

# 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 antimetabolic agent spongistatin 1 (althohyrtin A).

Spiroacetals are key structural elements in many bioactive polyketide natural products and related analogues.<sup>1–4</sup> As exemplified by the potent anticancer agent spongistatin 1/althohyrtin 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,<sup>5,6</sup> solid phase approaches remain a challenging task, in particular when used within the realm of complex natural product synthesis.<sup>7</sup> 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.

As part of our studies towards the synthesis of polyketide-like analogues,<sup>8,9</sup> 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.<sup>10</sup> This method relies on the preparation of differently substituted linear precursors, such as 3, by performing asymmetric boron-mediated aldol reactions on polymer support,<sup>11</sup> 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

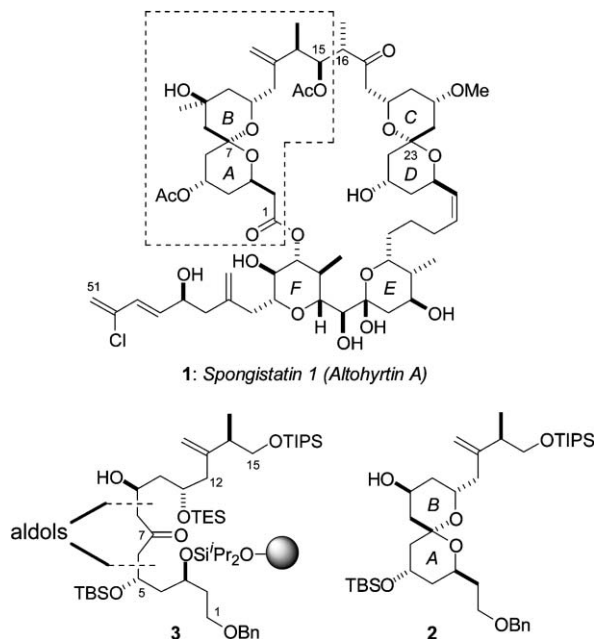
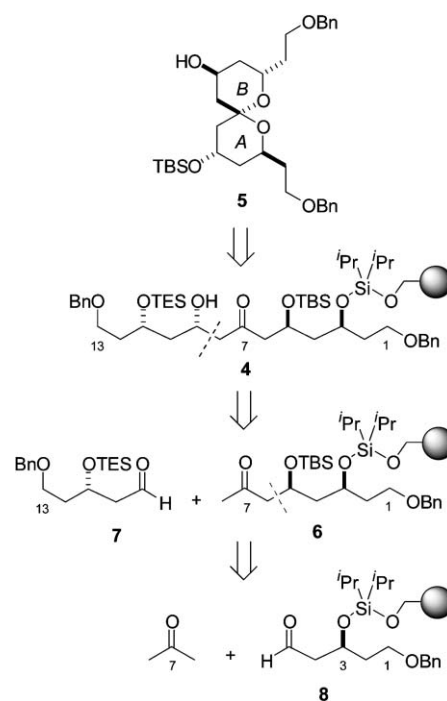


Fig. 1 Spiroacetals: a key structural element of the spongistatins.

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

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  $\beta$ -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  $^{13}\text{C}$ -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,<sup>9a,12</sup> via intermediate **10**, to give **11a** (loading: 0.6 mmol g<sup>-1</sup> 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<sub>4</sub>, Pb(OAc)<sub>4</sub>]. In agreement with our previous studies on similar systems in solution phase,<sup>13</sup> enolisation of acetone with (–)-Ipc<sub>2</sub>BCl/Et<sub>3</sub>N 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<sub>2</sub>BCl (3.0 equiv.) and Et<sub>3</sub>N (3.7 equiv.) in Et<sub>2</sub>O, followed by addition of aldehyde **7** (6 equiv.). Comparison of the  $^{13}\text{C}$ -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.<sup>11,13,14</sup>

