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# Studies in Marine Macrolide Synthesis: Synthesis of a $C_{16}$–$C_{28}$ Subunit of Spongistatin 1 (Altohyrtin A) Incorporating the CD-Spiroacetal Moiety.

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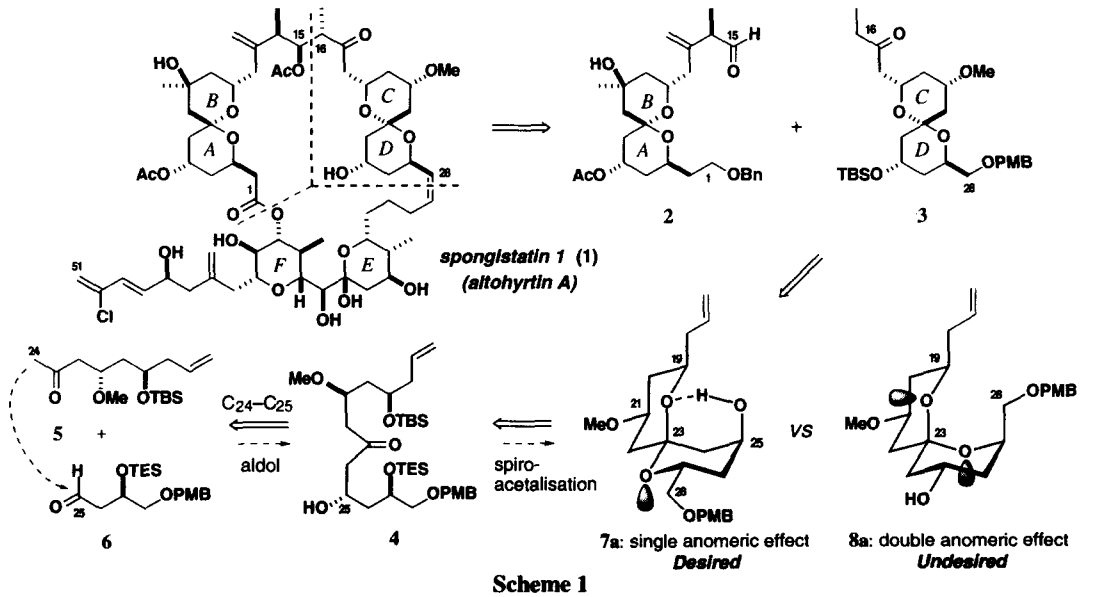
***Abstract***: The $C_{16}$–$C_{28}$ ketone **3**, containing the CD-spiroacetal of spongistatin 1 (**1**), was prepared in 17 steps from aldehyde **9**. Both thermodynamic and kinetic conditions were explored for controlling the CD-acetal configuration. © 1997 Elsevier Science Ltd.

The spongistatins[1,2] and altohyrtins[3] are a group of cytotoxic macrolides, which have been isolated in microscopic quantities from several different marine sponges. They display especially powerful growth inhibitory activity *in vitro* against multi-drug resistant cancer cells, apparently resulting from inhibition of tubulin polymerisation.[2] Their complex structures, *e.g.* **1** for spongistatin 1 (altohyrtin A) in **Scheme 1**, and potent antimitotic action, combined with an extremely meagre natural supply, has provided the impetus for a number of synthetic efforts.[4,5] We have recently reported[4a] an efficient synthesis of the AB-spiroacetal subunit **2**, a pivotal $C_1$–$C_{15}$ intermediate for the aldol-based assembly of the upper portion of spongistatin 1, as well as that of an F-ring containing subunit.[4b] We now describe two strategies for generating the corresponding CD-spiroacetal ring system, leading to a synthesis of the $C_{16}$–$C_{28}$ subunit **3**.

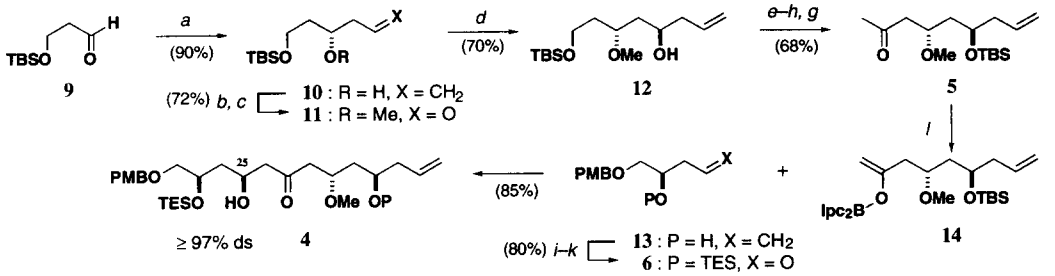



**Scheme 1**

Two complementary routes to the CD-spiroacetal subunit of the spongistatins (altohyrtins) were explored, using thermodynamic or, as described later, kinetic control in the acetal-forming step. Initially, the ketone **4** was selected as a potential open-chain precursor to the required spiroacetal **3** in **Scheme 1**. This should, in turn, be available from a stereocontrolled aldol reaction between the methyl ketone **5** and the aldehyde **6**. An important consideration for spiroacetalisation here is that, unlike the spongistatin AB-ring

