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Studies in Marine Macrolide Synthesis: Stereocontrolled Synthesis of the AB-Spiroacetal Subunit of Spongistatin 1 (Altohyrtin A).

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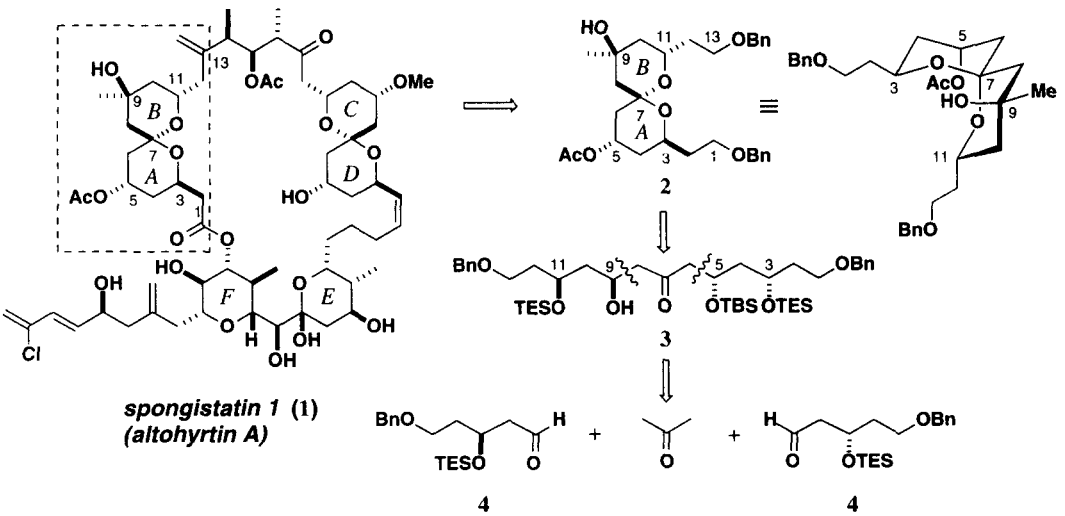
Abstract: The C_1–C_{13} subunit **2**, containing the AB-spiroacetal ring system of spongistatin 1 (**1**), was prepared in 11 steps with 90% ds from 3-benzyloxypropanal. Key steps include (*i*) the aldol reaction between **4** and **11** using (–)-Ipc_2BCl and (*ii*) the spiroacetalisation, **3** → **14**.

The spongistatins are a novel group of cytotoxic macrolides, isolated from marine sponges of the genus *Spongia*,[1] *Spirastrella*,[2] *Hyrtios*[3] and *Cinachyra*,[4] which were first reported in 1993 by Pettit *et al.*[1a] The complete relative and absolute stereochemistry of spongistatin 1 (≡ altohyrtin A), as defined by elaborate NOESY and Mosher ester ^1H NMR experiments, has recently been proposed as that shown in structure **1** by Kitagawa and coworkers.[3a] However, this configurational assignment is partially in conflict with the stereochemistry proposed by the Pettit[2b,5] and Fusetani[4] groups. The spongistatins are reported to be among the most potent compounds tested against a distinctive subset of highly chemoresistant tumour types in the US National Cancer Institute's panel of 60 human cancer cell lines (mean $GI_{50} = 10^{-11}$ *M*)[5] and are believed to function by inhibiting tubulin polymerisation.[6]

