.85 (3H, s, Me14), 1.57 (1H, dt, J = 13.5, 3.7, 3.7 Hz, H19b), 1.23 (1H, dd, J = 12.2, 12.2 Hz, H22b), 1.12 (3H, d, J = 7.0 Hz, Me[1]), 1.10 (3H, d, J = 6.7 Hz, Me[1]), 1.08 (9H, t, J = 8.0 Hz, Si(CH_2CH_3)$_3$), 1.03 (9H, t, J = 8.0 Hz, Si(CH_2CH_3)$_3$), 1.02 (9H, t, J = 7.8 Hz, Si-(CH_2CH_3)$_3$), 0.89 (3H, d, J = 6.9 Hz, Me16), 0.88 (3H, d, J = 6.7 Hz, Me[1]), 0.78 (3H, d, J = 7.1 Hz, Me[1]), 0.70 (6H, q, J = 8.1 Hz, Si(CH_2CH_3)$_3$), 0.68 (6H, q, J = 7.5 Hz, Si(CH_2CH_3)$_3$), 0.65 ppm (6H, q, J = 7.8 Hz, Si-(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, CD_3OD): δ_C = 149.6, 113.8, 99.8, 81.5, 77.7, 77.2, 76.9, 76.6, 71.6, 65.1, 55.4, 44.2, 43.1, 38.5, 36.6, 34.4, 33.5, 25.8, 20.1, 18.6, 15.6, 13.2, 9.4, 7.7, 7.4, 7.3, 6.9, 5.9, 5.9, 4.3 ppm; HRMS (ES+) calculated for $C_{42}H_{86}O_7Si_3Na$ [M+Na$^+$]: 787.5754, found: 787.5726.

Iodide 27: To a solution of alcohol **26** (3.5 mg, 4.4 μmol) in toluene (300 μL) at room temperature was added triphenylphosphine (1.4 mg, 5.2 μmol), followed by triethylamine (0.7 μL, 5.2 μmol). The resulting solution was cooled to 0 °C and a solution of iodine (1.1 mg, 5.2 μmol) in toluene (300 μL) was added slowly by cannula. After 5 min, imidazole (ca. 0.5 mg, catalytic) was added and the solution was allowed to warm to room temperature. After stirring at this temperature for 2 h the reaction was quenched by partitioning between Et_2O and H_2O. The phases were separated and the aqueous phase was extracted with Et_2O (3×2 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (5% EtOAc/hexanes) to yield iodide **27** (3.9 mg, 98%) as a colorless oil. R_f 0.88 (10% EtOAc/hexanes); $[\alpha]_D^{20}$ = +15.2 (c = 0.35, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1457, 1233, 1086, 1005 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H = 5.01 (1H, s, H13a), 4.84 (1H, s,

[1] H18, H24, H26, and H28 overlap in the ^{1}H NMR spectrum; the signals corresponding to Me18, Me24, Me26, and Me28 could not be unambiguously assigned.

H13b), 4.21 (1H, d, J=4.5 Hz, H17), 3.91 (1H, dd, J=5.5, 3.5 Hz, H27), 3.71 (1H, dt, J=12.2, 4.7, 4.7 Hz, H23), 3.63 (1H, dd, J=10.2, 2.1 Hz, H25), 3.53 (1H, t, J=2.8 Hz, H20), 3.46 (1H, dd, J=9.9, 2.9 Hz, H29a), 3.37 (3H, s, OMe), 3.39–3.32 (1H, obs, H15), 2.95 (1H, dd, J=9.8, 9.8, Hz, H29b), 2.39–2.31 (1H, m, H28), 2.18–2.07 (3H, m, H16, H18, and H24), 2.04 (1H, dd, J=12.8, 4.0 Hz, H22a), 1.95–1.87 (2H, m, H19a and H26), 1.83 (3H, s, Me14), 1.59 (1H, dt, J=13.5, 3.7, 3.7 Hz, H19b), 1.25 (1H, dd, J=12.1, 12.1 Hz, H22b), 1.18 (3H, d, J=6.9 Hz, Me28), 1.11 (3H, d, J=7.1 Hz, Me16), 1.07 (9H, t, J=8.0 Hz, $Si(CH_2CH_3)_3$), 1.04 (9H, t, J=8.0 Hz, $Si(CH_2CH_3)_3$), 1.02 (9H, t, J=9.0 Hz, $Si(CH_2CH_3)_3$), 0.92 (3H, d, J=7.0 Hz, Me26), 0.87 (3H, d, J=7.0 Hz, Me24), 0.80 (3H, d, J=6.6 Hz, Me18), 0.76 (6H, q, J=8.1 Hz, $Si(CH_2CH_3)_3$), 0.69 (6H, q, J=7.5 Hz, $Si(CH_2CH_3)_3$), 0.65 ppm (6H, q, J=7.8 Hz, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, CD_3OD): δ_C=149.5, 113.7, 99.9, 81.4, 78.4, 77.7, 76.7, 76.3, 71.5, 55.4, 44.5, 42.5, 38.9, 36.9, 34.3, 33.7, 25.9, 20.0, 19.2, 18.7, 13.6, 9.9, 7.6, 7.4, 7.3, 6.8, 6.0, 4.4 ppm; HRMS (ES+) calculated for $C_{42}H_{85}IO_6Si_3Na$ [M+Na^+]: 919.4591, found: 919.4622.

Silyl-migrated product 28: To a solution of (2*E*)-2-bromobutene (27 μL, 0.27 mmol) in THF (0.5 mL) at −78 °C was added *tert*-butyllithium (1.7 M in pentane, 0.31 mL, 0.53 mmol). The resulting stock solution was stirred at this temperature for 10 min and then an aliquot (84 μL) added to a solution of iodide **27** (8 mg, 8.9 μmol) in THF (0.5 mL) at −78 °C. After stirring at −78 °C for 10 min the solution was allowed to warm to 0 °C, stirred for a further 20 min, and then quenched by addition of saturated aqueous NH_4Cl (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (5% EtOAc/hexanes) to yield the undesired silyl-migrated product **28** (6.1 mg, 89%). R_f 0.76 (10% EtOAc/hexanes); $[\alpha]_D^{20}$ = +30.8 (c=0.61, $CHCl_3$); IR (neat): $\tilde{\nu}$=3605, 1458, 1380, 1233 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H=5.10 (1H, s, H13a), 4.89 (1H, s, H13b), 4.22 (1H, d, J=5.6 Hz, H27), 3.79–3.71 (2H, m, H23 and H25), 3.58 (1H, dd, J=5.4, 4.4 Hz, H17), 3.53 (1H, t, J=10.6 Hz, H20), 3.51 (1H, d, J=10.6, H15), 3.37 (3H, s, OMe), 2.21–2.12 (1H, m, H26), 2.04 (1H, dd, J=12.5, 4.4 Hz, H22a), 2.01–1.92 (3H, m, H16, H18, and H28), 1.90–1.80 (2H, m, H19a and H24), 1.77 (3H, s, Me14), 1.58 (1H, dt, J= 13.6, 3.6, 3.6 Hz, H19b), 1.24 (1H, dd, J=12.5, 12.5 Hz, H22b), 1.05 (3H, d, J=7.1 Hz, Me16), 1.04 (9H, t, J=7.8 Hz, $Si(CH_2CH_3)_3$), 1.02 (18H, t, J=6.5 Hz, 2×$Si(CH_2CH_3)_3$), 1.01 (1H, obs, H29a) ,0.98 (3H, d, J= 6.7 Hz, Me18), 0.87 (3H, d, J=7.0 Hz, Me24), 0.84 (3H, d, J=6.6 Hz, Me28), 0.78 (3H, d, J=7.1 Hz, Me26), 0.70 (6H, q, J=8.1 Hz, $Si(CH_2CH_3)_3$), 0.66 (6H, q, J=7.5 Hz, $Si(CH_2CH_3)_3$), 0.62 (6H, q, J= 7.8 Hz, $Si(CH_2CH_3)_3$), 0.34 ppm (1H, dd, J=15.0, 11.0 Hz, H29b); ^{13}C NMR (125 MHz, CD_3OD): δ_C=148.6, 114.4, 99.2, 80.9, 78.6, 78.2, 75.3, 75.0, 71.8, 55.4, 41.0, 37.4, 36.9, 34.9, 34.5, 33.2, 25.9, 20.6, 19.0, 18.7, 14.4, 10.3, 7.9, 7.6, 7.3, 6.0, 6.0, 5.1, 4.3 ppm; HRMS (ES+) calculated for $C_{42}H_{86}O_6Si_3Na$ [M+Na^+]: 793.5630, found: 793.5657.

Alcohol 17b: To a solution of PMB ether **17** (771 mg, 1.61 mmol) in CH_2Cl_2 (45 mL) and pH 7 buffer (6 mL) at 0 °C was added DDQ (437 mg, 1.93 mmol). The resulting solution was stirred at room temperature for 1 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organics were washed (H_2O), dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/toluene) to yield alcohol **17b** (542 mg, 93%) as a colorless oil. The data for this compound was in agreement with that reported.[45]

Iodide 32: To a solution of alcohol **17b** (310 mg, 0.86 mmol) in toluene (10 mL) at room temperature was added triphenylphosphine (271 mg, 1.03 mmol), followed by triethylamine (0.14 mL, 1.03 mmol). The resulting solution was cooled to 0 °C and a solution of iodine (262 mg, 1.03 mmol) in toluene (5 mL) was added slowly by cannula. After 5 min, imidazole (ca. 10 mg, catalytic) was added and the solution was allowed to warm to room temperature. After stirring at this temperature for 3 h the reaction was quenched by partitioning between Et_2O and H_2O. The phases were separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/40-60 petroleum ether) to yield alcohol **32** (395 mg, 98%) as a colorless oil. R_f 0.61 (10% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20}$ = −18.6 (c=2.25, $CHCl_3$); IR (neat): $\tilde{\nu}$=1462, 1379, 1226, 1092 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=3.50 (1H, dd, J=9.6, 8.0 Hz, H29a), 3.46–3.40 (3H, m, H29b, H25, and H27), 3.40–3.35 (2H, m, H23a and H23b), 1.89–1.82 (1H, m, H26), 1.70–1.62 (1H, m, H28), 1.46–1.38 (1H, m, H24), 1.35 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.29 (3H, s, $OC(CH_3)_a(CH_3)_b$), 0.93 (3H, d, J=6.9 Hz, Me24), 0.89 (9H, s, $SiC(CH_3)_3$), 0.88 (3H, d, J=6.8 Hz, Me28), 0.86 (3H, d, J=6.8 Hz, Me26), 0.04 (3H, s, $SiCH_3$), 0.03 ppm (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C=100.6, 73.6, 72.3, 64.8, 39.2, 34.9, 33.9, 26.1, 25.9, 23.6, 18.2, 17.0, 16.6, 12.3, 10.8, −5.4, −5.4 ppm; HRMS (ES+) calculated for $C_{19}H_{40}IO_3Si$ [M+H^+]: 471.1786, found: 471.1786.

