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Studies in Marine Macrolide Synthesis: Synthesis of the C_1–C_{15} Subunit of Spongistatin 1 (Altohyrtin A) and 15,16–*Anti* Aldol Coupling Reactions

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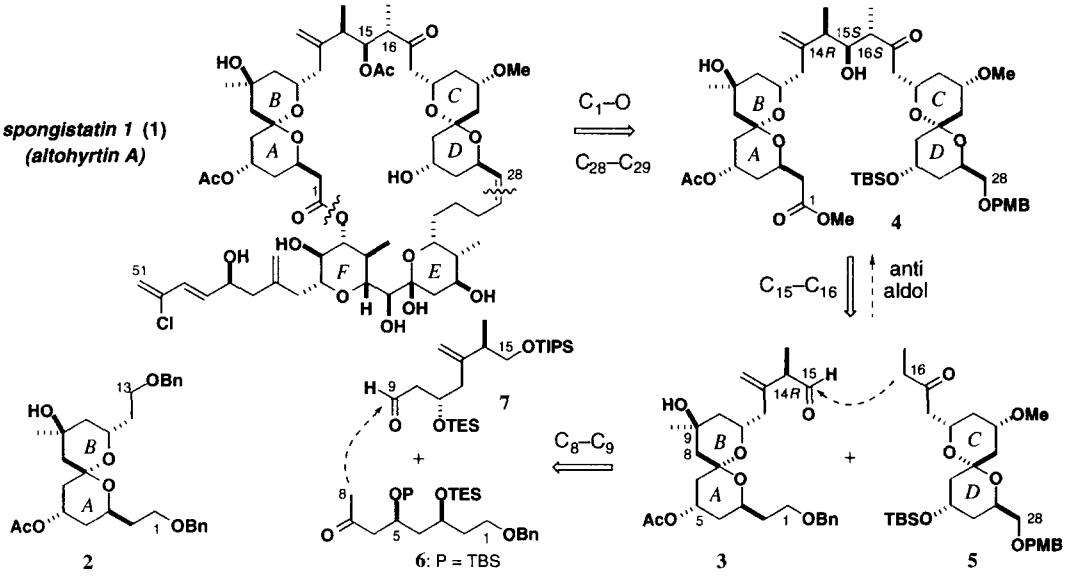
Abstract: The C_1–C_{15} aldehyde **3**, containing the AB-spiroacetal of spongistatin 1 (**1**), was prepared in 17 steps from methyl ketone (*S*)-**8**. The C_{15} and C_{16} stereocentres could be introduced together, relying on Felkin-Anh control, by using a boron-mediated, *anti* aldol coupling reaction, as in **22** → **25** and **26**. © 1997 Elsevier Science Ltd.

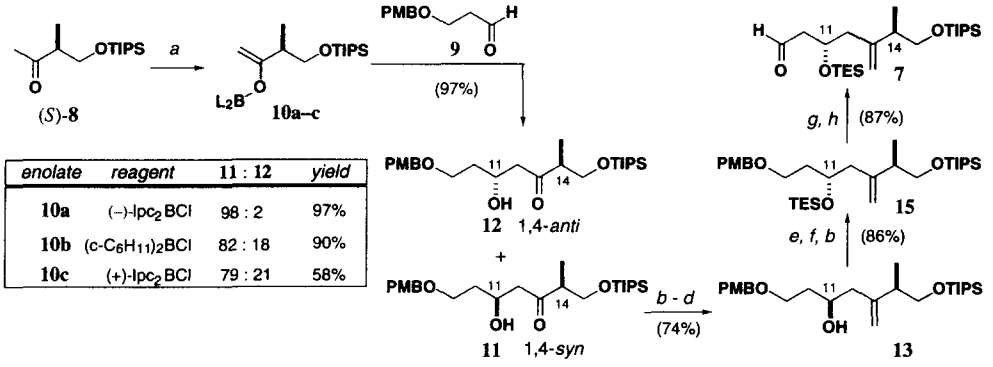
The spongistatins[1,2] and altohyrtins[3] are a group of rare marine macrolides,[4] which display remarkable potency as antimitotic agents. Pettit *et al.* have isolated spongistatins from sponges of the genus *Spongia*[1a,b] and *Spirastrella*,[1c,d] while the altohyrtins have been obtained by the Kobayashi and Kitagawa group from *Hyrtios altum*.[3] These compounds show especially powerful growth inhibitory activity *in vitro* against multi-drug resistant cancer cells and are believed to function by inhibiting tubulin polymerisation.[2] Due to their extremely meagre natural supply, synthetic efforts are required to firmly establish their structures which, at present, are best represented[3a,b] for altohyrtin A (spongistatin 1) by that depicted in **1** (**Scheme 1**).



