Towards the combinatorial synthesis of spongistatin fragment libraries by using asymmetric aldol reactions on solid support†

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By relying on asymmetric boron-mediated aldol reactions, solid phase methodology for the stereoselective synthesis of highly substituted spiroacetals was developed and applied to the preparation of a complex AB-spiroacetal subunit of the antimitotic agent spongistatin 1 (altohyrtin A).

Spiroacetals are key structural elements in many bioactive polyketide natural products and related analogues.[1–4] As exemplified by the potent anticancer agent spongistatin 1/altohyrtin A (**1**, Fig. 1), they are characterised by having diverse arrays of stereocentres, combined with a high level of oxygenation. While methods for the solution phase synthesis of such pharmacophore scaffolds have been developed,[5,6] solid phase approaches remain a challenging task, in particular when used within the realm of complex natural product synthesis.[7] By allowing extensive variation of the configuration and substitution pattern, a combinatorial strategy to construct elaborate spiroacetal libraries is attractive, especially if this can be accomplished on solid phase, where purification procedures are simplified and automation may become feasible.

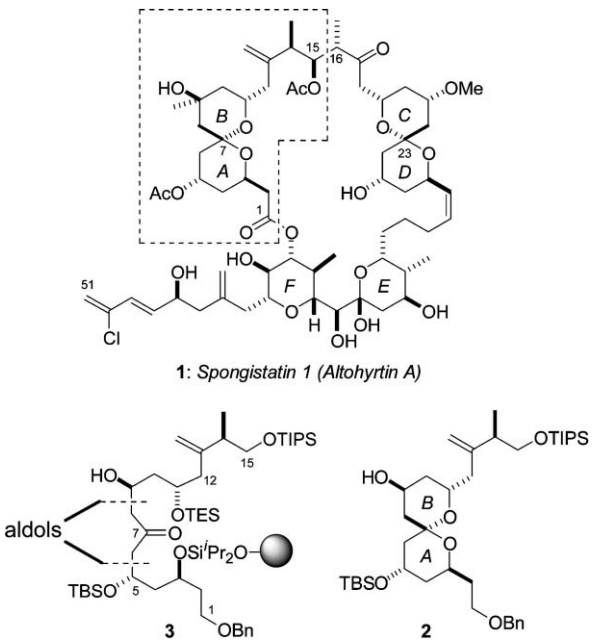
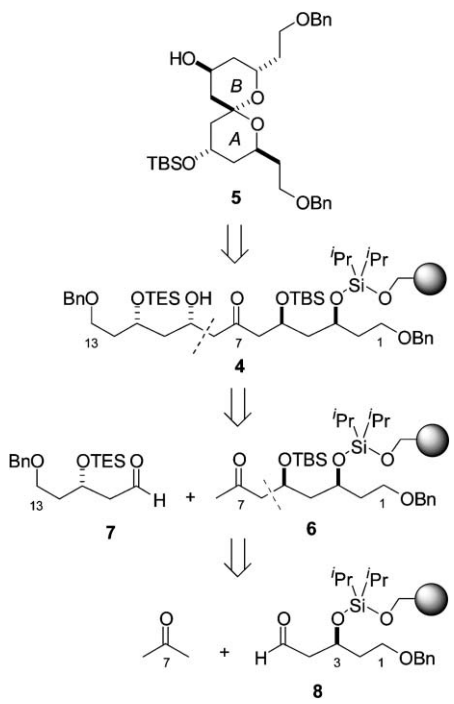


Fig. 1 Spiroacetals: a key structural element of the spongistatins.

As part of our studies towards the synthesis of polyketide-like analogues,[8,9] herein we report versatile methodology for the solid phase synthesis of architecturally complex spiroacetals, which is demonstrated by its successful application to the C1–C15 AB-subunit **2** of spongistatin.[10] This method relies on the preparation of differently substituted linear precursors, such as **3**, by performing asymmetric boron-mediated aldol reactions on polymer support,[11] with subsequent cleavage from the resin and *in situ* spiroacetalisation.

As a first target for developing appropriate solid phase methods, we chose to assemble the model resin-bound ketone **4** (Scheme 1) that already contains the stereochemical pattern required for generating the representative AB-spiroacetal subunit **5** of spongistatin. Our synthetic strategy called for first constructing its 'eastern' side, *i.e.* tetraketide **6**, and subsequently performing an aldol addition of this methyl ketone with chiral aldehyde **7**. In turn, it was planned that the ketone component **6** would be prepared by an aldol reaction of acetone with aldehyde **8**, attached at the C3 position through a suitable silyl ether linker to a resin support. Thus, this preliminary study would serve to test the



Scheme 1 Retrosynthetic analysis for the solid phase preparation of spongistatin AB-spiroacetal subunit **5**.

† Electronic supplementary information (ESI) available: experimental procedures, spectroscopic data for new compounds and copies of the NMR spectra for **2**. See http://dx.doi.org/10.1039/b505746a

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viability of performing such complex aldol coupling reactions with either the aldehyde or the enolate linked to the polymer support.