Alkene 33: To a solution of (2*E*)-2-bromobutene (1.72 g, 12.8 mmol) in dry THF (50 mL) at −100 °C was added *t*BuLi (1.58 M in pentane, 16.2 mL, 25.5 mmol) dropwise and the resulting yellow solution was stirred at −100 °C for 15 min. The organolithium solution was then transferred into a suspension of CuCN (0.57 g, 6.38 mmol) in dry Et_2O (50 mL) at −78 °C and the resulting pale yellow, homogeneous solution was stirred at −50 °C for 1 h. To this solution was added iodide **32** (1.50 g, 3.19 mmol) in dry Et_2O (15 mL) and the resulting bright yellow solution was stirred at −50 °C for 2 h. The reaction was warmed to 0 °C and stirred for 2 h, allowed to warm to room temperature, and stirred for a further 30 min. The reaction was quenched with saturated aqueous NH_4Cl and the phases were separated. The aqueous layer was extracted with Et_2O (3×60 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a pale yellow oil. Purification by flash chromatography (5% EtOAc/40-60 petroleum ether) afforded **33** (1.25 g, 98%) as a colorless oil. R_f 0.66 (10% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20}$ = + 0.6 (c=6.10, $CHCl_3$); IR (neat): $\tilde{\nu}$=1461, 1378, 1253, 1226, 1069 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=5.18 (1H, q, J=5.8 Hz, H31), 3.51 (1H, dd, J= 9.7, 7.9 Hz, H23a), 3.46–3.40 (2H, m, H23b and H25), 3.26 (1H, dd, J= 10.5, 4.2 Hz, H27), 2.58 (1H, d, J=13.3 Hz, H29a), 1.89–1.82 (1H, m, H26), 1.73–1.62 (2H, m, H28 and H24), 1.58 (3H, d, obs, H32), 1.57 (3H, s, Me30), 1.42 (1H, dd, J=13.3, 11.0 Hz, H29b), 1.30 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.26 (3H, s, $OC(CH_3)_a(CH_3)_b$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.87 (3H, d, J=6.9 Hz, Me24), 0.85 (3H, d, J=6.9 Hz, Me26), 0.70 (3H, d, J=6.6 Hz, Me28), 0.04 (3H, s, $SiCH_3$), 0.03 ppm (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C=134.7, 119.8, 100.4, 74.3, 73.8, 65.0, 43.8, 39.3, 35.4, 30.7, 25.9, 24.9, 23.7, 18.2, 15.5, 14.5, 13.4, 11.8, 10.8, −5.3, −5.4 ppm; HRMS (ES+) calculated for $C_{23}H_{47}O_3Si$ [M+H^+]: 399.3289, found: 399.3290.

Alcohol 33a: To a solution of TBS ether **33** (276 mg, 0.69 mmol) in THF (7 mL) at 0 °C was added TBAF (1 M in THF, 1.39 mL, 1.39 mmol). The resulting solution was allowed to warm to room temperature, stirred for 2 h, and then quenched by the addition of saturated aqueous NH_4Cl (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×1.5 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (20% EtOAc/40-60 petroleum ether) to yield alcohol **33a** (195 mg, 99%) as a pale yellow oil. R_f 0.50 (30% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20}$ = +5.6 (c=0.93, $CHCl_3$); IR (neat): $\tilde{\nu}$=3383, 1458, 1378, 1225, 1020 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=5.18 (1H, q, J=6.3 Hz, H31), 3.75 (1H, dd, J=7.3, 3.3 Hz, H23a), 3.63 (1H, dd, J=10.7, 3.9 Hz, H23b), 3.50 (1H, dd, J=7.2, 3.0 Hz, H25), 3.28 (1H, dd, J=10.3, 4.2 Hz, H27), 2.57 (1H, d, J=13.2 Hz, H29a), 1.96–1.89 (1H, m, H26), 1.88–1.82 (1H, m, H24), 1.71–1.65 (1H, m, H28), 1.58 (3H, d, obs, H32), 1.57 (3H, s, Me30), 1.43 (1H, dd, J=13.2, 10.7 Hz, H29b), 1.34 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.28 (3H, s, $OC(CH_3)_a(CH_3)_b$), 0.97 (3H, d, J=7.1 Hz, Me24), 0.88 (3H, d, J=6.6 Hz, Me26), 0.71 ppm (3H, d, J=6.6 Hz, Me28); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C=134.5, 120.0, 100.7, 78.1, 74.3, 67.2, 43.7, 37.7, 34.5, 30.7, 25.0, 23.7, 15.5, 14.4, 13.3, 12.4, 10.8 ppm; HRMS (ES+) calculated for $C_{17}H_{33}O_3$ [M+H^+]: 285.2424, found: 285.2425.

Aldehyde 31: To a solution of alcohol **33a** (157 mg, 0.55 mmol) in CH_2Cl_2 (3 mL) at room temperature was added $NaHCO_3$ (371 mg, 4.42 mmol) followed by Dess–Martin periodinane (937 mg, 2.21 mmol). The resulting solution was stirred at room temperature for 1 h and then

quenched by the addition of saturated aqueous $Na_2S_2O_3$ (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (15% EtOAc/40-60 petroleum ether) to provide aldehyde **31** (141 mg, 90%) as a colorless oil. R_f 0.41 (10% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20} = +46.4$ ($c = 1.40$, $CHCl_3$); IR (neat): $\tilde{\nu} = 1727$, 1456, 1376, 1221, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 9.71$, (1H, d, $J = 1.2$ Hz, CHO), 5.18 (1H, q, $J = 6.3$ Hz, H31), 3.75 (1H, dd, $J = 7.3$, 3.3 Hz, H25), 3.29 (1H, dd, $J = 10.5$, 4.2 Hz, H27), 2.57 (1H, d, $J = 13.4$ Hz, H29a), 2.42 (1H, qdd, $J = 7.0$, 3.7, 1.2 Hz, H24), 1.98–1.89 (1H, m, H26), 1.75–1.67 (1H, m, H28), 1.58 (3H, d, $J = 5.9$ Hz, H32), 1.57 (3H, s, Me30), 1.43 (1H, dd, $J = 13.2$, 11.0 Hz, H29b), 1.32 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.26 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.15 (3H, d, $J = 7.0$ Hz, Me24), 0.92 (3H, d, $J = 6.8$ Hz, Me26), 0.70 ppm (3H, d, $J = 6.6$ Hz, Me28); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C = 204.3$, 134.4, 120.0, 100.9, 74.2, 74.1, 49.2, 43.7, 35.0, 30.7, 24.6, 23.6, 15.5, 14.4, 13.3, 12.1, 7.9 ppm; HRMS (ES+) calculated for $C_{17}H_{30}O_3Na$ [M+Na^+]: 305.2072, found: 305.2087.

