Synthesis of the bis-spiroacetal C_{25}–C_{40} moiety of the antimitotic agent spirastrellolide B using a bis-dithiane deprotection/spiroacetalisation sequence†

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Use of a bis-dithiane deprotection–tandem bis-spiroacetalisation sequence was key to the successful synthesis of the [5,6,6]-bis-spiroacetal of the antimitotic agent spirastrellolide B, achieved in a highly convergent fashion involving successive dithiane alkylations.

The spirastrellolides are a family of polyketide macrolides first isolated in 2003 by Andersen and co-workers from the marine sponge *Spirastrella coccinea*.[1] Spirastrellolides A (**1**) and B (**2**) exhibited antimitotic activity which was later attributed to the potent (IC_{50} = 1 nM) inhibition of Ser/Thr protein phosphatase 2A (PP2A). PP2A is emerging as a novel medicinal target for the treatment of cancer,[2] and the isolation of the spirastrellolides is thus important not only for its potential as a therapeutic agent, but also for its use as a biological tool in the investigation of PP2A function.

The complex structure of the spirastrellolides and its unique biological activity has generated intense interest within the synthetic community.[3] Of particular interest to our research group is the intriguing [5,6,6]-bis-spiroacetal ring system (Fig. 1).[4] We sought to prepare this unit using a double dithiane deprotection/spiroacetalisation strategy.[5] The simultaneous deprotection of two dithiane moieties with concomitant cyclisation to form a bis-spiroacetal is hitherto unprecedented in the context of natural product synthesis.

The structure of the DEF bis-spiroacetal moiety benefits from full anomeric stabilisation with all of its substituents occupying equatorial positions. The desired configuration at

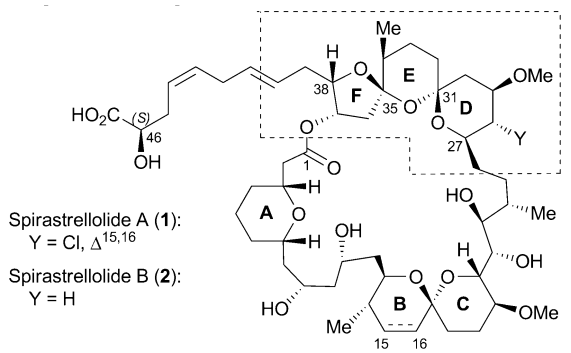

Fig. 1 Spirastrellolides A and B and the DEF bis-spiroacetal.

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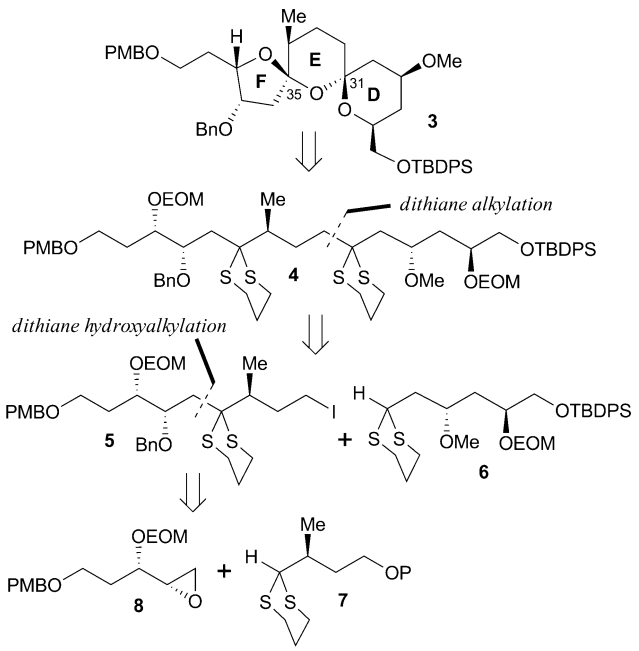
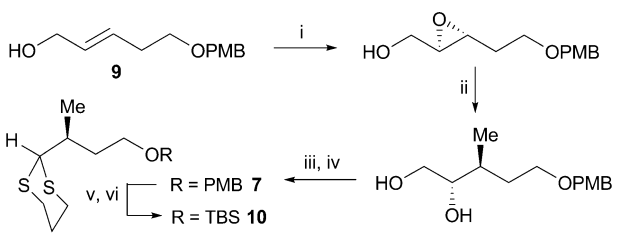
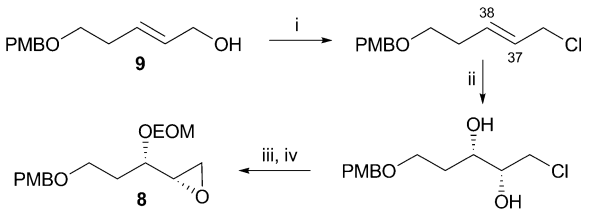