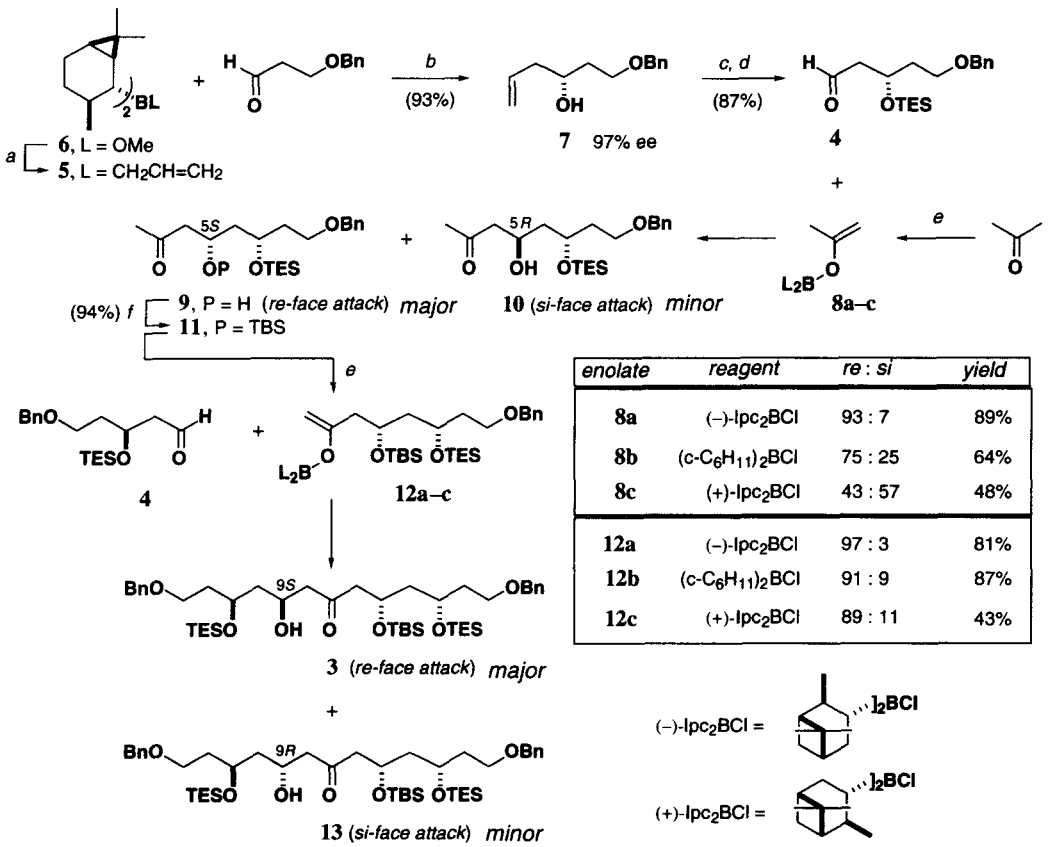


Scheme 1

Due to their extremely meagre natural supply (10^{-6} – 10^{-7}% isolated yield from the whole sponge) and the painstaking isolation procedure, synthetic efforts towards the spongistatins are required to firmly establish the structures and provide further material for biological testing. As part of our studies in marine macrolide synthesis,[7] we now report a stereocontrolled synthesis of the C_1–C_{13} spiroacetal segment **2** of spongistatin 1 (**1**) by using the asymmetric boron aldol reactions[8,9] of methyl ketones.

Central to our synthetic strategy for **2** is the thermodynamically-controlled spiroacetalisation of the open-chain precursor **3** in **Scheme 1**, followed by manipulation of the C_5 and C_9 hydroxyl groups. Note that the AB-spiroacetal subunit of the spongistatins possesses an energetically favourable, double anomeric effect and has the C_3 and C_{11} sidechains arranged equatorially on each tetrahydropyran ring. The stereocontrolled construction of the pseudo-C_2-symmetric chain in **3** was planned around the sequential, two-directional, aldol coupling of acetone with the chiral aldehyde **4**. Previously, we have reported the use of (+)- and (–)-diisopinocampheylboron chlorides (Ipc_2BCl) for asymmetric aldol reactions of methyl ketones with various aldehydes.[9] As part of a novel approach to 1,3-polyol synthesis,[10] we now extend this chemistry to double[9a] and triple[11] stereodifferentiating aldol reactions with β-oxygenated aldehydes such as **4** (**Scheme 2**).

