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Studies in Marine Macrolide Synthesis: Synthesis of a Fully Functionalised C_1–C_{28} Subunit of Spongistatin 1 (Altohyrtin A)

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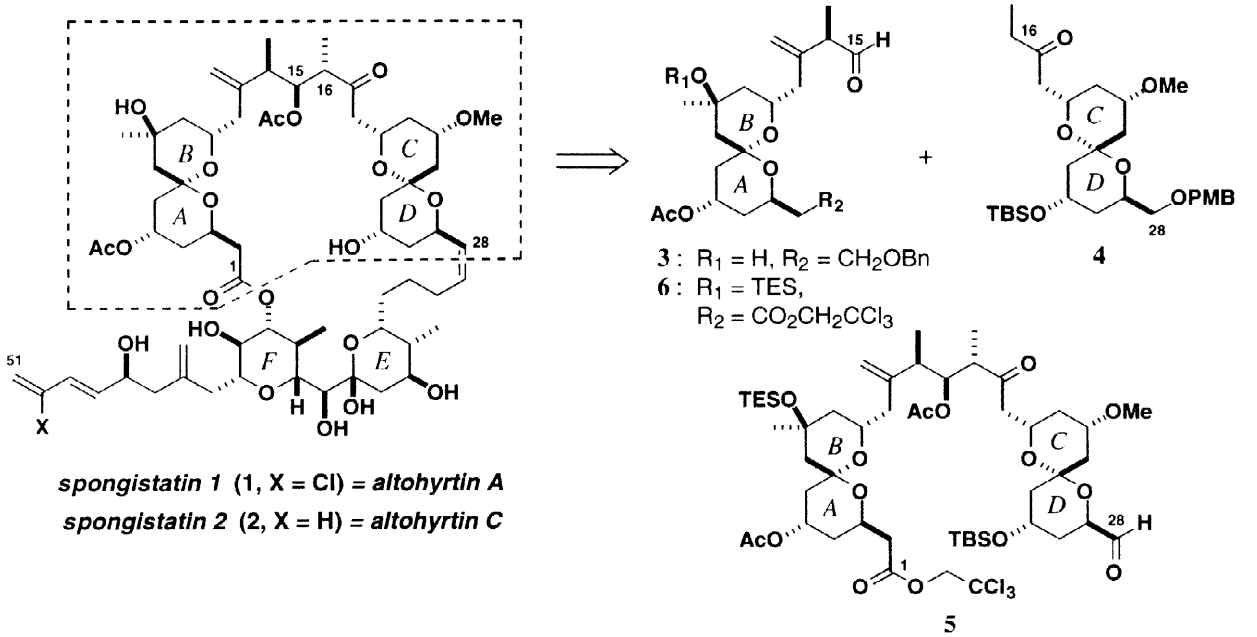
Abstract: The C_1–C_{28} aldehyde **5**, containing the AB- and CD-spiroacetal portions together with the bridging chain of spongistatin 1 (**1**), was prepared. The key step was a lithium-mediated, *anti*-aldol coupling between ethyl ketone **4** and aldehyde **6** under Felkin-Anh control.

The spongistatins[1,2] and altohyrtins[3] are a novel group of cytotoxic macrolides, which have been isolated in trace quantities from several different marine sponges. As antimitotic agents, these compounds show especially powerful growth inhibitory activity against multi-drug resistant cancer cells. They may function by inhibiting microtubule assembly by binding to the vinca alkaloid domain of tubulin.[2] Their complex, polyketide structures, *e.g.* **1** for spongistatin 1 (altohyrtin A) in **Scheme 1**, and potent cytotoxicity have provided the impetus for a growing number of synthetic efforts.[4-7] Notably, the first total syntheses of spongistatins 1 (**1**) and 2 (**2**) (identical to altohyrtins A and C, respectively) have recently been achieved independently by Kishi[5] and Evans,[6] which served to confirm the stereochemical assignment made earlier by the Kobayashi/Kitagawa group.[3]



spongistatin 1 **(1, X = Cl) = *altohyrtin A***

spongistatin 2 **(2, X = H) = *altohyrtin C***

Scheme 1

In our approach[4] to spongistatin 1 (**1**), we planned to introduce the bridging chain between the AB- and CD-spiroacetal ring systems by a suitable (C_{15}–C_{16}) *anti*-aldol coupling.[8] Towards this end, we have previously described an efficient synthesis of aldehyde **3**[4a] and the corresponding ethyl ketone **4**,[4b] as well as supportive model studies for their coupling using boron enolate chemistry.[4a] We now report the synthesis of aldehyde **5**, corresponding to a fully functionalised C_1–C_{28} subunit for spongistatin 1 (*cf.* boxed region in **1**), *via* a lithium-mediated aldol coupling between ethyl ketone **4** and the (C_1-oxidised) aldehyde **6**.

