Total synthesis of (−)-spirangien A and its methyl ester†‡

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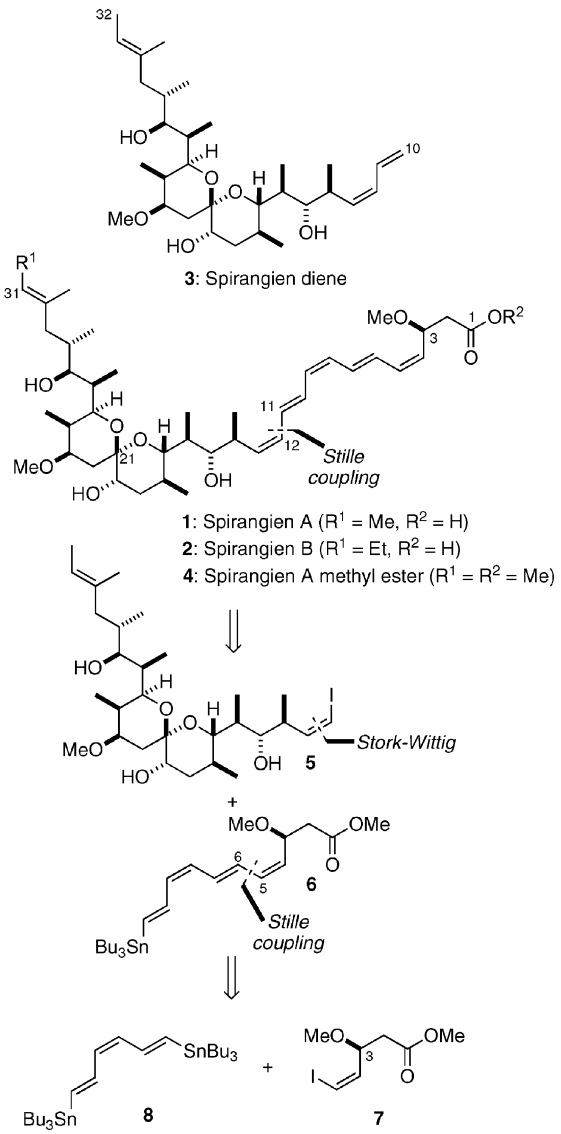
The first total synthesis of (−)-spirangien A, a cytotoxic and antifungal polyketide of myxobacterial origin, is reported; this exploits a Stork–Wittig olefination and double Stille cross-coupling sequence to install the sensitive pentaene side chain onto a fully elaborated spiroacetal core, leading initially to the methyl ester of spirangien A.

Spirangiens A (**1**, Scheme 1) and B (**2**) are microbial metabolites isolated by the Höfle group[1] from the epothilone-producing myxobacterium *Sorangium cellulosum* (strain So ce90). These complex polyketides[2] are potent cytotoxic agents (IC_{50} 0.7 ng mL^{-1} against L929 mouse fibroblast cell line) that also show significant antifungal activity. Structurally, the spirangiens possess 14 stereocentres, and include a densely functionalised [6,6]-spiroacetal core appended with an elaborate side chain bearing a delicate pentaene chromophore and a terminal carboxylic acid. To aid the stereochemical assignment, controlled chemical degradation of spirangien A was performed by Niggemann *et al.*[1a] to generate the fragment **3**, where X-ray diffraction analysis enabled the determination of the relative configuration. Recently, we reported an expedient aldol-based strategy for assembling the spiroacetal core,[3,4] leading to the synthesis of spirangien diene (+)-**3** and thus enabling assignment of the absolute configuration. Herein, we report the extension of these studies to install the sensitive, fully elaborated side chain, culminating in the first total synthesis of (−)-spirangien A (**1**) and its methyl ester derivative **4**.

At the outset, concerns over the instability of the spirangiens associated *inter alia* with facile isomerisation of the pentaene chromophore, which features alternating (*Z*)- and (*E*)-olefins, dictated the late-stage incorporation of the side chain onto a fully elaborated spiroacetal intermediate to initially produce spirangien A methyl ester (**4**). This approach would require a mild metal-mediated coupling protocol that was highly tolerant of other functional groups. As outlined in Scheme 1, we envisaged the use of sequential Stille cross-couplings[5] at C11–C12 and C5–C6, performed under carefully controlled conditions. This analysis reveals the advanced spiroacetal-containing fragment **5**, with a truncated right-hand side chain bearing a (*Z*)-vinyl iodide, and a suitable stannane partner **6**. Disconnection of this tetraene **6** then leads back to the (*Z*)-vinyl iodide **7** and the bis-stannylated (1*E*,3*Z*,5*E*)-triene linker **8**. Strategically, such a symmetrical linker also offers useful flexibility over the order of assembly of the full spirangien side chain.