Scheme 1 Retrosynthesis of DEF bis-spiroacetal **3**.

C_{31} and C_{35} should therefore result from bis-dithiane deprotection of acyclic precursor **4** under equilibrating conditions to form the desired bis-spiroacetal **3** (Scheme 1). Acyclic precursor **4** is accessible *via* alkylation of dithiane **6** with iodide **5**, which in turn is prepared *via* union of dithiane **7** with epoxide **8**. These two successive dithiane alkylations considerably simplify the carbon backbone of the target into three smaller fragments, thereby facilitating a highly convergent approach to DEF bis-spiroacetal **3**.



Scheme 2 *Reagents and conditions*: (i) $Ti(O\text{-}i\text{-}Pr)_4$, D-(−)-DET, TBHP, 4 Å MS, CH_2Cl_2, −30 °C, then **9**, −25 °C, 92% yield, >95% ee; (ii) Me_3Al, CH_2Cl_2–hexanes (1 : 1), 78%; (iii) $NaIO_4$, THF–H_2O (1 : 1), rt, 99%; (iv) 1,3-propanedithiol, $CoCl_2$, CH_3CN, rt, 80%; (v) $BF_3{\cdot}OEt_2$, Me_2S, CH_2Cl_2, rt, then **7**, 80%; (vi) TBSCl, NEt_3, DMAP, CH_2Cl_2, 85%.

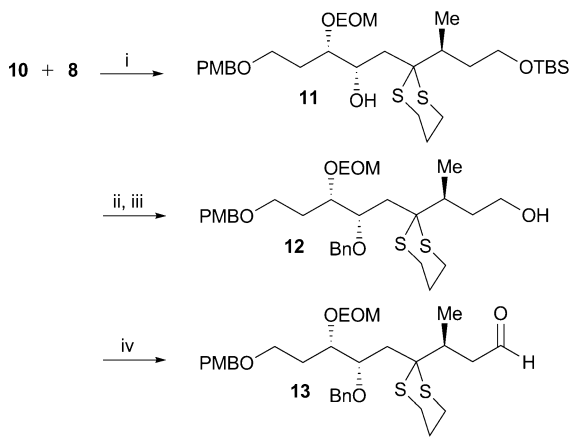


Scheme 3 *Reagents and conditions*: (i) NCS, DMS, CH_2Cl_2, then **9**, 0 °C to rt, 93%; (ii) $(DHQ)_2AQN$, OsO_4, $K_3[Fe(CN)_6]$, $CH_3SO_2NH_2$, K_2CO_3, $NaHCO_3$, *t*-BuOH–H_2O (1 : 1), 0 °C, 98%, 94% ee; (iii) NaOH, THF, 0 °C, 91%; (iv) EOMCl, *i*-Pr_2EtN, DMAP, CH_2Cl_2, rt, 87%.