Aldol adducts 30 and 35: To a solution of (−)-Ipc_2BCl (136 mg, 0.42 mmol) [dried by stirring under vacuum (1 mm Hg) at room temperature for 1.5 h] in Et_2O (2 mL) at 0 °C was added triethylamine (63 μL, 0.45 mmol), followed by ketone **11** (106 mg, 0.27 mmol) in Et_2O (2 mL) by cannula. The reaction mixture was stirred for 1 h, cooled to −78 °C, and a solution of aldehyde **31** (40 mg, 0.14 mmol) in Et_2O (2 mL) was then added by cannula. After 1 h at −78 °C and 16 h at −27 °C, the reaction mixture was quenched by the addition of pH 7 buffer (4 mL), MeOH (4 mL), and H_2O_2 (30% aqueous, 2 mL). After allowing to warm to room temperature and stirring for 1 h, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/40-60 petroleum ether) to yield aldol adducts **30** and **35** (51 mg, 53%, ca. 2:1 d.r. by ^1H NMR analysis) as an inseparable mixture. Major diastereomer **30**: R_f 0.25 (5% EtOAc/40-60 petroleum ether); IR (neat): $\tilde{\nu} = 3524$, 1716, 1458, 1379, 1224, 1018 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H = 5.18$ (1H, q, $J = 5.8$ Hz, H31), 4.93 (1H, s, H13a), 4.83 (1H, s, H13b), 4.19–4.12 (1H, m, H20), 4.08–4.00 (1H, m, H23), 3.69 (1H, d, $J = 7.4$ Hz, H15), 3.65 (1H, dd, $J = 7.7$, 1.7 Hz, H25), 3.37 (1H, dd, $J = 10.5$, 4.2 Hz, H17), 3.32–3.29 (1H, m, OH), 3.28–3.23 (1H, m, H27), 2.76 (2H, d, $J = 5.8$ Hz, H22a and H22b), 2.56 (1H, br d, $J = 13.8$ Hz, H29a), 2.13–2.05 (1H, m, H19a), 1.97–1.84 (3H, m, H16, H18, and H26), 1.77 (3H, s, Me14), 1.72–1.62 (2H, m, H24 and H28), 1.58 (3H, obs, H32), 1.56 (3H, s, Me30), 1.46–1.38 (1H, m, H29b), 1.34 (6H, s, $2\times OC(CH_3)_a(CH_3)_b$), 1.29 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.22 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.00–0.93 (3H, obs, Me24), 1.17–1.10 (1H, m, H19b), 0.96 (9H, t, $J = 8.0$ Hz, $Si(CH_2CH_3)_3$), 0.89–0.83 (9H, m, Me16, Me18, and Me26), 0.71 (3H, d, $J = 6.9$ Hz, Me28), 0.61 ppm (6H, q, $J = 8.0$ Hz, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta_C = 214.5$, 144.4, 134.6, 120.0, 111.8, 100.7, 100.4, 79.2, 77.4, 74.5, 74.3, 73.2, 43.8, 42.3, 40.9, 40.5, 37.9, 36.1, 35.2, 30.7, 29.1, 24.8, 24.7, 23.8, 23.7, 18.0, 15.5, 15.3, 14.5, 13.4, 12.0, 11.8, 10.4, 6.8, 4.9 ppm; HRMS (ES+) calculated for $C_{39}H_{72}O_7SiNa$ [M+Na^+]: 703.4945, found: 703.4937. Minor diastereomer **35**: R_f 0.25 (5% EtOAc/40-60 petroleum ether); IR (neat): $\tilde{\nu} = 3498$, 1710 1458, 1378, 1224, 1017 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H = 5.18$ (1H, q, $J = 6.7$ Hz, H31), 4.93 (1H, s, H13a), 4.84 (1H, s, H13b), 4.26–4.20 (1H, m, H23), 4.14 (1H, dd, $J = 9.4$, 3.8 Hz, H20), 3.69 (1H, d, $J = 7.3$ Hz, H15), 3.52 (1H, dd, $J = 7.5$, 2.4 Hz, H25), 3.37 (1H, dd, $J = 10.5$, 4.3 Hz, H17), 3.31 (1H, br s, OH), 3.29–3.23 (1H, m, H27), 2.76 (2H, d, $J = 6.3$ Hz, H22a and H22b), 2.56 (1H, br d, $J = 13.2$ Hz, H29a), 2.12–2.02 (1H, m, H19a), 1.93–1.84 (2H, m, H16 and H26), 1.81–1.72 (1H, obs, H18), 1.76 (3H, s, Me14), 1.72–1.60 (2H, m, H24 and H28), 1.58 (3H, obs, H32), 1.56 (3H, s, Me30), 1.42 (1H, dd, $J = 13.5$, 11.2 Hz, H29b), 1.36 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.34 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.29 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.28 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.18–1.10 (1H, m, H19b), 0.99–0.94 (3H, obs, Me24), 0.97 (9H, t, $J = 8.0$ Hz, $Si(CH_2CH_3)_3$), 0.89–0.84 (9H, m, Me16, Me18, and Me26), 0.70 (3H, d, $J = 6.9$ Hz, Me28), 0.62 ppm (6H, q, $J = 7.9$ Hz, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta_C = 213.8$, 144.5, 134.6, 119.9, 111.7, 100.7, 100.6, 79.2, 78.3, 74.2, 73.2, 71.2, 43.7, 41.8, 39.7, 38.1, 36.2, 35.6, 30.8, 30.7, 29.1, 24.9, 24.8, 23.9, 23.8, 18.0, 15.5, 15.4, 14.5, 13.3, 12.0, 11.8, 7.1, 6.8, 4.9 ppm; HRMS (ES+) calculated for $C_{39}H_{72}O_7SiNa$ [M+Na^+]: 703.4945, found: 703.4936.

Methyl ethers 36 and 37: To a solution of alcohols **30** and **35** (238 mg, 0.35 mmol) in CH_2Cl_2 (22 mL) at 0 °C was added Proton Sponge (450 mg, 2.10 mmol), followed by trimethyloxonium tetrafluoroborate (207 mg, 1.40 mmol). The resulting solution was strirred at room temperature for 1.5 h and quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were washed with citric acid (10% weight solution, 50 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (15% EtOAc/40-60 petroleum ether) to yield methyl ethers **36** and **37** (213 mg, 87%, ca. 2:1 d.r. by ^1H NMR analysis) as an inseparable mixture. Major diastereomer **36**: R_f 0.50 (5% EtOAc/40-60 petroleum ether); IR (neat): $\tilde{\nu} = 1718$, 1458, 1378, 1224, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H = 5.18$ (1H, q, $J = 6.3$ Hz, H31), 4.93 (1H, s, H13a), 4.83 (1H, s, H13b), 4.20–4.13 (1H, m, H20), 3.80–3.75 (1H, m, H23), 3.69 (1H, d, $J = 7.5$ Hz, H15), 3.43–3.33 (2H, m, H17 and H25), 3.28 (3H, s, OMe), 3.27–3.22 (1H, m, H27), 2.84 (1H, dd, $J = 17.4$, 9.2 Hz, H22a), 2.57 (1H, br d, $J = 13.8$ Hz, H29a), 2.55 (1H, dd, $J = 17.2$, 2.1 Hz, H22b), 2.03–2.17 (1H, m, H19a), 1.93–1.86 (1H, m, H16), 1.85–1.75 (3H, m, H18, H24, and H26), 1.76 (3H, s, Me14), 1.71–1.64 (2H, m, H19b and H28), 1.57 (3H, d, obs, H32), 1.56 (3H, s, Me30), 1.42 (1H, app. t, $J = 11.5$ Hz, H29b), 1.34 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.29 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.27 (3H, s, $OC(CH_3)_a(CH_3)_b$), 1.24 (3H, s, $OC(CH_3)_a(CH_3)_b$), 0.96 (9H, t, $J = 7.8$ Hz, $Si(CH_2CH_3)_3$), 0.92 (3H, d, $J = 7.0$ Hz, Me24), 0.88 (3H, d, $J = 7.1$ Hz, Me16), 0.87 (3H, d, $J = 7.0$ Hz, Me18), 0.86 (3H, d, $J = 7.0$ Hz, Me26), 0.70 (3H, d, $J = 6.8$ Hz, Me28), 0.61 ppm (6H, q, $J = 8.0$ Hz, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta_C = 212.4$, 144.5, 134.7, 119.9, 111.8, 100.7, 100.4, 79.6, 79.2, 75.0, 74.2, 73.3, 57.7, 43.8, 40.1, 38.8, 37.6, 37.4, 36.3, 36.2, 30.7, 29.1, 24.9, 24.7, 23.9, 23.6, 18.0, 15.5, 15.2, 14.5, 13.4, 12.0, 11.8, 8.4, 6.8, 4.9 ppm; HRMS (ES+) calculated for $C_{40}H_{74}O_7SiNa$ [M+Na^+]: 717.5102, found: 717.5117.

Spiroacetals 38 and 39: To a solution of ketones **36** and **37** (213 mg, 0.31 mmol) in MeOH (8 mL) at room temperature was added CSA (7.1 mg, 0.03 mmol). After stirring at room temperature for 16 h the reaction was quenched by addition of saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (30% EtOAc/40-60 petroleum ether) to yield spiroacetals **38** (78 mg, 52%) and **39** (31 mg, 21%) as colorless oils. Spiroacetal **38**: R_f 0.31 (30% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20} = +8.8$ ($c = 0.71$, MeOH); IR (neat): $\tilde{\nu} = 3436$, 1456, 1381, 1234, 1114 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): $\delta_H = 5.25$ (1H, q, $J = 6.5$ Hz, H31), 4.93 (1H, s, H13a), 4.90 (1H, s, H13b), 4.13 (1H, d, $J = 9.5$ Hz, H15), 3.79 (1H, dd, $J = 10.6$, 2.0 Hz, H25), 3.77 (1H, d, $J = 9.7$ Hz, H27), 3.73 (1H, app. t, $J = 11.9$, 4.7 Hz, H23), 3.61 (1H, dd, $J = 10.3$, 1.8 Hz, H17), 3.44 (1H, t, $J = 2.8$ Hz, H20), 3.38 (3H, s, OMe), 2.68 (1H, br d, $J = 13.1$ Hz, H29a), 2.18 (1H, m, H24), 2.10 (1H, dd, $J = 13.2$, 4.7 Hz, H22a), 2.04–1.97 (1H, m, H18), 1.88 (1H, dd, $J = 10.3$, 7.1 Hz, H26), 1.85–1.80 (2H, m, H16 and H19a), 1.80–1.76 (1H, m, H28), 1.76–1.69 (1H, obs, H19b), 1.74 (3H, s, Me14), 1.63 (3H, s, Me30), 1.63 (3H, d, $J = 5.9$ Hz, H32), 1.63 (1H, obs, H29b), 1.41 (1H, dd, $J = 12.5$, 12.5 Hz, H22b), 0.84 (3H, d, $J = 6.5$ Hz, Me26), 0.83 (3H, d, $J = 7.1$ Hz, Me18), 0.81 (3H, d, $J = 6.9$ Hz, Me24), 0.78 (3H, d, $J = 7.0$ Hz, Me16), 0.75 ppm (3H, d, $J = 6.7$ Hz, Me28); ^{13}C NMR (125 MHz, CD_3OD): $\delta_C = 147.7$, 136.0, 121.1, 114.3, 99.5, 78.8, 78.3, 75.8, 73.8, 72.0, 70.9, 55.5, 46.0, 37.7, 37.6, 37.3, 35.0, 33.9, 32.8, 26.0, 17.7, 16.2, 15.8, 15.6, 13.5, 9.6, 8.0, 4.0 ppm; HRMS (ES+) calculated for $C_{28}H_{50}O_6Na$ [M+Na^+]: 505.3505, found: 505.3498. Spiroacetal **39**: R_f 0.27 (30% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20} = +22.8$ ($c = 1.07$, MeOH); IR (neat): $\tilde{\nu} = 3429$, 1456, 1380, 1209, 1099 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): $\delta_H = 5.25$ (1H, q, $J = 6.5$ Hz, H31), 4.95 (1H, s, H13a), 4.90 (1H, s, H13b), 4.28 (1H, d, $J = 9.4$ Hz, H15), 4.11 (1H, dd, $J = 10.5$, 1.8 Hz, H25), 3.77 (1H, d, $J = 9.3$ Hz, H27), 3.63 (1H, dd, $J = 10.5$, 1.6 Hz, H17), 3.52–3.48 (1H, m, H23), 3.42 (3H, s, OMe), 3.37 (1H, obs, H20), 2.69 (1H, br d, $J = 13.1$ Hz, H29a), 2.26 (1H, dd, $J = 15.4$, 1.5 Hz, H22a), 2.04–1.95 (1H, m, H18), 1.93–1.86 (1H, m, H24), 1.86–1.78 (3H, m, H16, H26, and H28), 1.76–1.70 (1H,

