Synthesis of two diastereomeric C_1–C_{22} fragments of spirastrellolide A†

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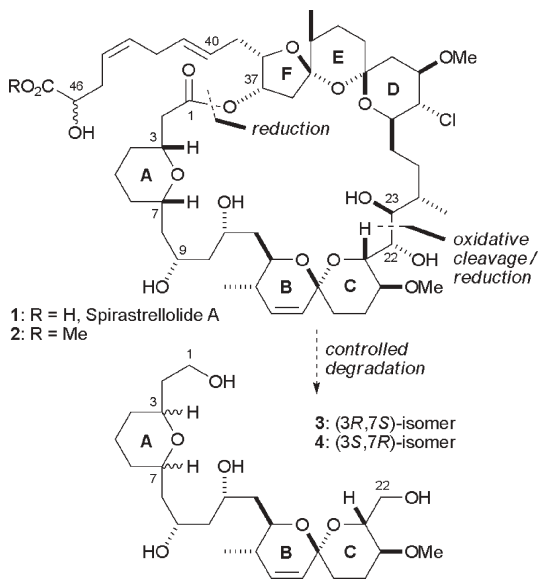
The optimisation of a synthetic strategy towards the ABC segment of the cytotoxic macrolide spirastrellolide A is reported, together with its application to the synthesis of two diastereomeric C_1–C_{22} fragments for stereochemical correlation purposes with a putative spirastrellolide degradation product.

The novel cytotoxic polyketide spirastrellolide A (**1**, Scheme 1), was isolated by Andersen and co-workers from the Caribbean sponge *Spirastrella coccinea* in 2003. Synthetic interest in spirastrellolide derives not only from its unique molecular architecture, but also from its potential development as an antitumour therapeutic agent, as it is a potent and selective inhibitor of protein phosphatase 2A (PP2A, IC_{50} = 1 nM).[1,2] As such, it appears to possess a similar mode of action to other Ser/Thr phosphatase inhibitors, including fostriecin, okadaic acid, and the calyculins, which induce premature cell mitosis. Given the central regulatory role of PP2A in the cell, spirastrellolide may also find further applications as a lead in the treatment of neurological and metabolic disorders.[3]

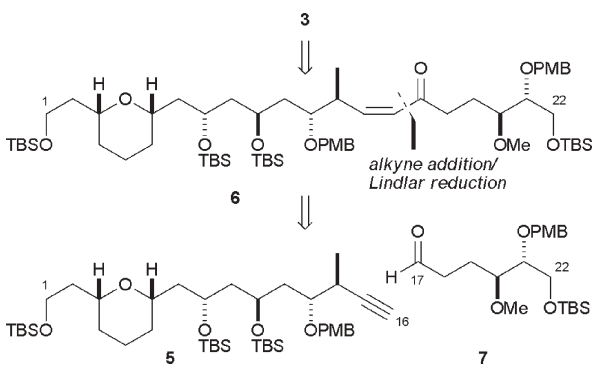
Although extensive NMR spectroscopic analysis of the spirastrellolide methyl ester derivative **2** was performed by the Andersen group, until recently[4] the relative stereochemistry between four stereoclusters (C_3–C_7, C_9–C_{24}, C_{27}–C_{38} and C_{46}), and the absolute configuration, remained unknown, leading to 16 possible stereoisomers. In view of this ambiguity, we had previously tried to determine the relative configuration between the C_3–C_7 *cis*-2,6-disubstituted tetrahydropyran (A ring) and the C_9–C_{24} BC spiroacetal-containing subunit by comparison of NMR data of two synthetic C_1–C_{25} diastereomeric fragments to that of spirastrellolide A methyl ester **2**.[5–7] Unfortunately, due to the presumed conformational differences between the macrocyclic natural product and our linear fragments, it was difficult to confirm the relative stereochemistry in this region.



Scheme 1 Spirastrellolide A and potential degradation route to fragments **3** and **4**.

At this juncture, a collaborative effort with the Andersen group was conceived towards the correlation of fragments from chemical degradations of spirastrellolide A with independently synthesised intermediates of defined stereochemistry. A C_1–C_{22} fragment **3** or **4** (Scheme 1) could potentially be prepared by oxidative cleavage of the C_{22}–C_{23} bond followed by reduction of the resulting carbonyl groups. Laboratory syntheses of both **3** and **4**, followed by comparison with the spirastrellolide degradation fragment, should then enable the assignment of the relative stereochemistry between C_3–C_7 and C_9–C_{24}, and also the absolute configuration. In addition, this project represented an opportunity to develop both an improved approach to the C_1–C_{16} alkyne **5** by removing our reliance on stoichiometric chiral reagents,[5] and also to optimise our spiroacetalisation strategy. We report herein the synthesis of the two C_1–C_{22} diastereomeric fragments **3** and **4**, and the improvements to our synthetic strategy.