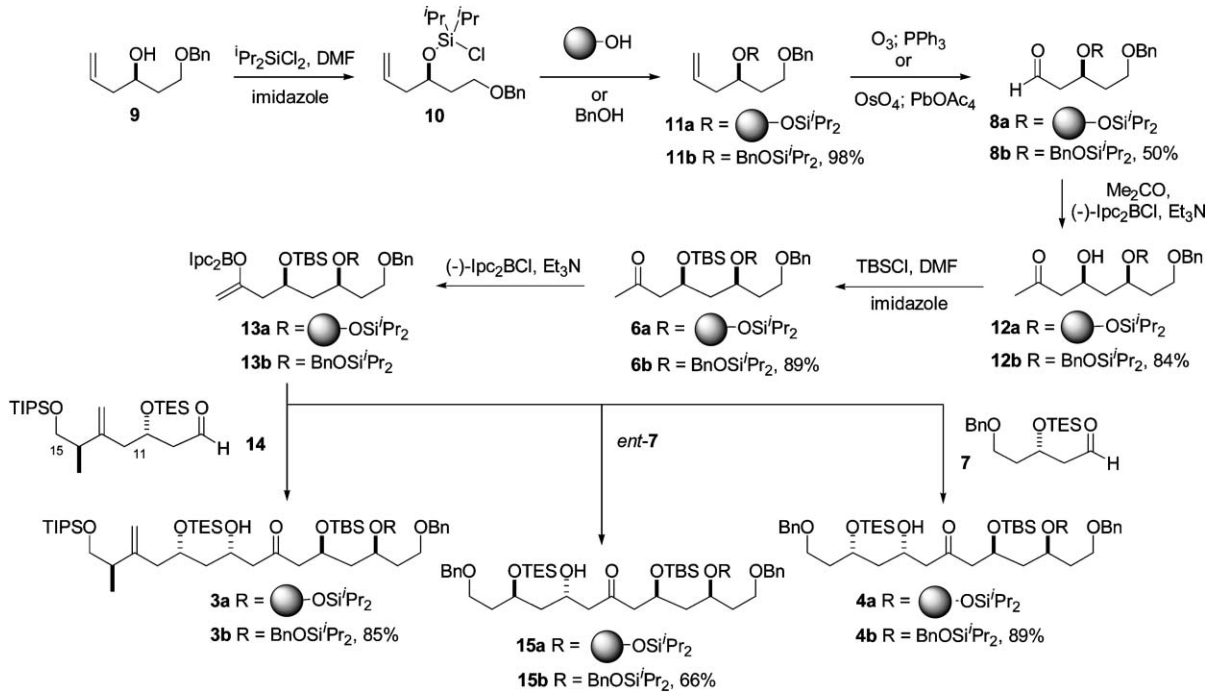
The synthesis of methyl ketone **6** and its subsequent aldol coupling with different β-silyloxy aldehydes, including **7**, are summarised in Scheme 2. This work was carried out both on solid phase (series **a**) and in solution (series **b**). To allow a facile characterisation of the resin-bound intermediates by gel-phase ^{13}C-NMR and FT-IR spectroscopy, benzyl alcohol was used in the equivalent solution phase chemistry as a mimic for the resin. In the first step, homoallylic alcohol **9** was attached to a hydroxymethylene-modified Merrifield resin by a diisopropylsilyl linker,[9a,12] *via* intermediate **10**, to give **11a** (loading: 0.6 mmol g^{-1} after capping), which was then oxidatively cleaved to give aldehyde **8a** in a straightforward fashion, either by ozonolysis or using a two-step protocol [OsO_4, $Pb(OAc)_4$]. In agreement with our previous studies on similar systems in solution phase,[13] enolisation of acetone with (−)-Ipc_2BCl/Et_3N constituted a matched case in its aldol reaction with the chiral aldehyde **8a** and led to the desired 1,3-*syn*-adduct **12a** with high diastereoselectivity (*ca.* 20:1 dr). After TBS protection of the newly installed hydroxyl group (TBSCl, imidazole, DMF), a second aldol chain extension now required formation of the boron enolate **13a** of the resin-bound methyl ketone **6a**. After extensive optimisation, this was best achieved using a preformed solution of (−)-Ipc_2BCl (3.0 equiv.) and Et_3N (3.7 equiv.) in Et_2O, followed by addition of aldehyde **7** (6 equiv.). Comparison of the ^{13}C-NMR spectrum of the resulting aldol adduct **4a** with that for **4b**, the corresponding model in solution, again indicated a high level of diastereoselectivity (*ca.* 20:1 dr), resulting from matched triple asymmetric induction.[11,13,14]

This two-directional aldol approach was then diversified and applied to access other potential linear precursors to spiroacetals on solid support. For example, the enantiomeric aldehyde *ent*-**7** was combined with the resin-bound enolate **13a** to generate the 11-*epi* aldol adduct **15a** with a similar level of stereocontrol. A key example employed the aldol coupling of enolate **13a** with the aldehyde **14** to generate the required linear precursor for the more elaborate AB-spiroacetal subunit **2** (Fig. 1), as employed in our recent total synthesis of spongistatin 1.[6a] This reaction proceeded smoothly on solid support and gave hexaketide **3a**[15,16] with high stereoselectivity, again benefiting from triple asymmetric induction.