The synthesis of the advanced spiroacetal intermediate **5** exploited the repeating pattern of four contiguous stereocentres (C15–C18 and C25–C28) present in the linear precursor **9** (Scheme 2). Following the aldol coupling of subunits **10**[6] and **11**, each derived from the common stereotetrad **12**,[7] spiroacetalisation of **9** generated the spirangien core which was elaborated to the alcohol **13**.[3,8] Following Dess–Martin oxidation of **13**, Stork–Wittig olefination of the resulting aldehyde using



Scheme 1 Retrosynthetic analysis of (−)-spirangien A (**1**).

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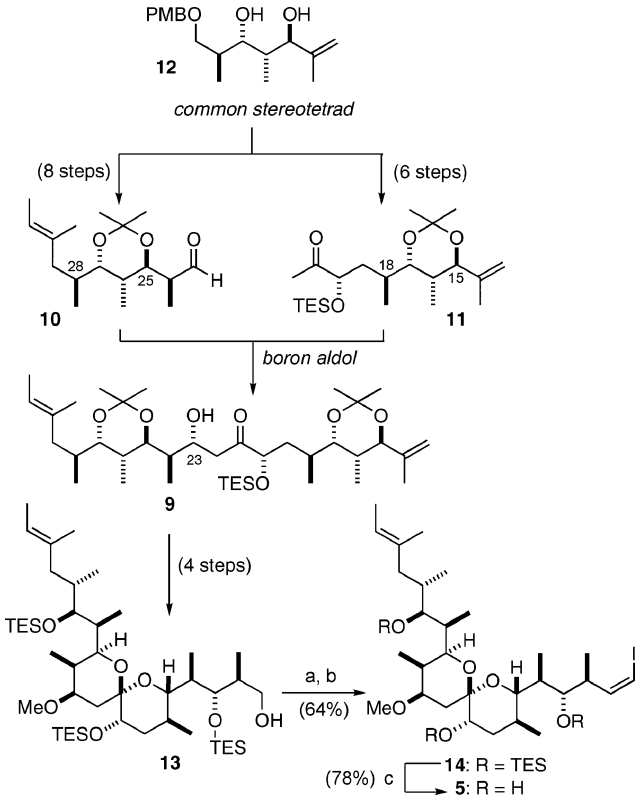
† Dedicated to the late Dr Jonathan (Joe) Spencer, a greatly missed colleague and friend.

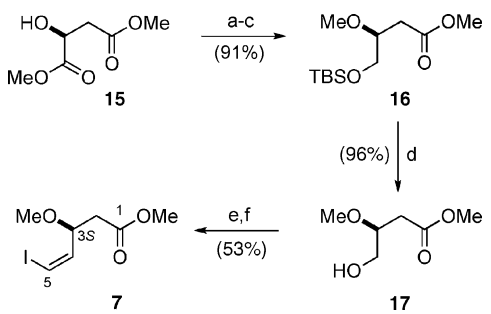
‡ Electronic supplementary information (ESI) available: Characterisation data, copies of NMR spectra and comparative listings. See DOI: 10.1039/b816229h



Scheme 2 *Reagents and conditions*: (a) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 20 °C; (b) $(Ph_3PCH_2I)^+I^-$, NaHMDS, HMPA, THF, −78 → 20 °C; (c) CSA, MeOH, 20 °C.

iodomethylenetriphenylphosphorane (generated using NaHMDS) in THF/HMPA afforded the (*Z*)-vinyl iodide **14** (74%; *Z* : *E* 3 : 1). Cleavage of the TES ethers using CSA/MeOH (78%) then enabled the isolation of configurationally pure iodide **5**, in readiness for attachment of the C1–C11 side chain.