system, the CD-acetal configuration does not benefit from a double anomeric stabilisation. The CD spiroacetal, as shown for **7a**, has only a single anomeric effect, however, the axial $C_{25}$ hydroxyl may hydrogen bond to an acetal oxygen. Hence, it is uncertain whether internal acetalisation of ketone **4** will lead to the desired spiroacetal **7a** rather than the potentially, more stable **8a**. Indeed, this point has recently been noted by Hayes and Heathcock[5a] in a model study for the CD spiroacetal (with methyl substituents at $C_{19}$ and $C_{27}$), where cyclisation of a β-diketone was employed instead.

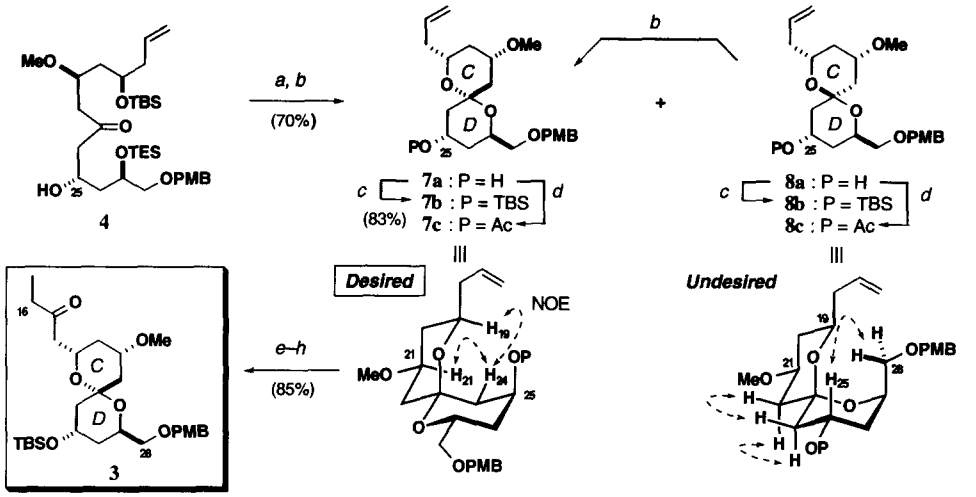
As shown in **Scheme 2**,[6] the two segments **5** and **6** required for the $C_{24}$–$C_{25}$ aldol coupling to give the spiroacetalisation substrate **4** were obtained using Brown allylboration chemistry.[7] First, an (–)-$Ipc_2$BOMe-promoted,[7a] asymmetric allylation of aldehyde **9** gave the alcohol (*S*)-**10** in 90% yield with 85% ee (MTPA ester analysis). Methyl ether formation and ozonolysis then gave the corresponding aldehyde **11**, which was subjected to allylation by the enantiomeric allylborane prepared from (+)-$Ipc_2$BOMe. This second, reagent-controlled, addition allowed enhancement of the enantiomeric purity. In this way, the 1,3-*anti* isomer **12** was isolated in 70% yield with ≥99% ee, which was then converted into **5** using standard procedures. Following the Brown protocol using (+)-2-carene,[7b] asymmetric allylboration of 2-(*para*-methoxybenzyloxy)ethanal gave the alcohol (*R*)-**13** in 90% yield with 94% ee.[8] After silyl protection of **13** as its TES ether, the aldehyde **6** was obtained by periodate cleavage of the derived glycol (80% over 3 steps).




**Scheme 2**: (*a*) (–)-$Ipc_2$BOMe, $H_2C{=}CHCH_2MgBr$, $Et_2O$, –78 → 20 °C, 2 h; **9**, –78 °C, 4 h; $H_2O_2$, NaOH, MeOH, 20 °C, 3 d; (*b*) NaH, MeI, THF, 20 °C, 16 h; (*c*) $O_3$, $CH_2Cl_2$, $NaHCO_3$, –78 °C, 10 min; $PPh_3$, 0 °C, 3 h; (*d*) as in (*a*) using (+)-$Ipc_2$BOMe and **11**; (*e*) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, –78 °C, 2 h; (*f*) PPTS, MeOH, 20 °C, 8 h; (*g*) Dess-Martin periodinane, $CH_2Cl_2$, 20 °C, 2 h; (*h*) MeMgBr, $Et_2O$, 0°C, 2 h; (*i*) TESOTf, 2,6-lutidine, $CH_2Cl_2$, –78 °C, 2 h; (*j*) $OsO_4$, NMO, $Me_2CO$, $H_2O$, *t*-BuOH, 20 °C, 2 d; (*k*) $NaIO_4$, MeOH, $H_2O$, 20 °C, 3 h; (*l*) (–)-$Ipc_2$BCl, $Et_3N$, $Et_2O$, 0 °C, 1 h; **6**, –78 °C, 3 h; $H_2O_2$, MeOH/pH 7 buffer.