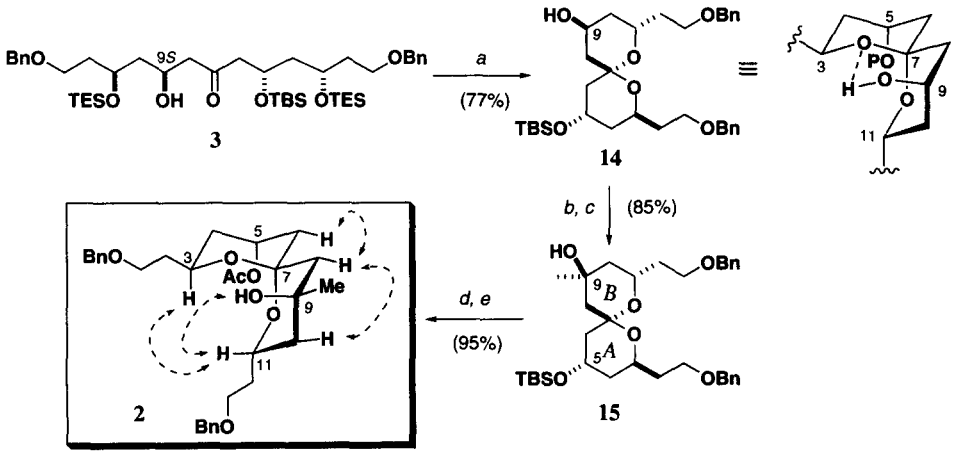
First, we required a practical asymmetric synthesis of (*S*)-**4** in high enantiomeric purity.[12] Following the Brown protocol,[13] addition (Et_2O, –78 °C) of the allylborane **5** (obtained from (+)-2-carene *via* **6**) to 3-benzyloxypropanal gave, after oxidative workup, a 93% yield of **7**. The homoallylic alcohol **7** was produced with 97% ee (MTPA ester) on a 4 g scale, which proved to be superior to all other enantioselective allylation methods we examined. Silyl protection as the TES ether, followed by ozonolysis, then gave the required (*S*)-aldehyde **4** in 87% yield.



enolate	reagent	re : si	yield
8a	(–)-Ipc_2BCl	93 : 7	89%
8b	$(c\text{-}C_6H_{11})_2BCl$	75 : 25	64%
8c	(+)-Ipc_2BCl	43 : 57	48%
12a	(–)-Ipc_2BCl	97 : 3	81%
12b	$(c\text{-}C_6H_{11})_2BCl$	91 : 9	87%
12c	(+)-Ipc_2BCl	89 : 11	43%

Scheme 2: (*a*) Allylmagnesium bromide, Et_2O, –78 °C, 15 min; 20 °C, 1 h; (*b*) **5** , –78 °C, 4 h; H_2O_2, NaOH, Δ, 19 h; (*c*) TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 2 h; (*d*) O_3, CH_2Cl_2, $NaHCO_3$, –78 °C; PPh_3, 20 °C, 3 h; (*e*) (–)-Ipc_2BCl, or $(c\text{-}C_6H_{11})_2BCl$ or (+)-Ipc_2BCl, Et_3N, Et_2O, 0 °C, 30 min; **4**, –78 °C, 5 h; H_2O_2, MeOH-pH 7 buffer; (*f*) TBSOTf, 2,6-lutidine, THF, –78 °C, 2 h.

We next explored the use of reagent control in the boron-mediated aldol reaction of acetone to aldehyde **4**. Using our standard conditions,[9a,b] the boron enolate **8a** was prepared by enolisation of acetone with (–)-Ipc_2BCl (Et_3N, Et_2O, 0 °C), followed by addition to **4** at –78 °C. This matched reaction proceeded in 89% yield to give predominantly the 1,3-*syn* isomer **9** with 93% ds by *re*-face attack. In comparison, the dicyclohexylboron[14] enolate **8b** produced **9** with 75% ds, indicating a moderate level of 1,3-*syn* induction from the aldehyde.[9a,15] The enolate **8c** prepared from (+)-Ipc_2BCl overturned this result, giving a small preference for formation of the corresponding 1,3-*anti* isomer **10**. After silyl protection of **9** as the TBS ether, methyl ketone **11** was obtained in 78% yield from **4**. The synthesis of the open-chain spiroacetal precursor **3** from **4** and **11** exploited *triple asymmetric induction*,[11] where the influence of all three chiral components (aldehyde, ketone and boron reagent) were matched. Using the boron enolate **12a** prepared from **11** with (–)-Ipc_2BCl, the aldol coupling with **4** proceeded in 81% yield to provide a 97 : 3 mixture of adducts, in favour of the 1,3-*syn* isomer **3**.[16] Here, the 1,3-syn preference of aldehyde **4** (*i.e. re*-face attack) and the remote 1,5-*anti* preference[17] of methyl ketone **11** act in a synergistic fashion, thereby providing excellent levels of stereocontrol. When using the dicyclohexylboron enolate **12b** alone, the selectivity of this aldol reaction was reduced to 91% ds, while the enolate **12c** formed from (+)-Ipc_2BCl gave 89% ds. In contrast to these boron aldol results, the corresponding lithium enolate (LDA, THF, –78 °C) led to a reversal in selectivity to give **13** with 66% ds (83% yield).