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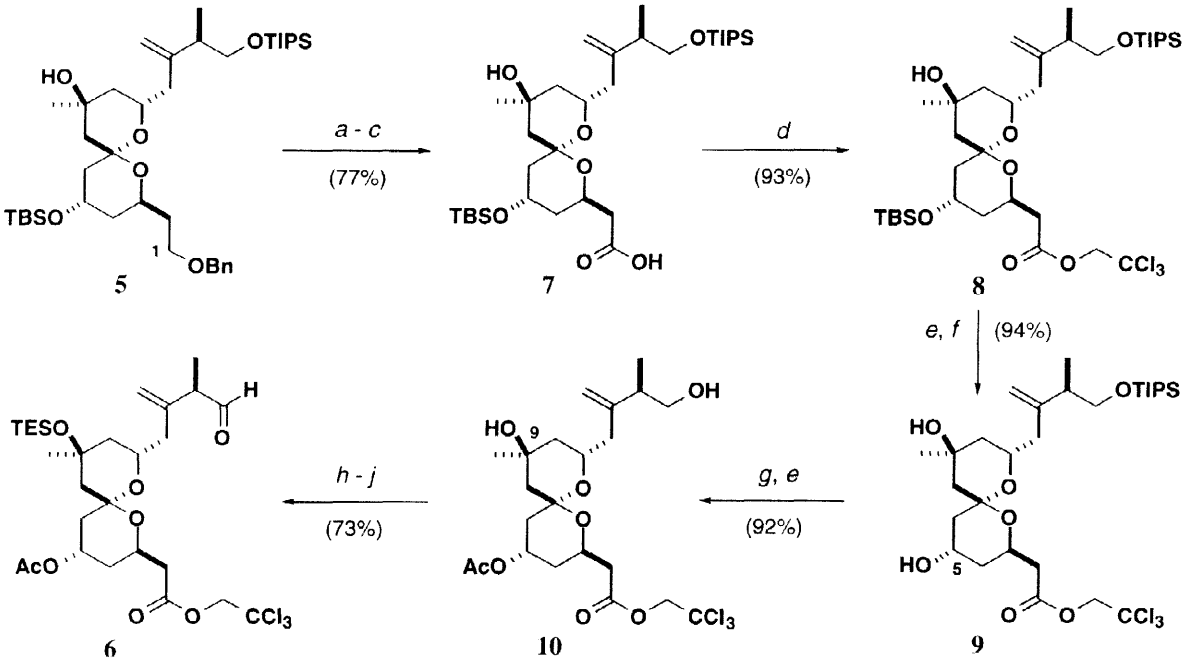
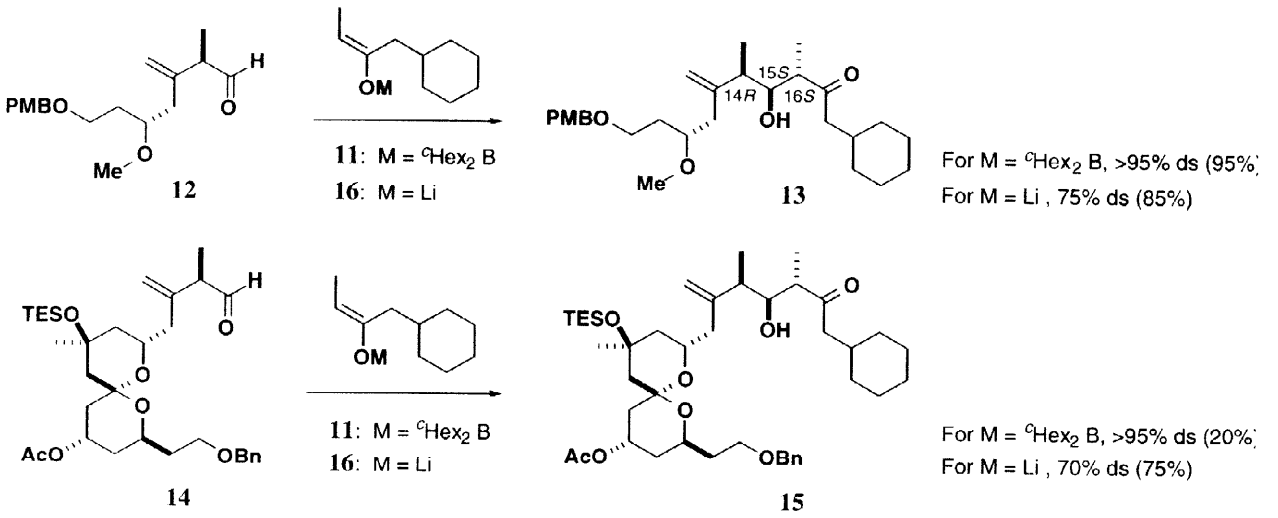
As outlined in **Scheme 1**, our retrosynthetic analysis[4a] for spongistatin 1 (**1**) is based on a 3-fold disconnection of the 42-membered macrolide ring, *i.e.* across the lactone (C_1–O), the C_{28} *cis*-alkene and the C_{15}–C_{16} bond in the bridging chain between the two spiroacetal ring systems. In order to minimise the number of steps required after fragment assembly, the introduction of the acid oxidation state at C_1 prior to the pivotal aldol coupling step was preferred. The synthesis of the required aldehyde **6** from intermediate **5**[4a] is shown in **Scheme 2**.[9] First, the benzyl ether in **5** was removed cleanly by reaction with LiDBB,[10] followed by a 2-step oxidation to give the acid **7** (77%). Esterification of **7** with 1,1,1-trichloroethanol under Steglich conditions then gave the corresponding ester **8**, which was transformed into the C_5 alcohol **9** in 87% overall yield.[11] Next, acetylation of the C_5-OH was performed, prior to TIPS removal (HF, MeCN), to give the primary alcohol **10** (92%). Finally, the C_9 tertiary hydroxyl in **10** was protected as its TES ether and the aldehyde **6** was obtained *via* oxidation of the C_{15} alcohol with Dess-Martin periodinane.