Scheme 1

As part of studies towards this goal,[5,6] we have previously described[5a] the synthesis of the AB-spiroacetal subunit **2**, as well as that of an F-ring containing subunit.[5b] We now elaborate on our synthetic strategy for **1** and report an efficient synthesis of the more advanced, C_1–C_{15}, aldehyde **3** using boron enolate aldol chemistry.[7] We also describe model studies for the installation of the 14,15-*syn*-15,16-*anti* sequence in ketone **4** by a boron aldol coupling (under Felkin-Anh control), as required for directly bridging the two preformed spiroacetal units present in **3** and **5**.

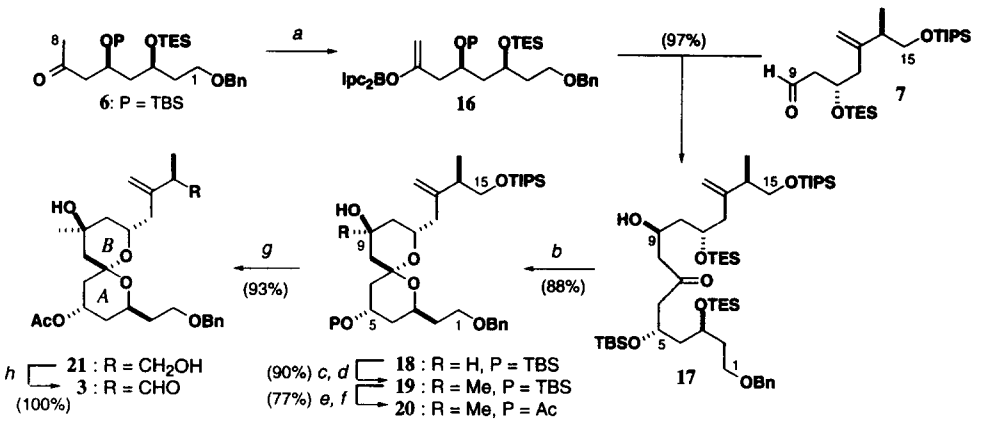
Our retrosynthetic analysis for spongistatin 1, as shown in **Scheme 1**, relies on disconnection of the 42-membered macrolide across the lactone linkage and the C_{28} *cis*-alkene to generate the upper, C_1–C_{28}, segment **4**, together with an appropriate lower segment containing the E and F rings. We were attracted by the possibility of obtaining **4** (and related advanced intermediates) by a stereocontrolled aldol coupling between the ethyl ketone **5** and the aldehyde **3**. If successful, this would ensure a highly convergent synthesis by directly installing the fully functionalised, bridging chain linking the AB and CD spiroacetal units. However, a major concern was the potential ease of enolisation of the sensitive α-methyl-β-methylene aldehyde **3** and whether the precarious (14*R*)-stereocentre could be relied on to induce the required (15*S*,16*S*)-configuration in the aldol bond-forming step. The synthesis of **3** was planned around the boron-mediated, aldol coupling of the previously prepared[5a] methyl ketone **6** and the new aldehyde **7**, exploiting the versatile strategy used in our earlier synthesis of the simpler spiroacetal **2**.