obs, H19a), 1.73 (3H, s, Me14), 1.66–1.60 (2H, obs, H19b and H29b), 1.63 (3H, s, Me30), 1.63 (3H, d, J=5.5 Hz, H32), 1.49 (1H, dd, J=15.4, 3.7 Hz, H22b), 0.94 (3H, d, J=6.5 Hz, Me24), 0.84 (3H, d, J=6.6 Hz, Me18), 0.82 (3H, d, J=7.1 Hz, Me26), 0.81 (3H, d, J=7.2 Hz, Me16), 0.75 ppm (3H, d, J=6.6 Hz, Me28); ^{13}C NMR (125 MHz, CD_3OD): δ_C= 148.1, 136.1, 121.0, 113.8, 98.2, 80.4, 78.2, 75.6, 74.0, 71.6, 67.6, 55.9, 45.9, 37.8, 37.6, 37.1, 35.2, 34.3, 29.0, 25.6, 17.7, 16.6, 15.8, 15.7, 13.5, 10.4, 10.0, 8.0 ppm; HRMS (ES+) calculated for $C_{28}H_{50}O_6$ [M+Na^+]: 505.3505, found: 505.3499.

TES ether 38a: To a solution of triol **38** (69 mg, 0.14 mmol) in CH_2Cl_2 (7 mL) at −78 °C was added 2,6-lutidine (67 μL, 0.57 mmol). The reaction mixture was stirred at −78 °C for 10 min before triethylsilyl trifluoromethanesulfonate (97 μL, 0.43 mmol) was added. The reaction mixture was allowed to warm to 0 °C over 20 min and then quenched by the addition of saturated aqueous NH_4Cl (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (5% EtOAc/40-60 petroleum ether) to yield TES-protected spiroacetal **38a** (184 mg, 93%). R_f 0.52 (10% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20}$=+10.3 (c=1.20, MeOH); IR (neat): $\tilde{\nu}$=1458, 1381, 1232, 1088, 1003 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H=5.23 (1H, q, J=6.4 Hz, H31), 5.00 (1H, s, H13a), 4.81 (1H, s, H13b), 4.22 (1H, d, J=5.7 Hz, H15), 3.93 (1H, dd, J=4.8, 1.9 Hz, H27), 3.70 (1H, app dt, J=11.8, 4.5 Hz, H23), 3.61 (1H, dd, J=9.9, 1.8 Hz, H25), 3.50 (1H, t, J=2.8 Hz, H20), 3.38 (1H, obs, H17), 3.37 (3H, s, OMe), 2.17 (1H, obs, H29a), 2.16–2.06 (4H, m, H16, H18, H24, H28), 2.03 (1H, dd, J=12.4, 4.3 Hz, H22a), 1.96–1.89 (1H, m, H26), 1.85 (3H, s, Me14), 1.84 (1H, obs, H19a), 1.74–1.67 (1H, m, H29b), 1.62 (3H, d, J=5.9 Hz, H32), 1.60 (3H, s, Me30), 1.57 (1H, dt, J=13.6, 3.9, 3.9 Hz, H19b), 1.23 (1H, dd, J=12.9, 12.4 Hz, H22b), 1.12 (3H, d, J=7.3 Hz, Me16), 1.08 (9H, t, J=8.0 Hz, Si(CH_2CH_3)$_3$), 1.03 (9H, t, J=7.9 Hz, Si(CH_2CH_3)$_3$), 1.02 (9H, t, J=7.7 Hz, Si(CH_2CH_3)$_3$), 0.91 (3H, J=6.9 Hz, Me24), 0.88 (3H, J=6.6 Hz, Me18), 0.86 (3H, J=6.5 Hz, Me26), 0.78 (3H, J=7.0 Hz, Me28), 0.75 (6H, q, J=7.4 Hz, Si(CH_2CH_3)$_3$) 0.68 (6H, q, J=8.0 Hz, Si(CH_2CH_3)$_3$) 0.65 ppm (6H, q, J=7.9 Hz, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, CD_3OD): δ_C=149.5, 135.7, 120.7, 113.9, 99.7, 81.6, 78.6, 77.8, 76.9, 76.6, 71.7, 55.4, 43.1, 42.7, 39.2, 37.8, 36.7, 34.3, 33.5, 25.8, 20.1, 18.6, 17.4, 15.8, 13.6, 13.1, 9.3, 7.7, 7.4, 7.3, 7.0, 6.0, 5.9, 4.4 ppm; HRMS (ES+) calculated for $C_{46}H_{93}O_6Si_3$ [M+H^+]: 825.6280, found: 825.6310.

Alcohol 40: To a solution of the alkene **38a** (14 mg, 16.9 μmol) in THF (0.5 mL) at 0 °C was added a freshly prepared solution of 9-BBN (0.5 M in THF, 101 μL, 50.7 μmol). The resulting solution was allowed to warm to room temperature and stirred at this temperature for 1 h, before recooling to 0 °C. The reaction was quenched by the addition of THF (0.5 mL), MeOH (0.5 mL), NaOH (10% aqueous, 1 mL), and H_2O_2 (30% aqueous, 0.5 mL) and then stirred for 1 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×4 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/40-60 petroleum ether) to yield alcohol **40** (10 mg, 70%) as a colorless oil. R_f 0.10 (10% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20}$=+17.5 (c=1.50, MeOH); IR (neat): $\tilde{\nu}$=3499, 1459, 1381, 1233, 1001 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H=5.24 (1H, q, J=6.5 Hz, H31), 3.93 (1H, dd, J=10.8, 3.2 Hz, H13a), 3.90 (1H, dd, J=5.0, 2.2 Hz, H27), 3.80 (1H, dd, J=3.4, 1.5 Hz, H15), 3.74 (1H, app dt, J=12.0, 4.7 Hz, H23), 3.55–3.50 (2H, m, H13b, H20), 3.44 (1H, dd, J=10.0, 2.1 Hz, H25), 3.36 (3H, s, OMe), 3.38–3.33 (1H, obs, H17), 2.49–2.39 (1H, m, H14), 2.26–2.19 (1H, m, H24), 2.19 (1H, br d, J=14.2 Hz, H29a), 2.16–2.06 (2H, m, H18 and H28), 2.09 (1H, dd, J=12.8, 4.7 Hz, H22a), 2.05–2.00 (1H, m, H16), 2.00–1.96 (1H, m, H26), 1.89–1.82 (1H, m, H19a), 1.72 (1H, dd, J=13.5, 10.3 Hz, H29b), 1.64–1.60 (1H, obs, H19b), 1.62 (3H, d, obs, H32), 1.61 (3H, s, Me30), 1.29 (1H, app t, J=12.5 Hz, H22b), 1.18 (3H, d, J= 7.1 Hz, Me14), 1.13 (3H, d, J=7.2 Hz, Me16), 1.10–1.01 (27H, m, 3×Si(CH_2CH_3)$_3$), 0.92 (3H, d, J=7.0 Hz, Me28), 0.91 (3H, d, J=7.3 Hz, Me18), 0.88 (3H, d, J=6.9 Hz, Me26), 0.81 (3H, d, J=7.0 Hz, Me24), 0.68 ppm (18H, m, 3×Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, CD_3OD): δ_C= 135.7, 120.8, 100.0, 82.7, 78.9, 78.5, 77.8, 77.4, 71.8, 65.8, 55.5, 43.5, 42.6, 39.3, 39.2, 38.1, 36.9, 34.4, 33.6, 25.9, 19.3, 18.6, 17.7, 15.8, 13.6, 13.2, 8.4, 7.7, 7.4, 7.3, 6.9, 6.1, 6.0, 4.4 ppm; HRMS (ES+) calculated for $C_{46}H_{95}O_7Si_3$ [M+H^+]: 843.6386, found: 843.6418.