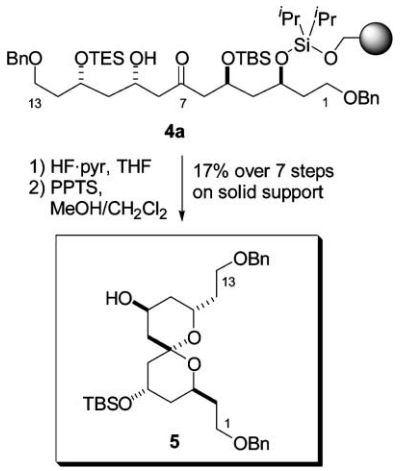
Having assembled the linear polyketide-type intermediates on solid support, it remained to demonstrate that they could indeed deliver the required spiroacetal segments. For realizing both the projected cleavage from the resin and *in situ* cyclisation, HF·pyr was chosen as a suitable reagent as it had previously shown its usefulness in similar transformations, allowing the TBS ether at C5 to be retained.[13] Gratifyingly, this enabled a one-pot process to be accomplished for ketone **4a**, allowing for cleavage of the silyl linker, the TES ether and spiroacetalisation (Scheme 3). Equilibration of the initial product mixture in solution,[17] by treatment with PPTS in MeOH–CH_2Cl_2, produced the desired, thermodynamically preferred, spiroacetal **5**. Overall, the spiroacetal **5** was produced in an acceptable 17% yield over the 7 steps performed on solid support and cleavage.

After this initial validation of our strategy, we then turned our attention to assembling a more challenging spongistatin intermediate on solid support, *i.e.* the authentic C1–C15 AB-spiroacetal subunit **2** (Scheme 4). Using again the HF·pyr conditions, both cleavage of the TES ether and the silyl linker of **3a** could be accomplished while retaining the TBS and TIPS ethers. A similar acid-mediated equilibration step then led to the isolation of the required spiroacetal **2**, obtained in 5% yield over 7 steps on solid support.[16,18]

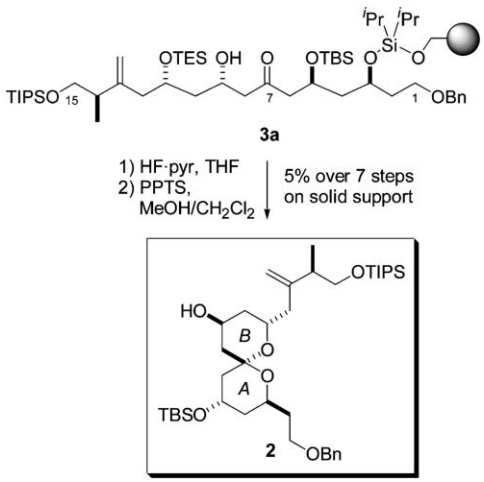
In conclusion, we have completed the stereocontrolled synthesis of some representative open-chain spiroacetal precursors related to spongistatin fragment libraries on solid support. Cleavage from the



Scheme 2 Synthesis of linear β-hydroxy ketone precursors: series **a** on solid support; series **b** solution phase equivalent.



Scheme 3 Cleavage of the linear precursor **4a** from the solid support and concomitant spiroacetalisation to give the model AB-spiroacetal **5** of spongistatin.



Scheme 4 Cleavage of the linear precursor **3a** from the solid support and concomitant spiroacetalisation to give the fully elaborated C1–C15 fragment **2** of spongistatin.

resin and selective removal of protecting groups then led to the isolation of the required spiroacetals, as in **3a** → **2** and **4a** → **5**. The use of different homoallylic alcohols and aldehydes as building blocks should enable the extension of this methodology to access many different spiroacetal scaffolds. In more general terms, a large variety of different starter units and a wide range of aldehydes may be used in a polymer-supported parallel synthesis fashion to generate large and structurally diverse libraries of polyketide sequences.[9] Current efforts are being directed to extend this methodology to the solid phase synthesis of other, structurally diverse, natural polyketide-like libraries.

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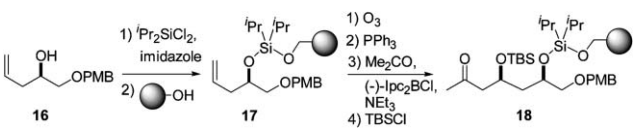

16 The additional methyl group attached to C9 in spongistatin is best introduced at a later stage, see: I. Paterson and R. M. Oballa, *Tetrahedron Lett.*, 1997, **38**, 8241.

17 The initial product mixture contains **5**, its C7-epimer and partially cyclised hemiacetals (ratio ~1:2:2): see ESI†.

18 The lower yield obtained here compared to **5** may be attributable to partial deprotection of the TIPS ether.