Scheme 2: (*a*) (–)-Ipc_2BCl, or (c-$C_6H_{11})_2BCl$ or (+)-Ipc_2BCl, Et_3N, Et_2O, 0 °C, 30 min; **9**, –78 °C, 5 - 6 h → -20 °C, 16 h; H_2O_2, MeOH/pH 7 buffer; (*b*) TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 2 h; (*c*) Cp_2TiMe_2, PhMe, 110 °C, 1.5 h; (*d*) PPTS, $MeOH/CH_2Cl_2$, 20 °C, 10 min; (*e*) *p*-$NO_2(C_6H_4)CO_2H$, DEAD, PPh_3, PhH, 20 °C, 20 min; (*f*) K_2CO_3, MeOH, 3 h; PPh_3, 20 °C, 3 h; (*g*) DDQ, CH_2Cl_2/pH 7 buffer, 0 °C, 45 min; (*h*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 25 min.

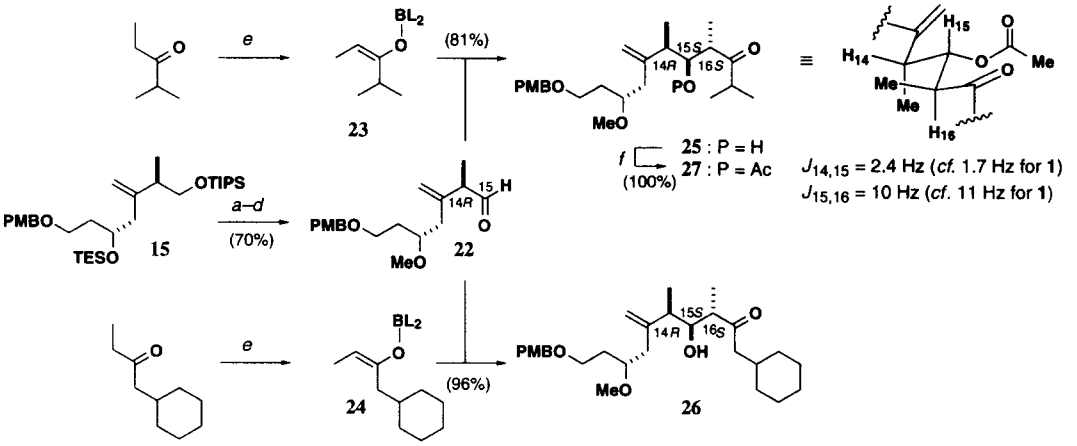
As shown in **Scheme 2**, our synthesis[8] of aldehyde **7** was initiated using an asymmetric boron aldol reaction[7,9] of the methyl ketone (*S*)-**8**[10] with aldehyde **9** to control the remote 1,4-stereorelationship between C_{11} and C_{14}. In previous work using such ketones,[11] we had shown that high levels of diastereoselectivity (≥95% ds) can be obtained for 1,4-*syn* aldol adducts by appropriate choice of Ipc ligand chirality. In this case, the required 1,4-*anti* relationship in **7** was best realised by combining a matched, boron-mediated, aldol addition with a subsequent Mitsunobu inversion at C_{11}. Enolisation of (*S*)-**8** with (–)-Ipc_2BCl and Et_3N in Et_2O gave the enol borinate **10a**, which reacted with aldehyde **9** to provide a 97% yield of the 1,4-*syn* adduct **11**[12] with 98% ds. This was then converted into the homoallylic alcohol **13** by Petasis olefination[13] *via* the corresponding TES ether. Mitsunobu inversion[14] using *p*-$NO_2(C_6H_4)CO_2H$, followed by ester hydrolysis and TES-protection, then gave the required 1,4-*anti* segment **15**. Deprotection of the PMB ether in **15** was performed with DDQ and the resulting alcohol was oxidised to the aldehyde **7** by Dess-Martin periodinane.[15]