Our retrosynthetic analysis of degradation fragment **3** is outlined in Scheme 2. According to our initial studies,[6] a double PMB deprotection/*in situ* spiroacetalisation strategy could be adopted for the construction of the BC spiroacetal from the (*Z*)-enone **6**. This enone might itself be derived from the coupling of



Scheme 2 Retrosynthesis of the C_1–C_{22} subunit **3**.

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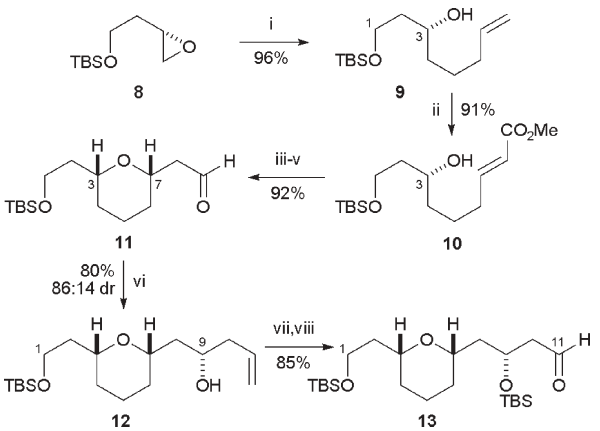
the lithiated alkyne **5** with aldehyde **7**, followed by reoxidation at C_{17} and Lindlar reduction. Alkyne **5** contains a modified array of protecting groups, which we hoped would allow selective deprotection/BC spiroacetalisation without recourse to harsh conditions.[5]

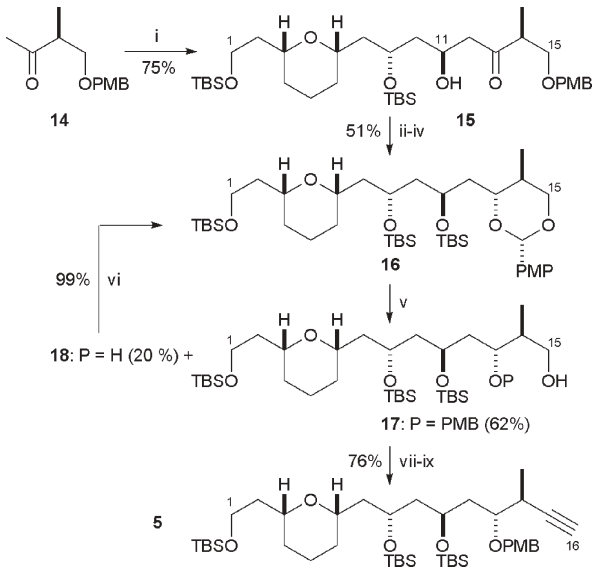
Our original approach to the C_1–C_{11} aldehyde **13** (Scheme 3) utilised two Brown allylations; we envisaged that the first of these (to control the C_3 stereocentre) could be replaced with a Jacobsen hydrolytic kinetic resolution (HKR).[8] Enantiopure epoxide **8** (46%, >99% ee), thus prepared by HKR of the corresponding racemic epoxide,[8] was subjected to ring-opening with 3-butenylmagnesium bromide to afford the secondary alcohol **9** (96%). Cross-metathesis[9] of **9** with methyl acrylate gave enoate **10** (91%), which underwent intramolecular Michael addition and oxidation state adjustment to give the *cis*-2,6-disubstituted tetrahydropyran aldehyde **11** as a single diastereomer (92%, three steps). The second Brown allylation of our original synthesis could be successfully replaced by a substrate-controlled allylation[10] with allyltrimethylsilane to give **12** (80%, 86 : 14 dr), which was subjected to TBS protection and ozonolysis to provide aldehyde **13** (85%, two steps).[5]