Aldehyde 41: To a solution of alcohol **40** (25 mg, 29.6 μmol) in CH_2Cl_2 (1.5 mL) at room temperature was added $NaHCO_3$ (20 mg, 0.24 mmol) followed by Dess–Martin periodinane (50 mg, 0.12 mmol). The resulting solution was stirred at room temperature for 1 h before saturated aqueous $Na_2S_2O_3$ (1.5 mL) and saturated aqueous $NaHCO_3$ (1.5 mL) were added. The resulting biphasic mixture was stirred for ca. 20 min before the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/40-60 petroleum ether) to yield aldehyde **41** (22 mg, 87%) as a colorless oil. R_f 0.45 (10% EtOAc/40-60 petroleum ether); $[\alpha]_D^{20}$=+15.4 (c=0.43, MeOH); IR (neat): $\tilde{\nu}$=1720, 1458, 1381, 1231, 1110 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H=9.94 (1H, d, J=2.9 Hz, CHO), 5.24 (1H, q, J=6.6 Hz, H31), 3.92 (1H, dd, J=3.2, 1.0 Hz, H15), 3.89 (1H, dd, J=4.8, 2.2 Hz, H27), 3.70 (1H, app dt, J=12.0, 4.5 Hz, H23), 3.53 (1H, t, J=2.6 Hz, H20), 3.38 (3H, s, OMe), 3.36–3.34 (2H, obs, H17 and H25), 3.21–3.15 (1H, m, H14), 2.23–2.04 (6H, m, H16, H18, H22a, H24, H28, and H29a), 2.02–1.94 (1H, m, H26), 1.89–1.82 (1H, m, H19a), 1.73 (1H, dd, J=13.3, 10.2 Hz, H29b), 1.64–1.60 (1H, obs, H19b), 1.62 (3H, d, J=6.6 Hz, H32), 1.61 (3H, s, Me30), 1.29 (1H, app t, J=1.25 Hz, H22b), 1.22 (3H, d, J=7.3 Hz, Me14), 1.09 (3H, d, J=7.2 Hz, Me16), 1.07 (9H, t, J=8.0 Hz, Si(CH_2CH_3)$_3$), 1.05 (9H, t, J=8.0 Hz, Si(CH_2CH_3)$_3$), 1.04 (9H, t, J=8.0 Hz, Si(CH_2CH_3)$_3$), 0.92 (3H, d, J=7.0 Hz, Me28), 0.91 (3H, d, J=7.1 Hz, Me26), 0.90 (3H, d, J=6.7 Hz, Me18), 0.82 (3H, d, J=6.7 Hz, Me24), 0.72 (6H, q, J=8.0 Hz, Si(CH_2CH_3)$_3$), 0.71 (6H, q, J= 8.0 Hz, Si(CH_2CH_3)$_3$), 0.67 ppm (6H, q, J=8.1 Hz, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, CD_3OD): δ_C=207.1, 135.6, 120.8, 100.0, 82.3, 78.8, 78.4, 78.0, 77.7, 71.7, 55.6, 50.0, 43.3, 42.7, 39.3, 38.1, 36.8, 34.1, 33.9, 25.9, 18.5, 17.6, 15.8, 15.8, 13.6, 13.1, 8.2, 7.7, 7.3, 7.3, 6.9, 6.0, 5.9, 4.6 ppm; HRMS (ES+) calculated for $C_{46}H_{92}O_7Si_3Na$ [M+Na^+]: 863.6043, found: 863.6031.

Spirangien diene 3: To a vial containing aldehyde **41** (6.2 mg, 7.3 μmol) at 0 °C was added 4 Å molecular sieves (pipette tip), followed by allyl borane reagent **45** (3 M in toluene, 50 μL). The resultant suspension was allowed to warm to room temperature and left for 16 h, after which time acetaldehyde (50 μL) was added. The solution was then dissolved with toluene (1 mL) and filtered through a short plug of celite, eluting with Et_2O (5 mL). After concentration in vacuo the resultant crude material was taken up in MeOH (0.25 mL) and THF (0.25 mL), cooled to 0 °C, and aqueous KOH (6 M, 0.5 mL) added. The resulting biphasic solution was allowed to warm to room temperature and stirred for 16 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×4 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/hexanes) to yield the desired diene **43** (3.0 mg, 50%). This material was taken up in THF (0.25 mL), cooled to 0 °C, and TBAF (1 M in THF, 17 μL, 17 μmol) was added. The resulting solution was allowed to warm to room temperature, stirred for 1 h, and then recooled to 0 °C. Further TBAF (1 M in THF, 17 μL, 17 μmol) was added and the resulting solution was allowed to warm to room temperature. After stirring at this temperature for 2 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4×2 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (0→20% EtOAc/40-60 petroleum ether) to yield diene **3** (1.3 mg, 71%) as a pale yellow oil. This material was further purified using reverse-phase HPLC, with a Varian column (250×4.6 mm), prepacked with Microsorb silica (5 μ, 100 Å), equipped with a Gilson UV detector (Model 118) at a wavelength of 254 nm. 85% MeOH/H_2O was used as the eluent and a flow rate of 1 mL min^{-1}. The observed retention time of spirangien diene **3** was 6 min and 36 s. R_f 0.53 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$=+34 (c=0.04, MeOH); IR (neat): $\tilde{\nu}$=3362, 1633, 1381, 1259, 1108 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H=6.72 (1H, dt, J=16.8, 11.2, 10.1 Hz, H11), 6.08 (1H, dd, J=11.1, 11.1 Hz, H12), 5.61 (1H, dd, J=10.6, 10.6 Hz, H13), 5.25 (1H, m, H31), 5.23 (1H, dd, J=16.8, 2.2 Hz, H10a), 5.14 (1H, br d, J= 10.2 Hz, H10b), 3.73 (1H, dd, J=10.1, 2.0 Hz, H25), 3.69 (1H, m, H27),

3.67 (1H, m, H23), 3.64 (1H, dd, J=10.5, 1.3 Hz, H17), 3.57 (1H, dd, J=9.8, 2.5 Hz, H15), 3.43 (1H, m, H20), 3.38 (3H, s, OMe), 2.95 (1H, m, H14), 2.70 (1H, br d, J=12.3 Hz, H29a), 2.16 (1H, m, H24), 2.07 (1H, dd, J=12.9, 4.8 Hz, H22a), 1.96 (1H, m, H18), 1.87 (1H, m, H26), 1.78 (1H, m, H19a), 1.76 (1H, m, H28), 1.71 (1H, ddd, J=13.5, 3.4, 3.3 Hz, H19b), 1.64 (3H, m, Me30), 1.63 (2H, m, H16 and H29b), 1.62 (3H, m, H32), 1.41 (1H, dd, J=12.9, 12.8 Hz, H22b), 1.14 (3H, d, J=7.0 Hz, Me14), 0.85 (3H, d, J=7.0 Hz, Me26), 0.83 (3H, d, J=7.0 Hz, Me16), 0.81 (3H, d, J=7.0 Hz, Me24), 0.79 (3H, d, J=6.6 Hz, Me18), 0.75 ppm (3H, d, J=6.7 Hz, Me28); ^{13}C NMR (125 MHz, CD_3OD): δ_C=136.0, 133.7, 133.5, 130.5, 121.1, 117.7, 99.5, 78.8, 76.5, 76.1, 75.1, 72.4, 71.0, 55.4, 46.0, 40.0, 37.8, 37.3, 35.8, 35.4, 34.0, 32.9, 25.6, 19.6, 18.0, 15.8, 15.6, 13.5, 9.4, 7.9, 4.1 ppm; HRMS (ES+) calculated for $C_{31}H_{54}O_6Na$ [M+Na$^+$]: 545.3818, found: 545.3832. This data is in accord with that reported by Niggemann et al.[7] for material prepared by degradation of spirangien A; see the Supporting Information.

TBS ether 47a: To a solution of (*S*)-malic acid dimethyl ester **47** (1.50 g, 9.25 mmol) in THF (14 mL) at 0 °C was added borane dimethyl sulfide (0.89 mL, 9.39 mmol) slowly. The reaction mixture was allowed to warm to room temperature and was stirred for 45 min before being recooled to 0 °C. $NaBH_4$ (17 mg, 0.46 mmol) was added slowly and the resulting reaction mixture was stirred for 45 min at 0 °C, by which time gas evolution had subsided. The ice bath was removed and the reaction was stirred for 1 h at room temperature. The organic volatiles were then removed in vacuo and the product was azeotroped with methanol (3×10 mL) and then toluene (1×10 mL) to afford the 1,2-diol as an oil that was used directly in the next step. To a solution of the crude diol (1.24 g, 9.25 mmol) in CH_2Cl_2 (30 mL) at room temperature was added imidazole (0.79 g, 11.6 mmol) followed by TBSCl (1.53 g, 10.2 mmol). The resulting reaction mixture was stirred for 12 h at room temperature and then quenched by the addition of water (30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/hexanes) to yield TBS ether **47a** (2.21 g, 96%) as a colorless oil. The data for this compound was in agreement with that reported.[46]

Methyl ether 48: To a solution of alcohol **47a** (2.00 g, 8.06 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added Proton Sponge (10.4 g, 48.4 mmol) followed by trimethyloxonium tetrafluoroborate (3.50 g, 24.2 mmol). The resulting solution was stirred at room temperature for 1 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with citric acid (10% weight solution, 40 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (10% EtOAc/hexanes) to yield methyl ether **48** (2.0 g, 95%) as a colorless oil. R_f 0.31 (10% EtOAc/hexanes); $[\alpha]_D^{20}$=−13.8 (c=1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$=2931, 2858, 1743, 1437, 1257, 1116, 1082 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=3.71–3.68 (2H, m, H4), 3.67 (3H, s, OMe), 3.57–3.52 (1H, m, H3), 3.39 (3H, s, OMe), 2.57 (1H, dd, J=15.7, 4.5 Hz, H2a), 2.45 (1H, dd, J=15.7, 7.4 Hz, H2b), 0.87 (9H, s, $SiC(CH_3)_3$), 0.04 ppm (6H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C=172.3, 78.5, 64.2, 58.2, 51.7, 37.0, 26.0, 18.4, −5.3 ppm; HRMS (ES+) calculated for $C_{12}H_{26}O_4SiNa$ [M+Na$^+$]: 262.1498, found: 262.1502.

Alcohol 49: To a solution of TBS ether **48** (700 mg, 2.67 mmol) in THF (30 mL) at 0 °C was added TBAF (1 M in THF, 5.3 mL, 5.3 mmol). The resulting solution was allowed to warm to room temperature, stirred for 16 h, and then quenched by the addition of saturated aqueous NH_4Cl (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (50% EtOAc/hexanes) to yield the alcohol **49** (380 mg, 96%) as a colorless oil. R_f 0.34 (70% EtOAc/hexanes); $[\alpha]_D^{20}$=−19.9 (c=1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$=3439, 2937, 1733, 1439, 1166, 1100, 1066 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=3.77–3.72 (2H, m, H4), 3.70 (3H, s, OMe), 3.59–3.52 (1H, m, H3), 3.42 (3H, s, OMe), 2.62 (1H, dd, J=15.7, 6.6 Hz, H2a), 2.53 ppm (1H, dd, J=15.7, 6.0 Hz, H2b); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C=172.0, 78.1, 63.4, 57.6, 51.9, 36.1 ppm.