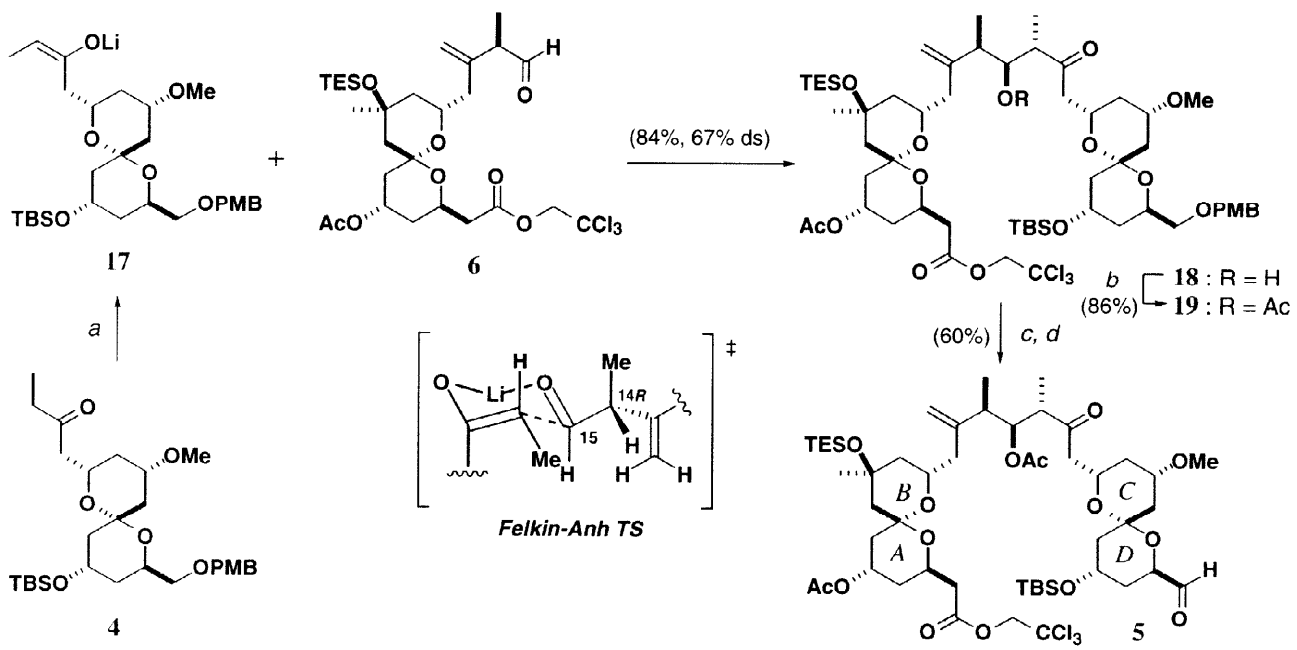
Scheme 2: (*a*) LiDBB, THF, –78 °C, 1 h; (*b*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 2 h; (*c*) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, THF, *t*-BuOH, H_2O, 20 °C, 3 h; (*d*) CCl_3CH_2OH, DCC, DMAP, CH_2Cl_2, 20 °C, 16 h; (*e*) aq HF, MeCN, 20 °C, 1 h; (*f*) TIPSCl, Imid, CH_2Cl_2, 20 °C, 16 h; (*g*) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 6 d; (*h*) TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 2 h; (*i*) PPTS, CH_2Cl_2, MeOH, 0 °C, 2 h; (*j*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 1 h.