The synthesis of the targeted alkyne **5** was completed as depicted in Scheme 4. A boron-mediated 1,4-*syn*-aldol reaction of ketone **14** with aldehyde **13** provided aldol adduct **15** (75%, >95 : 5 dr).[11] Selective 1,3-*anti*-reduction,[12] followed by hydroxyl-differentiating PMP acetal formation (DDQ) and TBS protection, then gave PMP acetal **16** (51%). Although DIBALH proved ineffective in initial attempts to cleave this PMP acetal, reductive acetal-opening (to **17**) was successfully achieved with borane at high temperature (100 °C).[13] A small amount of over-reduced diol **18** was also isolated (20%), which could be recycled by reprotection to PMP acetal **16** (99%). Oxidation of alcohol **17**, followed by Corey–Fuchs alkynylation,[14] provided the C_1–C_{16} alkyne **6** (76%). This scalable route to **5** proceeded in 11% overall yield (16 steps) from epoxide **8**.

The synthesis of aldehyde coupling partner **7** commenced with commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol **19** (Scheme 5). Oxidative cleavage of the glycol and subsequent



Scheme 3 *Reagents and conditions*: (i) 3-butenylMgBr, CuI (cat.), THF; (ii) Grubbs catalyst (second generation, 0.5 mol%), methyl acrylate, DCM; (iii) KO*t*-Bu, THF, −20 °C; (iv) $LiAlH_4$, Et_2O; (v) Dess–Martin periodinane, DCM; (vi) allyltrimethylsilane, $TiCl_4$, DCM, −78 °C; (vii) TBSCl, imidazole, DMAP (cat.), DMF; (viii) O_3, DCM, −78 °C; PPh_3.

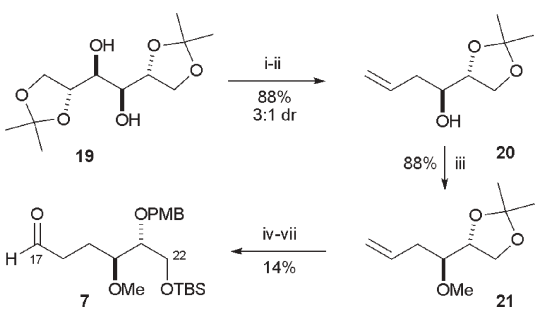


Scheme 4 *Reagent and conditions*: (i) **14**, (−)-Ipc_2BCl, Et_3N, Et_2O, 0 °C; **13**, −78 °C; (ii) $Me_4NBH(OAc)_3$, MeCN–AcOH (3 : 1), −30 °C; (iii) DDQ, 4 Å MS, DCM; (iv) TBSOTf, 2,6-lutidine, DCM; (v) $BH_3{\cdot}Me_2S$, toluene, 100 °C; (vi) $PMPCH(OMe)_2$, *p*-TsOH, DCM; (vii) Dess–Martin periodinane, DCM; (viii) CBr_4, PPh_3, Et_3N, DCM, −78 °C; (ix) *n*-BuLi, THF.

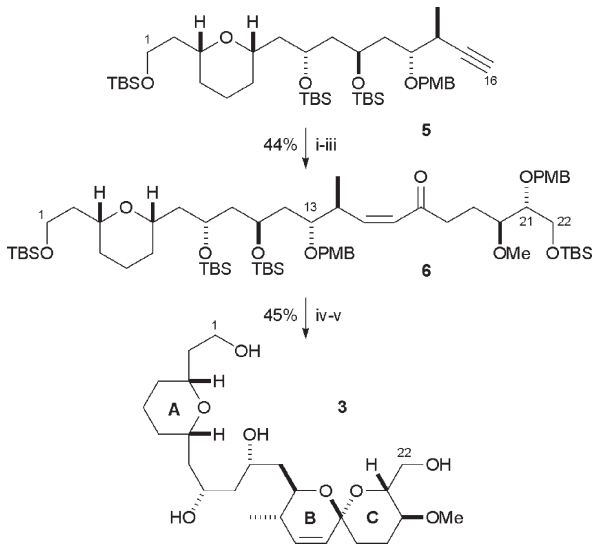
Barbier-type allylation[15] gave allylic alcohol **20** (88%) as an inseparable mixture of diastereomers (3 : 1). Fortunately, separation by flash column chromatography proved possible after methylation (**21**, 88%). Functional group manipulation completed the preparation of aldehyde **7**.

With **5** and **7** in hand, we were now ready to prepare C_1–C_{22} diastereomer **3**. Lithiation of alkyne **5**, followed by addition of aldehyde **7**, gave the desired coupled propargylic alcohols as a 1 : 1 epimeric mixture at C_{17} (Scheme 6). Dess–Martin oxidation followed by Lindlar reduction delivered (*Z*)-enone **5** (44%, three steps).