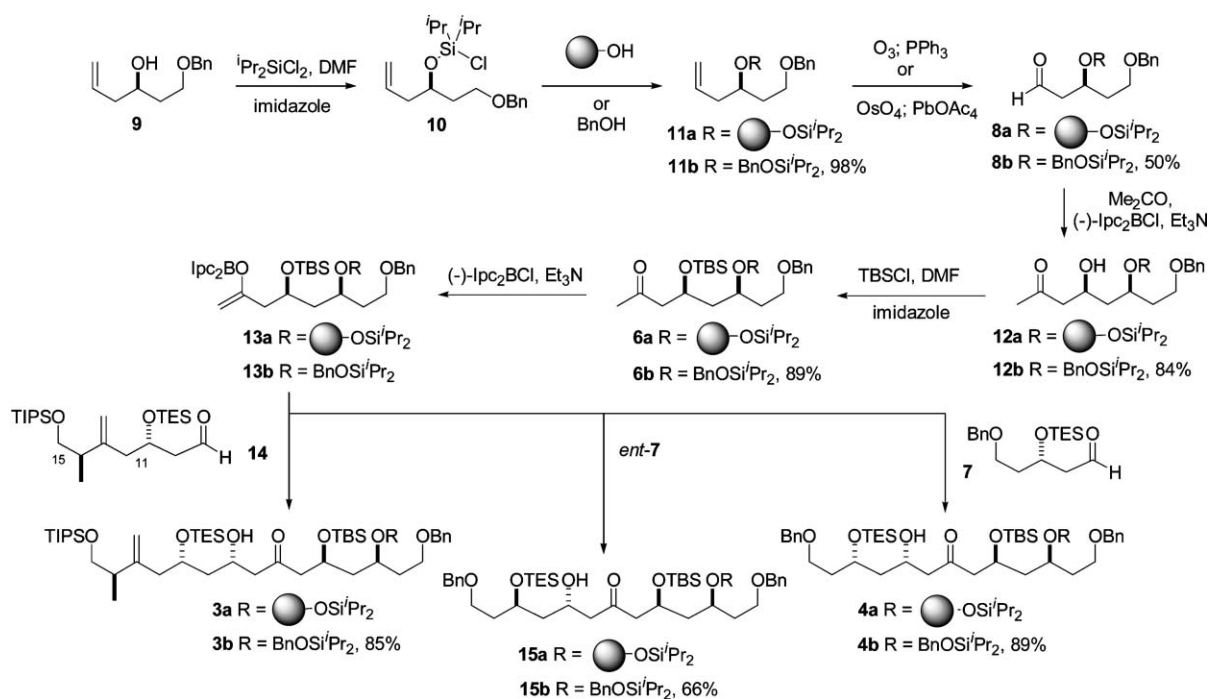
This two-directional aldol approach was then diversified and applied to access other potential linear precursors to spiroacetals on solid support. For example, the enantiomeric aldehyde *ent*-**7** was combined with the resin-bound enolate **13a** to generate the

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.<sup>6a</sup> This reaction proceeded smoothly on solid support and gave hexaketide **3a**<sup>15,16</sup> with high stereoselectivity, again benefiting from triple asymmetric induction.

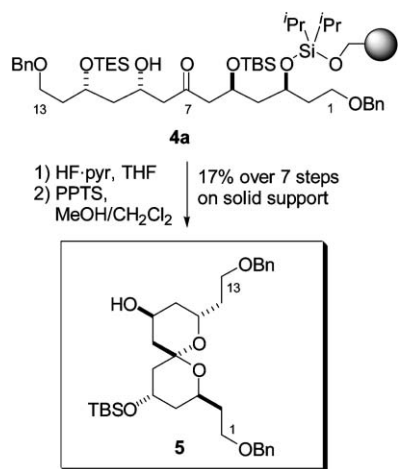
Having assembled the linear polyketide-type intermediates on solid support, it remained to demonstrate that they could indeed deliver the required spiroacetal segments. For realizing both the projected cleavage from the resin and *in situ* cyclisation, HF·pyr was chosen as a suitable reagent as it had previously shown its usefulness in similar transformations, allowing the TBS ether at C5 to be retained.<sup>13</sup> 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,<sup>17</sup> by treatment with PPTS in MeOH–CH<sub>2</sub>Cl<sub>2</sub>, 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.<sup>16,18</sup>

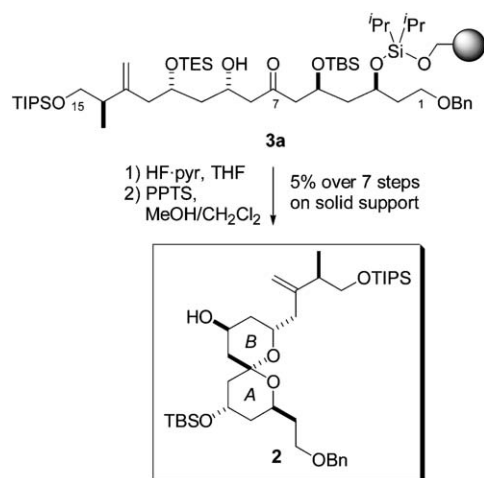
In conclusion, we have completed the stereocontrolled synthesis of some representative open-chain spiroacetal precursors related to spongistatin fragment libraries on solid support. Cleavage from the



**Scheme 2** Synthesis of linear  $\beta$ -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.

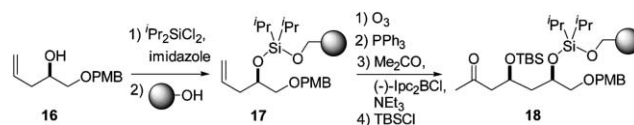
resin and selective removal of protecting groups then led to the isolation of the required spiroacetals, as in **3a** → **2** and **4a** → **5**. The use of different homoallylic alcohols and aldehydes as building blocks should enable the extension of this methodology to access many different spiroacetal 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.<sup>9</sup> 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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- 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.
- The initial product mixture contains **5**, its C7-epimer and partially cyclised hemiacetals (ratio ~1:2:2); see ESI†.
- The lower yield obtained here compared to **5** may be attributable to partial deprotection of the TIPS ether.