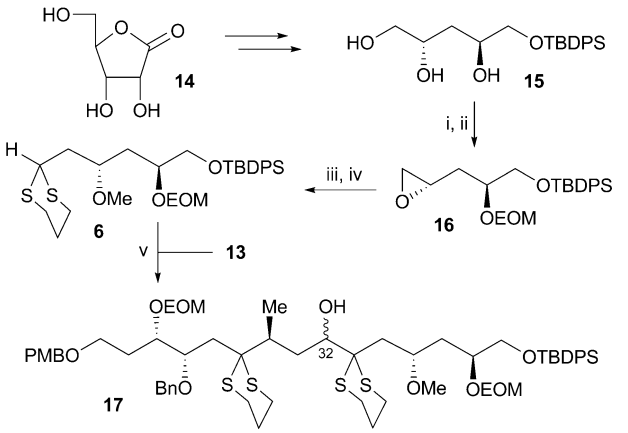
The first fragment dithiane **7** was prepared using Sharpless asymmetric epoxidation[6] of allylic alcohol **9** (Scheme 2). Subsequent epoxide opening using trimethylaluminium,[7] followed by oxidative cleavage and treatment with 1,3-propanedithiol in the presence of $CoCl_2$[8] furnished dithiane **7**. Dithiane **7** however, proved ineffective for subsequent alkylation reactions and deuterium exchange experiments indicated incomplete lithiation of the 1,3-dithiane to be the problem. In view of previous reports of interactions between π systems and the C–S σ* orbital,[9] the PMB ether was replaced with a TBS ether (Scheme 2). Dithiane **10** was efficiently lithiated, with 80% deuterium incorporation being observed.

The synthesis of epoxide **8** began with chlorination of allylic alcohol **9**, followed by Sharpless dihydroxylation[10] to install the stereocentres at C_{37} and C_{38} (Scheme 3). Use of the AQN[11] linker allowed access to the diol in 94% ee, higher than the previously reported example using PHAL (88% ee).[12] Treatment with NaOH to form the epoxy alcohol, followed by protection as an ethoxymethyl (EOM) ether provided epoxide **8** in 72% over the 4 steps.

Union of dithiane **10** and epoxide **8** was efficiently achieved by treatment of dithiane **10** (1.6 eq.) with *n*-BuLi at rt, followed by the addition of epoxide **8** (Scheme 4). The coupled product **11** was isolated in quantitative yield, with the excess dithiane **10** fully recovered. Benzyl protection of the resulting alcohol, followed by removal of the primary TBS group provided alcohol **12** in 82% yield over the 2 steps. Attempts to convert alcohol **12** into the corresponding iodide for



Scheme 4 *Reagents and conditions*: (i) *n*-BuLi, THF, rt, 5 min, then **8**, 98%; (ii) KH, BnBr, THF, rt, 85%; (iii) TBAF, THF, rt, 97%; (iv) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 86%.



Scheme 5 *Reagents and conditions*: (i) KHMDS, 0 °C, THF, then *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole; (ii) EOMCl, *i*-Pr_2EtN, DMAP, CH_2Cl_2, rt, 53% over 2 steps; (iii) 1,3-dithiane, *n*-BuLi, THF, −20 °C, then **16**, 0 °C, 88%; (iv) *t*-BuOK, MeI, THF, rt, 82%; (v) *n*-BuLi/Bu_2Mg (4 : 1), THF, rt, then **13**, 78% (3 : 2 ratio of diastereomers).

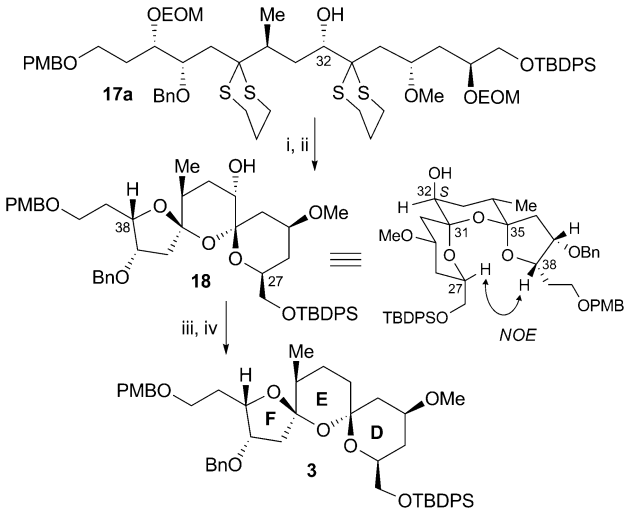
subsequent alkylation resulted only in decomposition of the starting material.[13] Alcohol **12** was therefore converted to aldehyde **13** using TPAP/NMO,[14] with the hope that the superfluous hydroxyl group formed following hydroxyalkylation could be readily removed *via* Barton–McCombie[15] deoxygenation.