In the degradation studies performed on spirangien A, the isolated C3 methoxy-bearing stereocentre was assigned as having the (*S*)-configuration.[1a] Hence, the (*Z*)-vinyl iodide **7** required for construction of the side chain was prepared from the corresponding dimethyl (*S*)-malate (**15**), as shown in Scheme 3. Following a chemoselective reduction of **15** ($BH_3{\cdot}SMe_2$, cat. $NaBH_4$),[9] the 1,2-diol product was sequentially selectively silylated (TBSCl) and methylated with Meerwein's

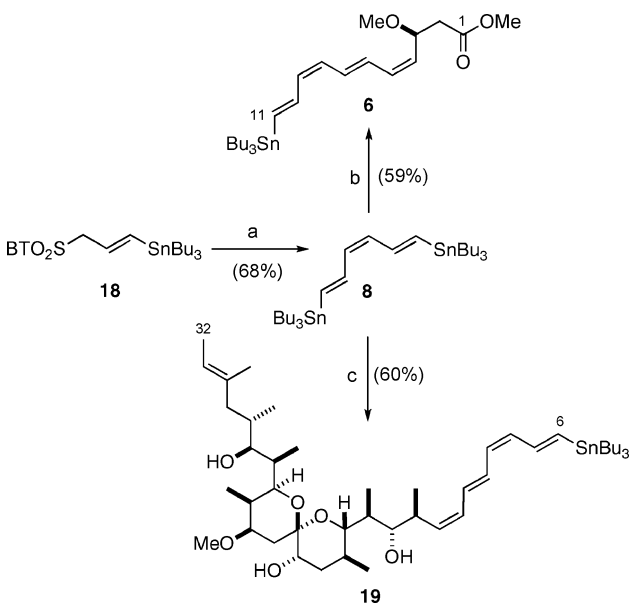


Scheme 3 *Reagents and conditions*: (a) $BH_3{\cdot}SMe_2$, THF, 0 → 20 °C; $NaBH_4$, 0 → 20 °C; (b) TBSCl, imid., 0 → 20 °C; (c) Me_3OBF_4, proton sponge, CH_2Cl_2, 0 → 20 °C; (d) TBAF, AcOH, THF, 0 → 20 °C; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 → 20 °C; (f) $(Ph_3PCH_2I)^+I^-$, NaHMDS, HMPA, THF, −100 → 20 °C.

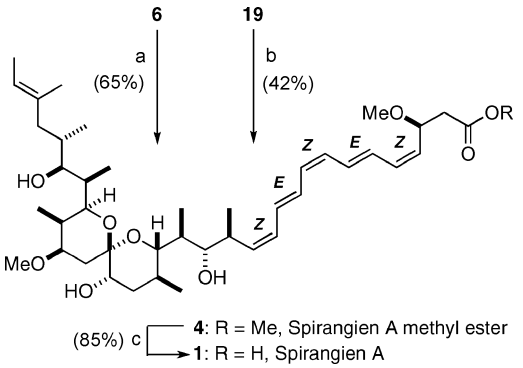
reagent to afford **16**. Cleavage of the TBS ether provided alcohol **17** (87% from **15**). Swern oxidation led to the aldehyde which was subjected to a Stork–Wittig olefination to afford the required (*Z*)-vinyl iodide **7** selectively (53%, *Z* : *E* 19 : 1).

With the iodide **7** now in hand, access to the bis-stannylated triene **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 co-workers,[10a] *via* a (*Z*)-selective, modified Julia olefination between the benzothiazolylsulfone **18** and (*E*)-$Bu_3SnCH{=}CHCHO$.[10] Conveniently, the use of this triene linker **8** offered flexibility with regards to the order of assembly of the (4*Z*,6*E*,8*Z*,10*E*,12*Z*)-pentaene of the spirangiens. A Stille cross-coupling reaction[5] between **7** and **8** to form tetraene **6**, followed by a second Stille coupling to append the spiroacetal core, was viewed as the more convergent option (Scheme 4). However, initial formation of the tetraene **19**, then attachment of the remaining C1–C5 unit **7**, was an alternative scenario. Owing to the pronounced acid- and light-sensitivity of the resulting conjugated polyenes,[12] we elected to explore both coupling sequences.