Scheme 3: (*a*) PPTS, CH_2Cl_2/MeOH (1:1), 20 °C, 3 h; (*b*) TPAP, NMO, MeCN, 4Å powdered mol. sieves, 20 °C, 1 h; (*c*) MeMgBr, THF, –78 °C → –20 °C, 2 h; (*d*) CSA, MeOH, 20 °C, 2 h; (*e*) Ac_2O/CH_2Cl_2 (4:1), DMAP, 20 °C, 90 min.

As shown in **Scheme 3**, treatment of **3** with PPTS in $MeOH/CH_2Cl_2$ led to clean removal of both TES protecting groups and *in situ* acetalisation to produce a single spiroacetal **14** in 77% yield. Note that although the C_9 stereocentre is later destroyed by oxidation, efficient thermodynamic spiroacetalisation only proceeds with the (9*S*)-configuration.[18] A possible rationale for this observation is the extra stabilisation obtained by the intramolecular hydrogen bond which develops in **14** between the C_9 *axial* hydroxyl and the spiroacetal oxygen. TPAP oxidation[19] of the alcohol **14** and equatorial addition of MeMgBr to the resultant ketone then gave the tertiary alcohol **15** in 85% yield. Finally, conversion of the TBS-protected alcohol at C_5 to the corresponding acetate was accomplished in 2 steps (95%) to provide the desired spiroacetal **2**, $[\alpha]_D^{20} = -67.2°$ (*c* 1.17, $CHCl_3$). The ^1H and ^{13}C NMR spectral data obtained[12] for **2** closely resembles that reported for the corresponding segment of the spongistatins. In particular, the NOESY results and coupling constants for **2** are in full accord with that described for spongistatin 1 (altohyrtin A), which supports the structure proposed for the C_1–C_{13} region containing the AB-spiroacetal ring system (*cf.* boxed region of **1**).

In summary, this synthesis of the C_1–C_{13} spiroacetal subunit **2** of spongistatin 1 (altohyrtin A) proceeds in 11 steps (32% yield) with 90% overall diastereoselectivity. This work, together with that reported in the accompanying paper,[17] demonstrates that high diastereoselectivity can be obtained for methyl ketone aldol reactions using chiral boron enolates, providing a practical entry into the synthesis of 1,3-polyols. Studies directed towards the total synthesis of spongistatin 1 (**1**) are currently underway.

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12. All new compounds gave spectroscopic data in agreement with the assigned structures. NMR data for spiroacetal **2**: ^{1}H NMR δ (500 MHz, DMSO-d_6) 1.03 (3H, s, C_9-Me), 1.21 (1H, t, J = 12.3 Hz, H_{10A}), 1.38 (1H, d, J = 13.9 Hz, H_{8A}), 1.51-1.46 (2H, m, H_{4A} and H_{10B}), 1.71-1.55 (7H, m, H_{2A}, H_{2B}, H_{4B}, H_{6A}, H_{8B}, H_{12A} and H_{12B}), 1.77 (1H, d, J = 15 Hz, H_{6B}), 1.89 (3H, s, -OC(O)C$\underline{H}_3$), 3.44-3.35 (2H, m, -C$\underline{H}_2$OBn), 3.56 (2H, dt, J = 5.7, 1.8 Hz, -C$\underline{H}_2$OBn), 3.89 (1H, br t, J = 12.3 Hz, H_{11}), 3.99-3.95 (1H, m, H_3), 4.21 (1H, s, 9-O$\underline{H}$), 4.36-4.27 (4H, m, 2 x -OC$\underline{H}_2$Ph), 4.89 (1H, br s, H_5), 7.32-7.22 (10H, m, aromatic); ^{13}C NMR δ (100 MHz, DMSO-d_6) 21.2, 30.4, 34.2, 35.0, 35.4, 36.7, 43.6, 45.4, 62.2, 62.6, 66.5, 66.7, 67.0, 67.4, 72.1, 72.2, 97.3, 127.4, 127.5, 127.7, 128.3, 138.3, 138.6, 169.9.
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