(*Z*)-Vinyl iodide 7: To a solution of oxalyl chloride (0.33 mL, 3.88 mmol) in CH_2Cl_2 (12 mL) at −78 °C was added dimethyl sulfoxide (0.4 mL, 5.67 mmol). After 15 min, a solution of alcohol **49** (280 mg, 1.89 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The resultant solution was stirred for 30 min at −78 °C, then Et_3N (1.6 mL, 11.3 mmol) was added. The reaction mixture was maintained at −78 °C for 30 min, then allowed to warm to room temperature and quenched by the addition of water (7 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and the corresponding aldehyde was used without further purification. To a suspension of (iodomethyl)triphenylphosphonium iodide (1.50 g, 2.84 mmol) in THF (4.5 mL) at room temperature was added NaHMDS (1 M in THF, 2.80 mL, 2.84 mmol). The resulting solution was stirred at room temperature for 10 min, cooled to −78 °C, and HMPA (0.82 mL, 4.73 mmol) added. The resulting solution was then cooled to −100 °C before a solution of aldehyde (276 mg, 1.89 mmol) in THF (0.5 mL) was added by cannula. The solution was stirred at −100 °C for 15 min, −78 °C for 30 min, and then allowed to warm to room temperature. After stirring for 20 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (10% CH_2Cl_2/hexanes→100% CH_2Cl_2) allowed separation of (*Z*)- and (*E*)-vinyl iodides to yield (*Z*)-vinyl iodide **7** (268 mg, 53%) as a pale yellow oil. R_f 0.31 (20% EtOAc/hexanes); $[\alpha]_D^{20}$=+15.5 (c=1.68, $CHCl_3$); IR (neat): $\tilde{\nu}$=2930, 1738, 1609, 1436, 1345, 1280, 1208, 1153, 1102 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=6.54 (1H, d, J=7.9 Hz, H5), 6.19 (1H, app t, J=7.9 Hz, H4), 4.43–4.38 (1H, m, H3), 3.70 (3H, s, OMe), 3.32 (3H, s, OMe), 2.60 (1H, dd, J=15.2, 8.1 Hz, H2a), 2.51 ppm (1H, dd, J=15.3, 4.9 Hz, H2b); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C=170.5, 140.1, 85.2, 79.5, 56.9, 51.8, 39.2 ppm; HRMS (ES+) calculated for $C_7H_{11}IO_3Na$ [M+Na$^+$]: 292.9645, found: 292.9635.

Bis-stannane 8: To a solution of (*E*)-Bu_3SnCH=$CHCHO$ (440 mg, 1.27 mmol) and sulfone **50** (890 mg, 1.66 mmol) in THF (16 mL) at −78 °C was added KHMDS (0.5 M in toluene, 3.2 mL, 1.59 mmol). The resulting solution was allowed to warm to room temperature and stirred for 16 h before quenching by addition of H_2O (20 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3×15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (3% Et_3N in 100% hexanes) yielded bis-stannane **8** (571 mg, 68%) as a colorless oil. The data for this compound was in agreement with that reported.[38a]

(*Z*)-Vinyl iodide 5: To a suspension of (iodomethyl)triphenylphosphonium iodide (54 mg, 0.11 mmol) in THF (0.3 mL) at room temperature was added NaHMDS (1 M in THF, 0.11 mL, 0.11 mmol). The resulting solution was stirred at room temperature for 10 min, cooled to −78 °C, and HMPA (25 μL) was added, followed by a solution of aldehyde **41** (17 mg, 19.9 μmol) in THF (0.7 mL) by cannula. After allowing to warm to room temperature and stirring for 20 min, the reaction was quenched by the addition of hexanes (2 mL) and filtered through a plug of celite, eluting with hexanes (20 mL). The hexanes fractions were then concentrated in vacuo and purified by flash column chromatography (5% EtOAc/hexanes) to yield vinyl iodide (14.2 mg, 74%, ca. 3:1 *Z*/*E*) as a colorless oil. To a solution of this material (14.2 mg, 14.7 μmol) in MeOH (1.5 mL) at room temperature was added CSA (catalytic). After stirring at room temperature for 1 h the reaction was quenched by addition of saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (30% EtOAc/hexanes) allowed separation of (*Z*)- and (*E*)-vinyl iodides to yield (*Z*)-vinyl iodide **5** (7.1 mg, 78%) as a colorless oil. R_f 0.37 (30% EtOAc/hexanes); $[\alpha]_D^{20}$=+33.7 (c=0.43, MeOH); IR (neat): $\tilde{\nu}$=3444, 1457, 1383, 1108, 996 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H=6.36 (1H, app. t, J=2.5 Hz, H13), 6.36 (1H, d, J=2.6 Hz, H12), 5.25 (1H, q, J=6.7 Hz, H31), 3.73 (1H, dd, J=10.3, 1.8 Hz, H25), 3.71–3.66 (2H, m, H23 and H27), 3.62 (1H, dd, J=10.3, 1.1 Hz, H17), 3.61 (1H, dd, J=9.8, 2.1 Hz, H15) 3.43 (1H, app t, J=2.9 Hz, H20) , 3.39 (3H, s, OMe), 2.78–2.72 (1H, m, H14), 2.70 (1H, br d, J=13.7 Hz, H29a),

2.20–2.13 (1H, m, H24), 2.08 (1H, dd, J=13.0, 4.7 Hz, H22a), 2.04–1.92 (1H, m, H18), 1.91–1.82 (1H, m, H26), 1.81–1.68 (3H, m, H19a, H19b, and H28), 1.68–1.54 (2H, obs, H16 and H29b), 1.64 (3H, s, Me30), 1.63 (3H, d, J=6.4 Hz, H32), 1.41 (1H, app. t, J=12.4 Hz, H22b), 1.12 (3H, d, J=7.0 Hz, Me14), 0.87 (3H, d, J=7.0 Hz, Me16), 0.85 (3H, d, J=7.1 Hz, Me26), 0.81 (3H, d, J=6.9 Hz, Me24), 0.80 (3H, d, J=6.7 Hz, Me18), 0.75 ppm (3H, d, J=6.7 Hz, Me28); ^{13}C NMR (125 MHz, CD_3OD): δ_C=142.7, 135.9, 121.2, 99.5, 82.9, 78.8, 76.2, 75.7, 75.0, 72.4, 71.0, 55.4, 46.0, 43.2, 40.2, 37.8, 37.3, 35.3, 33.9, 32.9, 25.6, 18.0, 17.6, 15.8, 15.6, 13.5, 9.6, 7.9, 4.1 ppm; HRMS (ES+) calculated for $C_{29}H_{51}IO_6Na$ [M+Na^+]: 645.2623, found: 645.2619.

Tetraene 6: This standard Stille coupling procedure, including the workup and purification, was performed in the absence of light and using base-washed amberized glassware. To a solution of (*Z*)-vinyl iodide **7** (12 mg, 44.4 μmol) and triene **8** (70 mg, 0.11 mmol) in DMF (1.2 mL) and THF (0.3 mL) at room temperature was added [Pd_2(dba)$_3$] (2 mg, 2.22 μmol) and Ph_3As (1.8 mg, 5.78 μmol). The resulting solution was purged by evacuating for 1 min and then flushing with Ar (×3) and then stirred at room temperature for 16 h. The reaction was then quenched by addition of H_2O (2 mL) and diluted with EtOAc (containing 2% Et_3N). The phases were separated and the aqueous phase was extracted with EtOAc (containing 2% Et_3N; 3×3 mL). The combined organics were washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (2% Et_3N in 5%→7% EtOAc/hexanes) yielded tetraene **6** (13.5 mg, 59%) as a yellow oil. R_f 0.40 (20% EtOAc/hexanes); $[\alpha]_D^{20}$=+12.9 (c=0.50, MeOH); IR (neat): $\tilde{\nu}$=1740, 1590, 1103 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H=7.12 (1H, dd, J=18.5, 9.7 Hz, H10), 6.86 (1H, dd, J=14.6, 10.0 Hz, H7), 6.68 (1H, dd, J=13.9, 11.4 Hz, H6), 6.42–6.36 (2H, m, H5 and H11), 6.10–6.05 (2H, m, H8 and H9), 5.34 (1H, app t, J=10.2 Hz, H4), 4.69–4.64 (1H, m, H3), 3.70 (3H, s, OMe), 3.29 (3H, s, OMe), 2.65 (1H, dd, J=15.1, 8.0 Hz, H2a), 2.49 (1H, dd, J=15.1, 5.4 Hz, H2b), 1.61–1.57 (6H, m, $SnCH_2CH_2CH_2CH_3$), 1.42–1.38 (6H, m, $SnCH_2CH_2CH_2CH_3$), 1.03–0.97 (6H, m, $SnCH_2CH_2CH_2CH_3$), 0.96 ppm (9H, t, J=7.5 Hz, $SnCH_2CH_2CH_2CH_3$); ^{13}C NMR (125 MHz, CD_3OD): δ_C=172.8, 143.2, 137.7, 134.6, 133.8, 131.7, 131.4, 129.3, 129.0, 74.6, 56.6, 52.2, 41.7, 30.3, 28.3, 14.1, 10.4 ppm; HRMS (ES+) calculated for $C_{25}H_{44}O_3SnNa$ [M+Na^+]: 535.2204, found: 535.2215.