The third fragment dithiane **6** was synthesised from triol **15**, which in turn was available from D-(+)-ribono-γ-lactone **14** (Scheme 5).[16] Epoxide formation using KHMDS and *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole,[17] followed by EOM protection furnished epoxide **16** in 53% yield over the 2 steps. Alkylation of epoxide **16** with 1,3-dithiane, followed by methylation provided the desired dithiane **6**.

Deuterium exchange experiments demonstrated effective lithiation of dithiane **6** using *n*-BuLi as well as *t*-BuLi in THF/HMPA, but both of these methods failed to effect the union of dithiane **6** with aldehyde **13**. Further experiments suggested that the lifetime of the anion was relatively short at the temperatures required for successful alkylation. Therefore a *n*-BuLi/Bu_2Mg[18] mixture was employed to extend the lifetime of the lithiated species. Use of this mixed organometallic reagent allowed effective coupling of dithiane **6** with aldehyde **13** in 78% yield (3 : 2 ratio of diastereomers).

Several methods were investigated for the deoxygenation of alcohol **17**, including Barton–McCombie conditions. Formation of the xanthate derivative of alcohol **17** was successful, but subsequent treatment with Bu_3SnH and AIBN and heating in toluene resulted in decomposition of the starting material. Attempts to form the thiocarbonyldiimidazole derivative met with failure.

The desire to progress with the synthesis led to the decision to postpone the deoxygenation of the C_{32} secondary alcohol to allow investigation of the critical bis-dithiane deprotection–bis-spiroacetalisation sequence. To this end, the two diastereomeric alcohols were separated to facilitate ^1H NMR and ^{13}C NMR interpretation in the following steps. However, steric hindrance at the C_{32} alcohol prevented introduction of bulky protecting groups capable of withstanding the acidic conditions required for removal of the EOM groups.



Scheme 6 *Reagents and conditions*: (i) PPTS, *t*-BuOH, reflux, 63%; (ii) $HgCl_2$, CH_3CN–H_2O (4 : 1), rt, 74%; (iii) $C(S)Im_2$, THF, reflux, 78%; (iv) Bu_3SnH, AIBN, toluene, reflux, 40% **3** and 30% **18**.

As a result, unprotected alcohol **17a** was carried through the bis-dithiane deprotection–spiroacetalisation sequence with the intent of removing the superfluous hydroxyl group at a late stage.[19] The best results for EOM deprotection was obtained by use of PPTS in *t*-BuOH[20] at reflux to furnish the corresponding triol in 63% yield (Scheme 6). Gratifyingly, the critical bis-dithiane deprotection step was accomplished by treatment of the bis-dithiane with $HgCl_2$, resulting in concomitant bis-spiroacetalisation to generate the desired bis-spiroacetal **18** in 74% yield. Bis-spiroacetal **18** was formed as a single diastereomer, with no sign of competing cyclisations. The double anomerically stabilised configuration was confirmed by a strong NOE correlation between the C_{27} and C_{38} methine protons.

An attempt to form the xanthate derivative of **18** in readiness for a Barton–McCombie deoxygenation reaction met with failure. However, the thiocarbonylimidazole derivative of bis-spiroacetal **18** was successfully formed, presumably due to the lower steric encumbrance at C_{32} following bis-spiroacetal formation. Treatment of the thiocarbonylimidazole derivative of **18** with Bu_3SnH and AIBN in toluene under reflux furnished the desired DEF bis-spiroacetal of spirastrellolide B (**3**) in 40% yield, with 30% recovered bis-spiroacetal **18**. Efforts towards improving the efficiency of the deoxygenation step are ongoing and will be reported in due course.

In summary, the successful synthesis of the DEF bis-spiroacetal ring system of spirastrellolide B has been achieved using a novel bis-dithiane deprotection–tandem bis-spiroacetalisation strategy. Features of this highly convergent synthesis include the use of successive dithiane alkylations and a late stage Barton–McCombie deoxygenation reaction. This methodology can also be used to access C_{32} analogues of the DEF bis-spiroacetal in order to investigate their PP2A activity.

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