In the event, the coupling of bis-stannyl triene **8** with either **7** or **5** using catalytic $Pd_2(dba)_3$ (5 mol%) and Ph_3As (13 mol%)[11] in DMF/THF afforded the desired stannyl tetraenes **6** (59%) and **19** (60%), respectively, with only minor amounts (≤10%) of isomers evident by ^1H and ^{13}C NMR analysis. Necessarily, this was performed with strict exclusion of light to avoid isomerisation. The stage was now set for the second, crucial Stille coupling reaction to install the remainder of the delicate pentaene moiety to give spirangien A methyl ester **4** (Scheme 5). Under the same conditions ($Pd_2(dba)_3$, Ph_3As), reaction of tetraenes **6** and **19** with the corresponding (*Z*)-vinyl iodides, **5** and **7**, afforded the coupled product **4**. At this point, the pentaene product was isolated and submitted to careful HPLC purification.[12] Gratifyingly, other than having the additional methyl signal, the ^1H and ^{13}C NMR spectroscopic data obtained for the thus formed methyl ester (−)-**4**, $[\alpha]_D^{20}$



Scheme 4 *Reagents and conditions*: (a) (*E*)-$Bu_3SnCH{=}CHCHO$, KHMDS, THF, −78 → 20 °C; (b) **7**, $Pd_2(dba)_3$, Ph_3As, DMF/THF (4 : 1), 20 °C; (c) **5**, $Pd_2(dba)_3$, Ph_3As, DMF/THF (4 : 1), 20 °C.



Scheme 5 *Reagents and conditions*: (a) **5**, $Pd_2(dba)_3$, Ph_3As, DMF/THF (4 : 1), 20 °C; (b) **7**, $Pd_2(dba)_3$, Ph_3As, DMF/THF (4 : 1), 20 °C; (c) KOH, EtOH/H_2O (2 : 1), 20 °C.

−26.2 (*c* 0.08, MeOH), matched those for spirangien A (**1**),[1a,13] indicating that the full stereostructure, including the (4*Z*,6*E*,8*Z*,10*E*,12*Z*)-pentaene moiety, had been introduced correctly.

Finally, having secured the synthesis of spirangien A methyl ester, the task still remained to hydrolyse it to the corresponding acid, all the time avoiding isomerisation of the delicate pentaene moiety. After considerable experimentation, optimal results were achieved using KOH in aqueous EtOH, which delivered the unstable[14] carboxylic acid **1** (85%) having spectroscopic data in accordance with that reported for natural (−)-spirangien A.[1a] The measured specific rotation, $[\alpha]_D^{20}$ −17.5 (*c* 0.04, MeOH) *cf.* −19.4 (*c* 1.0, MeOH), was also a match, both in terms of magnitude and sign, thereby validating the full configurational assignment of the spirangiens. Notably, the methyl ester **4** was found to be more stable than spirangien A itself.[13]

In summary, a highly convergent and flexible synthetic strategy has been developed for the spirangiens, making use of Stork–Wittig olefination and Stille cross-coupling reactions to introduce the sensitive side chain, in combination with our boron aldol chemistry to construct the spiroacetal core.[3] Overall, this first total synthesis of (–)-spirangien A, along with its more stable methyl ester derivative **4**, proceeds in 18 steps and 2.0% yield (*via* **6**) from the readily available common stereotetrad **12**,[7] and rigorously defines the relative and absolute configuration. This work also offers a secure platform from which to progress SAR studies of the spirangiens, and enable the determination of their mechanism of action. By suitable editing of the side chain, potentially more stable analogues may be designed that retain the associated potent biological activity.

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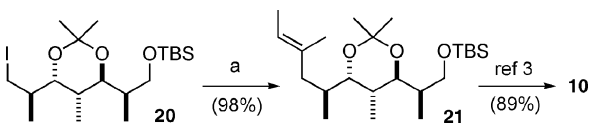
6 We have developed an improved synthesis of the C23–C32 subunit **10** using a Cu-mediated alkylation reaction of iodide **20** (ref. 3) with (*E*)-2-lithiobut-2-ene to give **21**: (a) (*E*)-2-bromobut-2-ene, *t*BuLi, THF, −100 °C; CuCN, Et_2O, −78 → −50 °C; **19**, −50 → 20 °C.



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12 Strict exclusion from exposure to light and the use of base-washed amber glassware were found to be crucial.
13 While the methyl ester **4** had been prepared previously from natural spirangien A, unfortunately no comparison NMR data were available (J. Niggemann, personal communication). We found that spirangien A methyl ester could be stored in MeOH at −20 °C for extended periods without deterioration.
14 Following the hydrolysis step, spirangien A was submitted to careful HPLC purification to remove any traces of minor isomers that may have formed during the acidic work-up.