Spirangien tetraene 46: In this case, stock solutions of [Pd_2(dba)$_3$] and Ph_3As were used: [Pd_2(dba)$_3$] (2 mg) dissolved in a mixture of DMF (200 μL) and THF (100 μL) and Ph_3As (2 mg) dissolved in DMF (200 μL) and THF (100 μL). The standard Stille reaction procedure (see above) was followed, using (*Z*)-vinyl iodide **5** (2 mg, 3.2 μmol) and triene **8** (21 mg, 32.1 μmol). Purification by flash column chromatography (3% Et_3N in 20%→7% EtOAc/hexanes) yielded tetraene **46** (1.7 mg, 60%) as a yellow oil. R_f 0.44 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, CD_3OD): δ_H=7.11 (1H, dd, J=18.6, 10.2 Hz, H7), 6.77 (1H, dd, J=14.4, 11.0 Hz, H10), 6.62 (1H, dd, J=14.1, 11.3 Hz, H11), 6.33 (1H, d, J=18.5 Hz, H6), 6.19 (1H, app t, J=11.3 Hz, H12), 6.06 (1H, app t, J=10.8 Hz, H9), 6.00 (1H, app t, J=10.8 Hz, H8), 5.67 (1H, app t, J=10.8 Hz, H13), 5.26 (1H, q, J=6.2 Hz, H31), 3.87 (1H, dd, J=10.3, 1.6 Hz, H25), 3.71–3.65 (2H, m, H23 and H27), 3.62 (1H, d, J=10.8 Hz, H17), 3.60 (1H, dd, J=9.9, 2.0 Hz, H15) 3.43 (1H, app t, J=2.7 Hz, H20), 3.39 (3H, s, OMe), 3.04–2.95 (1H, m, H14), 2.71 (1H, br d, J=12.5 Hz, H29a), 2.19–2.13 (1H, m, H24), 2.07 (1H, dd, J=13.0, 4.5 Hz, H22a), 1.99–1.93 (1H, m, H18), 1.90–1.84 (1H, m, H26), 1.78–1.76 (1H, m, H19a), 1.76–1.74 (1H, m, H28), 1.73–1.70 (1H, m, H19b), 1.68–1.54 (2H, obs, H16 and H29b), 1.64 (3H, s, Me30), 1.63 (3H, d, obs, H32), 1.62–1.57 (6H, m, $SnCH_2CH_2CH_2CH_3$), 1.43–1.37 (7H, m, H22b and $SnCH_2CH_2CH_2CH_3$), 1.16 (3H, d, J=7.0 Hz, Me14), 1.03–0.97 (6H, m, $SnCH_2CH_2CH_2CH_3$), 0.96 (9H, t, J=7.5 Hz, $SnCH_2CH_2CH_2CH_3$), 0.85 (3H, d, J=6.9 Hz, Me26), 0.84 (3H, d, J=6.9 Hz, Me16), 0.81 (3H, d, J=7.3 Hz, Me24), 0.80 (3H, d, J=7.0 Hz, Me18), 0.75 ppm (3H, d, J=6.6 Hz, Me28); HRMS (ES+) calculated for $C_{47}H_{84}O_6SnNa$ [M+Na^+]: 887.5182, found: 887.5197.

Spirangien A methyl ester (4): In this case, stock solutions of [Pd_2(dba)$_3$] and Ph_3As were used: [Pd_2(dba)$_3$] (2 mg) dissolved in a mixture of DMF (200 μL) and THF (100 μL) and Ph_3As (2 mg) dissolved in a mixture of DMF (200 μL) and THF (100 μL). The standard Stille reaction procedure (see above) was followed, using either (*Z*)-vinyl iodide **5** (1.5 mg, 2.4 μmol) and tetraene **6** (12.3 mg, 24.1 μmol) or (*Z*)-vinyl iodide **7** (4.0 mg, 17.4 μmol) and tetraene **46** (1.5 mg, 1.7 μmol). In each case, purification by flash column chromatography (3% Et_3N in 40% EtOAc/hexanes) yielded spirangien methyl ester **4** (1.0 mg, 65% from **5**) as a yellow oil. R_f 0.41 (50% EtOAc/hexanes); $[\alpha]_D^{20}$=−26.2 (c=0.08, MeOH); IR (neat): $\tilde{\nu}$=1740, 1491, 1472, 1381, 1103, 991 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H=6.90 (1H, dd, J=14.6, 11.3 Hz, H7), 6.83 (1H, dd, J=14.4, 11.0 Hz, H10), 6.69 (1H, m, H6), 6.64 (1H, m, H11), 6.40 (1H, app t, J=11.3 Hz, H5), 6.22 (1H, app t, J=11.2 Hz, H12), 6.20 (1H, app t, J=11.1 Hz, H9), 6.15 (1H, app t, J=11.1 Hz, H8), 5.69 (1H, app t, J=10.9 Hz, H13), 5.33 (1H, app t, J=10.3 Hz, H4), 5.26 (1H, q, J=6.6 Hz, H31), 4.66 (1H, m, H3), 3.73 (1H, dd, J=10.2, 1.8 Hz, H25), 3.70 (3H, s, CO_2Me), 3.70 (1H, obs, H27), 3.69 (1H, m, H23), 3.63 (1H, dd, J=10.6, 1.0 Hz, H17), 3.60 (1H, dd, J=9.9, 2.1 Hz, H15), 3.43 (1H, t, J=2.8 Hz, H20), 3.38 (3H, s, OMe23), 3.29 (3H, s, OMe3), 2.99 (1H, m, H14), 2.70 (1H, br d, J=13.1 Hz, H29a), 2.65 (1H, dd, J=15.2, 8.2 Hz, H2a), 2.49 (1H, dd, J=15.0, 5.4 Hz, H2b), 2.16 (1H, m, H24), 2.07 (1H, dd, J=13.2, 4.9 Hz, H22a), 1.97 (1H, m, H18), 1.87 (1H, m, H26), 1.77 (1H, m, H19a), 1.76 (1H, m, H28), 1.72 (1H, m, H19b), 1.65 (3H, m, Me30), 1.63 (5H, m, H16, H29b, and H32), 1.41 (1H, app t, J=12.5 Hz, H22b), 1.14 (3H, J=7.0 Hz, Me14), 0.85 (3H, d, J=7.2 Hz, Me26), 0.84 (3H, d, J=7.2 Hz, Me16), 0.81 (3H, d, J=6.9 Hz, Me24), 0.79 (3H, d, J=6.6 Hz, Me18), 0.75 ppm (3H, d, J=6.6 Hz, Me28); ^{13}C NMR (125 MHz, CD_3OD): δ_C=172.9, 136.0, 134.8, 134.0, 132.3, 132.1 (2C), 131.0, 130.2, 130.0, 129.5, 129.0, 121.1, 99.5, 78.8, 76.6, 76.1, 75.2, 74.6, 72.5, 71.0, 56.6, 55.4, 52.2, 46.0, 41.7, 40.1, 37.8, 37.3, 36.1, 35.4, 34.0, 32.9, 25.6, 19.6, 18.1, 15.8, 15.6, 13.5, 9.4, 7.9, 4.1 ppm; HRMS (ES+) calculated for $C_{42}H_{68}O_9Na$ [M+Na^+]: 739.4756, found: 739.4788. For comparison with the NMR data reported by Niggemann et al.[7] for spirangien A, see the Supporting Information.

Spirangien A (1): To a solution of spirangien A methyl ester **4** (1 mg, 1.4 μmol) in MeOH (0.6 mL) and H_2O (0.3 mL) at room temperature was added aqueous KOH (10%, 25 μL) dropwise. After 16 h at room temperature, the reaction mixture was partitioned between pH 4 buffer (1 mL) and CH_2Cl_2 (2 mL). The phases were separated and the aqueous phase washed with CH_2Cl_2 (5×2 mL). The combined organic phases were then dried (Na_2SO_4) and concentrated in vacuo. Purification by analytical HPLC (Hypersil C18, 250×4.6 mm, H_2O/MeCN 57%, 50 mM K_2HPO_4/NaH_2PO_4, pH 7; flow rate: 1 mL min^{-1}; R_t=12 min, UV: 320 nm) to remove any traces of minor isomers afforded spirangien A (**1**) (0.83 mg, 85%). The compound deteriorated over time, even when stored at −20 °C. R_f 0.37 (100% EtOAc); $[\alpha]_D^{20}$=−17.5 (c=0.04, MeOH); IR (neat): $\tilde{\nu}$=3520, 1742, 1471, 1389, 1218, 1109 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ_H=6.89 (1H, dd, J=14.6, 10.9 Hz, H7), 6.82 (1H, dd, J=14.5, 11.0 Hz, H10), 6.69 (1H, m, H6), 6.64 (1H, m, H11), 6.40 (1H, app t, J=11.2 Hz, H5), 6.22 (1H, app t, J=11.1 Hz, H12), 6.20 (1H, app t, J=11.1 Hz, H9), 6.14 (1H, app t, J=11.1 Hz, H8), 5.68 (1H, app t, J=10.6 Hz, H13), 5.34 (1H, app t, J=10.4 Hz, H4), 5.25 (1H, q, J=6.6 Hz, H31), 4.66 (1H, m, H3), 3.73 (1H, dd, J=10.2, 1.9 Hz, H25), 3.70 (1H, m, H27), 3.68 (1H, m, H23), 3.63 (1H, dd, J=10.5, 1.0 Hz, H17), 3.60 (1H, dd, J=9.7, 2.3 Hz, H15), 3.43 (1H, t, J=2.9 Hz, H20), 3.38 (3H, s, OMe23), 3.30 (3H, s, OMe3), 2.99 (1H, m, H14), 2.70 (1H, br d, J=13.1 Hz, H29a), 2.59 (1H, dd, J=15.1, 8.2 Hz, H2a), 2.43 (1H, dd, J=15.0, 5.2 Hz, H2b), 2.16 (1H, m, H24), 2.07 (1H, dd, J=13.1, 4.9 Hz, H22a), 1.97 (1H, m, H18), 1.87 (1H, m, H26), 1.77 (1H, m, H19a), 1.75 (1H, m, H28), 1.72 (1H, m, H19b), 1.64 (3H, m, Me30), 1.63 (5H, m, H16, H29b, and H32), 1.41 (1H, app t, J=12.5 Hz, H22b), 1.15 (3H, J=7.0 Hz, Me14), 0.85 (3H, d, J=7.0 Hz, Me26), 0.84 (3H, d, J=7.2 Hz, Me16), 0.81 (3H, d, J=6.9 Hz, Me24), 0.79 (3H, d, J=6.6 Hz, Me18), 0.75 ppm (3H, d, J=6.6 Hz, Me28); HRMS (ES+) calculated for $C_{41}H_{66}O_9Na$ [M+Na^+]: 725.4605, found: 725.4570. This data is in accord with that reported by Niggemann et al.[7] for natural spirangien A; see the Supporting Information.