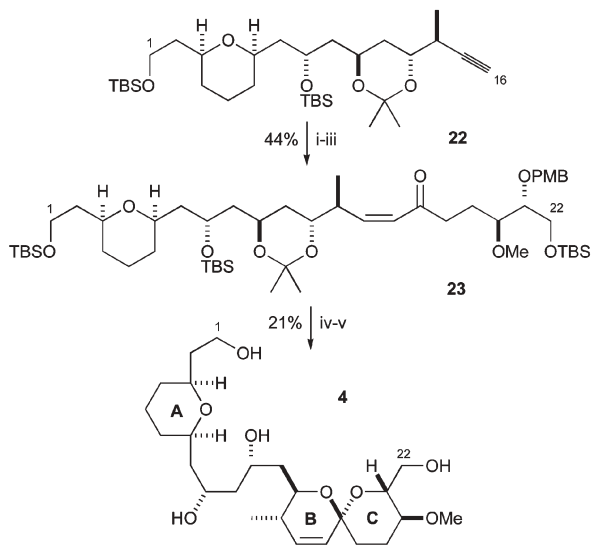
The key spiroacetalisation was then realised by DDQ deprotection of the PMB groups at both C_{13} and C_{21}, smooth spiroacetalisation to a single isomer being observed *in situ*. Gratifyingly, from the viewpoint of our long term synthetic strategy, this transformation could be achieved without affecting



Scheme 5 *Reagents and conditions*: (i) $NaIO_4$/silica gel, DCM; (ii) allylBr, Zn, THF, NH_4Cl; (iii) NaH, MeI, THF; (iv) *p*-TsOH, MeOH; (v) TBSCl, imidazole, DCM; (vi) PMBTCA, TfOH, DCM; (vii) 9-BBN, THF; H_2O_2, pH 7 buffer; (vii) Dess–Martin periodinane, $NaHCO_3$, DCM.



Scheme 6 *Reagents and conditions*: (i) *n*-BuLi, THF, −20 °C; **7**, −78 °C; (ii) Dess–Martin periodinane, $NaHCO_3$, DCM; (iii) H_2, $Pd/CaCO_3/Pb$, quinoline, EtOH; (iv) DDQ, pH 7 buffer/DCM; (v) TBAF, THF.



Scheme 7 *Reagents and conditions*: (i) *n*-BuLi, THF, −20 °C, then **21**, −78 °C; (ii) Dess–Martin periodinane, $NaHCO_3$, DCM; (iii) H_2, $Pd/CaCO_3/Pb$, quinoline, EtOH; (iv) DDQ, pH 7 buffer/DCM; (v) 40% aq. HF, MeCN.

any of the silyl protecting groups. Finally, global TBS-deprotection with TBAF provided the (3*R*,7*S*)-C_1–C_{22} fragment **3** (45%).

The preparation of the complementary (3*S*,7*R*)-fragment **4** was conveniently achieved using alkyne **22** (Scheme 7), which had been prepared previously. As above, addition of alkyne **22** to aldehyde **7**, followed by Dess–Martin oxidation and Lindlar reduction, gave (*Z*)-enone **23**. Stepwise deprotections of the PMB ether (DDQ), followed by the acetonide and TBS groups (HF/MeCN), provided the (3*S*,7*R*)-C_1–C_{22} fragment **4**. The completion of **3** and **4** thus enabled a potential correlation with a suitable degradation product from spirastrellolide A (Scheme 1).

At this point, the Andersen group reported the isolation of a new member of the spirastrellolide family, spirastrellolide B, and its degradation/conversion to a *p*-bromophenacyl ester.[16] The resulting X-ray crystal structure of this derivative has solved the stereochemical ambiguities within the spirastrellolide macrocycle, thereby validating structure **1** (Scheme 1) for spirastrellolide A.

In conclusion, we have developed syntheses of two diastereomeric C_1–C_{22} subunits corresponding to a potential degradation fragment from spirastrellolide A. In addition, we have further optimised our synthetic route to the ABC region of spirastrellolide by exploiting Jacobsen HKR and cross-metathesis methodology to access the pivotal alkyne **5**, and by developing an improved BC spiroacetalisation strategy. Ongoing work is directed towards the extension of this approach to encompass the DEF segment and completion of the total synthesis of spirastrellolide A.

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