A second Ipc boron aldol reaction was now performed (**Scheme 3**), again using (–)-Ipc_2BCl in Et_2O, enabling the efficient coupling of the methyl ketone **6**[5a] with aldehyde **7**. In this fully matched reaction of boron enolate **16**, a single adduct **17** was obtained in 97% yield. In general, we now recommend these improved conditions for Ipc boron aldol reactions[5a,c,9] *using Et_2O as the preferred solvent*. Treatment[5a] of **17** with PPTS in $MeOH/CH_2Cl_2$ led to clean removal of both TES groups and *in situ* acetalisation to produce a single spiroacetal **18** in 88% yield. Dess-Martin oxidation of alcohol **18** and addition of MeMgBr to the resulting ketone then gave the axial alcohol **19** (90%). At this stage, the TBS ether was selectively deprotected with CSA in CH_2Cl_2/MeOH and the resulting secondary alcohol selectively acetylated to give **20**. Next, the TIPS ether was removed by brief treatment with HF/MeCN to give the primary alcohol **21**.



Scheme 3: (*a*) (–)-Ipc$_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 40 min; **7**, –78 °C, 6 h; H_2O_2, MeOH/pH 7 buffer; (*b*) PPTS, MeOH/CH_2Cl_2, 20 °C, 40 min; (*c*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 1.5 h; (*d*) MeMgBr, THF, –78 °C → 20 °C, 3 h; (*e*) CSA, CH_2Cl_2/MeOH, 75 min; (*f*) Ac_2O/CH_2Cl_2 (1:1), DMAP, 20 °C, 2.5 h; (*g*) aq HF, MeCN, THF, 20 °C, 10 min; (*h*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 1.5 h.

The NOESY results for the C_1-C_{15} AB spiroacetal **21** are consistent with those reported for the natural product[3] and those obtained for compound **2**.[5a] At this stage, we screened a variety of oxidising agents and conditions to enable clean conversion into aldehyde **3**. Under carefully controlled conditions, using freshly prepared Dess-Martin reagent and avoiding chromatography, this demanding oxidation gave the sensitive aldehyde **3** in high yield.



Scheme 4: (*a*) PPTS, MeOH/CH_2Cl_2, 10 min; (*b*) MeOTf, di-*tert*-butylpyridine, CH_2Cl_2, 0 °C → 20 °C, 1 h; (*c*) CSA, MeOH/CH_2Cl_2, 20 °C, 63 h; (*d*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 3 h; (*e*) (c-$C_6H_{11})_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 1 h; **22**, –78 °C, 4 h → –20 °C, 16 h; H_2O_2, MeOH/pH 7 buffer; (*f*) Ac_2O/CH_2Cl_2 (1:4), DMAP, 20 °C, 1 h.

We were now ready to explore the selectivity in the crucial C_{15}–C_{16} aldol bond-forming step. Aldehyde **22** was selected as a model for **3** and this was prepared in 4 steps from the common intermediate **15** (**Scheme 4**). Based on the (14*R*,15*S*,16*S*)-configuration assigned to altohyrtin A,[3a,b] we required an *anti* aldol addition to **22** under Felkin-Anh control. The (*E*)-enol borinates **23** and **24** were first obtained by selective enolisation[16] of the corresponding ethyl ketones with (*c*-$C_6H_{11})_2$BCl/Et$_3$N in Et$_2$O. On addition to the freshly prepared aldehyde **22**, these enolates generated the *anti* adducts **25** and **26**, respectively, accompanied by high levels of diastereoselectivity (≥95% ds). In the case of **25**, the required (15*S*)-configuration, resulting from

Felkin-Anh induction, was established from ^{1}H NMR analysis of the diastereomeric pair of Mosher esters.[12] Finally, acetylation of **25** gave the corresponding acetate **27**, which had ^{1}H NMR spectral data[8] in accord with that reported[1a] for the corresponding region of spongistatin 1 (altohyrtin A).

In summary, this synthesis of the C_1–C_{15} spiroacetal subunit **3** of spongistatin 1 (altohyrtin A) proceeds in 17 steps (30% yield) from (*S*)-**8** with 98% overall diastereoselectivity. We have also demonstrated that the bridging chain between the AB and CD spiroacetal ring systems can be introduced by a boron-mediated, *anti* aldol coupling (*cf.* **22** → **25** and **26**). Further studies directed towards the total synthesis of spongistatin 1 (**1**) are currently underway.

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