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[1] a) D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461; b) I. Paterson, E. A. Anderson, *Science* **2005**, *310*, 451; c) F. E. Koehn, G. T. Carter, *Nat. Rev. Drug Discovery* **2005**, *4*, 206; d) M. S. Butler, *Nat. Prod. Rep.* **2005**, *22*, 162.
[2] M. S. Butler, *J. Nat. Prod.* **2004**, *67*, 2141.
[3] S. C. Wenzel, R. Müller, *Nat. Prod. Rep.* **2007**, *24*, 1211.
[4] S. Schneiker, O. Perlova, O. Kaiser, K. Gerth, A. Alici, M. O. Altmeyer, D. Bartels, T. Bekel, S. Beyer, E. Bode, H. B. Bode, C. J. Bolten, J. V. Choudhuri, S. Doss, Y. A. Elnakady, B. Frank, L. Gaigalat, A. Goesmann, C. Groeger, F. Gross, L. Jelsbak, L. Jelsbak, J. Kalinowski, C. Kegler, T. Knauber, S. Konietzny, M. Kopp, L. Krause, D. Krug, B. Linke, T. Mahmud, R. Martinez-Arias, A. C. McHardy, M. Merai, F. Meyer, S. Mormann, J. Munoz-Dorado, J. Perez, S. Pradella, S. Rachid, G. Raddatz, F. Rosenau, C. Rueckert, F. Sasse, M. Scharfe, S. C. Schuster, G. Suen, A. Treuner-Lange, G. J. Velicer, F. J. Vorholter, K. J. Weissman, R. D. Welch, S. C. Wenzel, D. E. Whitworth, S. Wilhelm, C. Wittmann, H. Blocker, A. Puhler, R. Müller, *Nat. Biotechnol.* **2007**, *25*, 1281.
[5] K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem.* **1998**, *110*, 2120; *Angew. Chem. Int. Ed.* **1998**, *37*, 2014.
[6] G. Höfle, N. Bedorf, K. Gerth, H. Reichenbach, DE-4211056, **1993** [*Chem. Abstr.* **1993**, *119*, 180598].
[7] J. Niggemann, N. Bedorf, U. Florke, H. Steinmetz, K. Gerth, H. Reichenbach, G. Höfle, *Eur. J. Org. Chem.* **2005**, 5013.
[8] M. A. Brimble, D. P. Furkert, *Curr. Org. Chem.* **2003**, *7*, 1461.
[9] J. E. Aho, P. M. Pihko, T. K. Rissa, *Chem. Rev.* **2005**, *105*, 4406.
[10] a) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, J. Genovino, P. Maltas, C. Moessner, *Angew. Chem.* **2008**, *120*, 3058; *Angew. Chem. Int. Ed.* **2008**, *47*, 3016; b) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, J. Genovino, P. Maltas, C. Moessner, *Angew. Chem.* **2008**, *120*, 3063; *Angew. Chem. Int. Ed.* **2008**, *47*, 3021.
[11] I. Paterson, D. Y. K. Chen, M. J. Coster, J. L. Acena, J. Bach, K. R. Gibson, L. E. Keown, R. M. Oballa, T. Trieselmann, D. J. Wallace, A. P. Hodgson, R. D. Norcross, *Angew. Chem.* **2001**, *113*, 4179; *Angew. Chem. Int. Ed.* **2001**, *40*, 4055.
[12] For a preliminary report of some of this work, see: a) I. Paterson, A. D. Findlay, E. A. Anderson, *Angew. Chem.* **2007**, *119*, 6819; *Angew. Chem. Int. Ed.* **2007**, *46*, 6699; b) I. Paterson, A. D. Findlay, C. Noti, *Chem. Commun.* **2008**, 6408.
[13] For synthetic work towards the spirangiens from the Kalesse group, see: a) M. Lorenz, M. Kalesse, *Tetrahedron Lett.* **2007**, *48*, 2905; b) M. Lorenz, M. Kalesse, *Org. Lett.* **2008**, *10*, 4371.
[14] For analysis of the biosynthetic gene cluster of the spirangiens, see: B. Frank, J. Knauber, H. Steinmetz, M. Sharfe, H. Blöcker, S. Beyer, R. Müller, *Chem. Biol.* **2007**, *14*, 221.
[15] J. K. Stille, *Angew. Chem.* **1986**, *98*, 504; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508; V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1997**, *50*, 1; K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
[16] a) I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, N. Sereinig, *J. Am. Chem. Soc.* **2001**, *123*, 9535; b) I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, *Angew. Chem.* **2000**, *112*, 385; *Angew. Chem. Int. Ed.* **2000**, *39*, 377.
[17] a) I. Paterson, E. A. Arnott, *Tetrahedron Lett.* **1998**, *39*, 7185; b) I. Paterson, M. Donghi, K. Gerlach, *Angew. Chem.* **2000**, *112*, 3453; *Angew. Chem. Int. Ed.* **2000**, *39*, 3315.
[18] a) I. Paterson, J. M. Goodman, M. Isaka, *Tetrahedron Lett.* **1989**, *30*, 7121; b) I. Paterson, R. D. Norcross, R. A. Ward. P. Romea, M. A. Lister, *J. Am. Chem. Soc.* **1994**, *116*, 11287.
[19] a) R. S. Paton, J. M. Goodman, *Org. Lett.* **2006**, *8*, 4299; b) R. S. Paton, J. M. Goodman, *J. Org. Chem.* **2008**, *73*, 1253; c) I. Paterson, K. Ashton, R. Britton, G. Cecere, G. Chouraqui, G. J. Florence, H. Knust, J. Stafford, *Chem. Asian J.* **2008**, *3*, 367.
[20] a) D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560; b) A. K. Saksena, P. Mangiaracina, *Tetrahedron Lett.* **1983**, *24*, 273.
[21] D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447.
[22] I. Paterson, J. A. Channon, *Tetrahedron Lett.* **1992**, *33*, 797.
[23] Confirmation of the stereochemical outcome was achieved by formation of the corresponding terminal acetonides (from both the major triol **16** and minor triol **16a**); see the Supporting Information for details.
[24] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.
[25] a) A. G. Myers, B. H. Yang, H. Chen, J. L. Gleason, *J. Am. Chem. Soc.* **1994**, *116*, 9361; b) A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.* **1997**, *119*, 6496.
[26] I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.
[27] I. Paterson, J. M. Goodman, M. A. Lister, R. C. Schumann, C. K. McClure, R. D. Norcross, *Tetrahedron* **1990**, *46*, 4663.
[28] D. A. Evans, A. M. Ratz, B. E. Huff, G. S. Sheppard, *Tetrahedron Lett.* **1994**, *35*, 7171.
[29] A. B. Smith, T. J. Beauchamp, M. J. LaMarche, M. D. Kaufman, Y. P. Qiu, H. Arimoto, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 8654.
[30] J. F. McGarrity, C. A. Ogle, *J. Am. Chem. Soc.* **1985**, *107*, 1805.
[31] D. W. Jeffery, M. V. Perkins, J. M. White, *Org. Lett.* **2005**, *7*, 1581.
[32] W. C. Still, J. C. Barrish, *J. Am. Chem. Soc.* **1983**, *105*, 2487.
[33] I. Paterson, A. Schlapbach, *Synlett* **1995**, 498.
[34] S. S. Harried, C. P. Lee, G. Yang, T. I. H. Lee, D. C. Myles, *J. Org. Chem.* **2003**, *68*, 6646.
[35] a) W. R. Roush, L. K. Hoong, M. A. J. Palmer, J. C. Park, *J. Org. Chem.* **1990**, *55*, 4109; b) W. R. Roush, P. T. Grover, *Tetrahedron* **1992**, *48*, 1981.
[36] S. Saito, T. Ishikawa, A. Kuroda, K. Koga, T. Moriwake, *Tetrahedron* **1992**, *48*, 4067.
[37] G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, *30*, 2173.
[38] A. Sorg, K. Siegel, R. Brückner, *Chem. Eur. J.* **2005**, *11*, 1610; B. Vaz, R. Alvarez, J. A. Souta, A. R. de Lera, *Synlett* **2005**, 294.
[39] P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563.
[40] a) R. S. Coleman, X. Lu, I. Modolo, *J. Am. Chem. Soc.* **2007**, *129*, 3826; b) V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585.
[41] See the Supporting Information for the preparation and characterization details for model iodide **51**.
[42] While the methyl ester **4** had been prepared previously from natural spirangien A, unfortunately no comparison NMR data were available (J. Niggemann, personal communication).
[43] A range of hydrolysis conditions were tested on the model ester **53** containing the pentaene chromophore, including TMSOK, TMSONa, Me_3SnOH, LiOH, and $Ba(OH)_2$.
[44] Following hydrolysis, spirangien A was submitted to careful HPLC purification to remove any traces of minor isomers formed during the acidic workup.
[45] I. Paterson, E. A. Anderson, A D. Findlay, C. S. Knappy, *Tetrahedron* **2008**, *64*, 4768.
[46] A. M. Szpilman, D. M. Cereghetti, N. R. Wurtz, J. M. Manthorpe, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 4407; *Angew. Chem. Int. Ed.* **2008**, *47*, 4335.

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