With both the required α-chiral aldehyde **6** and ketone **4** now in hand, attention was focused on realising the key fragment coupling reaction. To install the correct stereochemistry at C_{15} and C_{16}, an *anti*-aldol operating with Felkin-Anh control was required. Previous studies had shown that simple (*E*)-enol borinates, *e.g.* **11** in **Scheme 3**, reacted with the model aldehyde **12** to afford high levels of diastereoselectivity (>95% ds) for the adduct **13** having the desired (14*R*,15*S*,16*S*)-configuration.[4a] Although this selectivity was reproduced with the spiroacetal-containing aldehyde **14**, in our hands,[8] the conversion to **15** achieved (*ca.* 20% on a 0.1 mmol scale) was unacceptably low and so attention was turned to the more reactive lithium enolates. Silylation experiments showed that the (*E*)-enolate **16** could be obtained in >85% isomeric purity using lithium 2,2,6,6-tetramethylpiperidide (LiTMP), in the presence of LiBr, for ketone enolisation.[12] Furthermore, the lithium enolate **16** reacted rapidly with aldehydes **12** and **14** (THF, –78 °C, 2 min) with 70–75% diastereoselectivity in favour of the desired *anti*-aldol products **13** and **15**, respectively.[13] Notably, good yields were obtained even on small scale runs.



Scheme 3

Based on these encouraging results, a lithium-mediated aldol coupling between the fragments **4** and **6** was undertaken under conditions of kinetic control (**Scheme 4**). When an excess of the lithium enolate **17** (2 equiv) was employed with aldehyde **6** (THF, –78 °C, 2 min; AcOH), both good conversion (84% yield) and stereocontrol were achieved. In this way, the desired aldol adduct **18** was isolated as the major isomer[14] in 55% yield, where (as with the boron reaction) the Felkin-Anh TS is presumably favoured. The unreacted ketone **4** was recovered in quantitative yield.



Scheme 4: (*a*) LiTMP, LiBr, THF, –78 °C, 30 min; **6**, 2 min, AcOH; (*b*) Ac_2O, pyridine, DMAP, 20 °C, 16 h; (*c*) DDQ, CH_2Cl_2, pH 7 buffer, 20 °C, 30 min; (*d*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 2 h.

With a workable method for generating the desired *anti*-aldol adduct **18**, its conversion into the C_{28} aldehyde **5** was completed in three further steps. First, acetylation of the C_{15} hydroxyl proceeded cleanly under standard conditions to afford **19**.[9] Finally, oxidative removal of the PMB group was achieved using DDQ and Dess-Martin oxidation of the resulting alcohol gave the aldehyde **5**, corresponding to a fully functionalised C_1–C_{28} subunit for spongistatin 1 (*cf.* boxed region in **1**).

Completion of the synthesis of spongistatin 1 (**1**) requires the Wittig coupling of the fully functionalised aldehyde **5** with a suitable EF fragment, followed by macrolactonisation (and deprotection, as necessary). Studies towards this end are currently underway.

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References and Notes

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8. Note that a boron-mediated aldol coupling was employed successfully in the Evans total synthesis of altohyrtin C (*cf.* ref 6c).
9. All new compounds gave spectroscopic data in agreement with the assigned structures. **19** had: $[\alpha]_D^{20}$ -15.0° (*c* 1.6, $CHCl_3$); ^1H NMR (400 MHz, CD_3CN) δ 7.26 (2H, d, *J* = 8.4 Hz, ArH), 6.86 (2H, d, *J* = 8.4 Hz, ArH), 5.15 (1H, dd, *J* = 10.0, 2.5 Hz, H_{15}), 4.95 (1H, s, $=CH_AH_B$), 4.93 (1H, m, H_5), 4.86 (1H, s, $=CH_AH_B$), 4.84 (1H, d, *J* = 12.2 Hz, $CH_AH_BCCl_3$), 4.74 (1H, d, *J* = 12.2 Hz, $CH_AH_BCCl_3$), 4.48-4.38 (3H, m, H_{27}, CH_2Ar), 4.31 (1H, m, H_3), 4.23 (1H, m, H_{11}), 4.14 (1H, m, H_{25})), 3.88 (1H, m H_{19}), 3.78 (3H, s, $ArOCH_3$), 3.46 (1H, br, tt, *J* ≈ 11.3, 4.4 Hz, H_{21}), 3.38 (2H, m, H_{28A}), 3.24 (3H, s, $C_{21}OCH_3$), 3.00 (1H, dq, *J* = 10.0, 7.1 Hz, H_{16}), 2.80 (1H, dd, *J* = 17.5, 3.8 Hz, H_{18A}), 2.72 (1H, dd, *J* = 16.6, 5.5 Hz, H_{2A}), 2.71 (1H, dd, *J* = 17.5, 8.8 Hz, H_{18B}), 2.54 (1H, dd, *J* = 16.6, 7.9 Hz, H_{2B}), 2.57 (1H, m, H_{14}), 2.28 (1H, dd, *J* = 14.4, 3.7 Hz, H_{12A}), 2.18-2.10 (3H, m H_{20A}, H_{24A}, H_{12B}), 2.00 (1H, m, H_{22A}), 1.96 (3H, s, $COCH_3$), 1.86 (3H, s, $COCH_3$), 1.85 (1H, m, H_{6A}), 1.76-1.71 (2H, m H_{4A}, H_{6B}), 1.63-1.44 (6H, m, H_{26AB}, H_{10A}, H_{8A}, H_{4B}, H_{24B}), 1.34 (1H, d, *J* = 14.2 Hz, H_{8B}), 1.24-1.20 (4H, m, C_9CH_3 H_{10B}), 1.12 (1H, br, t *J* ≈11.8 Hz, H_{22B}), 1.06 (3H, d, *J* = 7.0 Hz, $C_{16}CH_3$), 1.03 (3H, d, *J* = 7.1 Hz, $C_{14}CH_3$), 0.93 (9H, m, $Si(CH_2CH_3)_3$), 0.88 (1H, m, H_{20B}), 0.86 (9H, s, $SiC(CH_3)_3$), 0.58 (6H, m, $Si(CH_2CH_3)_3$), 0.03 (3H, s, $SiCH_3$), 0.02 (3H, s $SiCH_3$); ^{13}C NMR (100.6 MHz, CD_3CN) δ 210.1, 170.5, 169.1, 169.0, 147.3, 130.7, 129.4, 113.6, 113.3, 98.2, 97.0, 95.1, 74.0 73.5, 73.1, 72.4, 70.5, 66.8, 66.3, 64.8, 64.4, 63.9, 60.6, 54.9, 54.6, 49.2, 47.6, 47.4, 45.0, 43.3, 42.4, 39.7, 38.1, 37.4, 36.9, 34.9, 34.8, 33.5, 31.3, 25.4, 20.8, 20.1, 18.7, 17.8, 13.0, 11.2, 10.7, 6.8, 6.5, –5.6, –5.7.
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11. Although selective removal of the secondary TBS ether in **8** could be achieved in moderate yield, in practice, it proved more efficient to remove both silicon protecting groups with aqueous HF and reintroduce the TIPS ether to give **9**.
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13. Both the boron and lithium (*E*)-enolates of the spiroacetal-containing ketone **4** reacted with an achiral aldehyde (^{i}PrCHO) with negligible π-facial selectivity to give a mixture of predominantly two *anti* aldol products, indicating that a low level of substrate-based induction was attributable to the enolate component.
14. While it has not proved possible to form MTPA esters of compound **18**, NMR coupling constants, extensive model studies (*cf.* **Scheme 3** and ref 4a) and the excellent NMR spectroscopic agreement of the derived acetate **19** (ref 9) with spongistatin 1 (**1**) allows for the confident assignment of the major isomer as the desired.