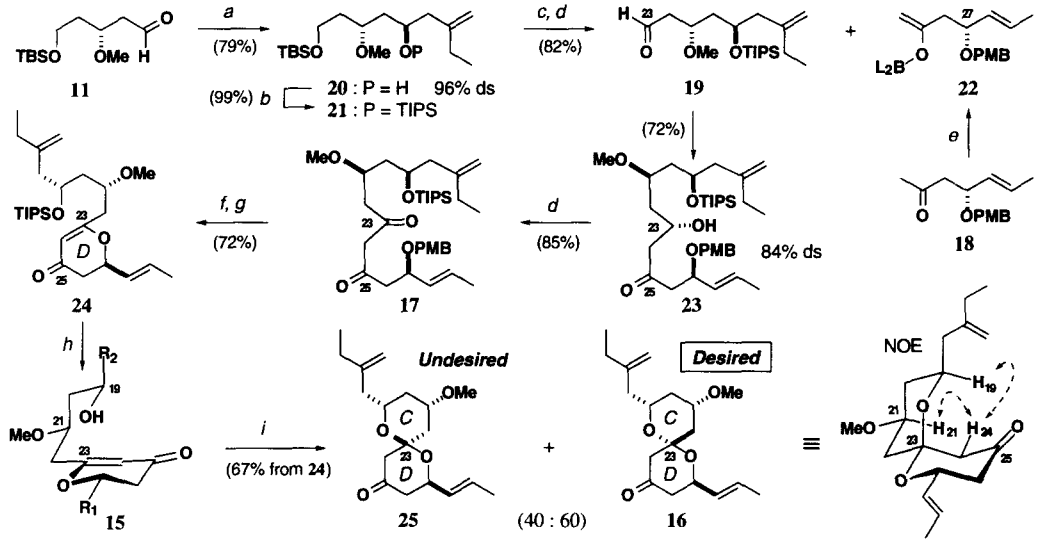
Using the conditions developed from our earlier work on the spongistatin AB-spiroacetal system,[4a,c] the key aldol coupling step between **5** and **6** proceeded smoothly to introduce the required $C_{25}$ stereocentre. Treatment of **5** with (–)-$Ipc_2$BCl / $Et_3N$ in $Et_2O$ led to regioselective formation of the enol borinate **14,** which was coupled with **6** (–78 °C, 3 h) to give the adduct **4** in 85% yield with ≥97% ds. Notably, this boron-mediated aldol reaction[9] exploits triple asymmetric induction, where the influence of all three chiral components (aldehyde, ketone and boron reagent) are matched.

We were now ready to explore the spiroacetalisation selectivity for the ketone **4** (**Scheme 3**). Brief treatment with HF in MeCN (20 °C, 10 min) led to clean desilylation and *in situ* acetalisation to give an 80% yield of the two spiroacetals **7a** and **8a**; formed in a ratio of *ca.* 1 : 5 by $^1H$ NMR analysis. Derivatisation of the $C_{25}$ hydroxyl as the TBS ether (**7b** and **8b**) or acetate (**7c** and **8c**) facilitated chromatographic separation of the mixture and assignment of stereochemistry. Extensive NOE studies unambiguously showed that the major compound formed from the HF treatment was the *undesired* spiroacetal **8a**. Most notably, NOEs were observed between the equatorial $H_{24}$ and the axial $H_{19}$ and $H_{21}$ protons in the derivatives **7b-c** obtained from the minor spiroacetal **7a**. These were absent in the corresponding derivatives **8b-c** obtained from the major spiroacetal **8a**, which displayed a strong NOE between the axial $H_{25}$ and both $H_{28}$ protons. Diagnostic NOEs were observed around the C-ring in all cases, confirming the 1,3-diaxial relationship of $H_{19}$ and $H_{21}$.



**Scheme 3**: (*a*) HF(aq), MeCN, 20 °C, 10 min; (*b*) HCl, $Et_2O$, $CDCl_3$, 20 °C, 1 h; separate by HPLC; (*c*) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C, 2 h; (*d*) $Ac_2O$, DMAP, pyridine, 20 °C, 2 h; (*e*) $OsO_4$, NMO, acetone, $H_2O$, *t*-BuOH, 20 °C, 3 h; (*f*) $NaIO_4$, MeOH, $H_2O$, 20 °C, 1 h; (*g*) EtMgBr, $Et_2O$, 0 °C, 2 h; (*h*) Dess-Martin periodinane, $CH_2Cl_2$, 20 °C, 2 h.

We next focussed on obtaining more useful quantities of the correct spiroacetal **7a**. Under acid treatment with anhydrous HCl in $CDCl_3$ (20 °C, 1 h), equilibration of the initially formed 5 : 1 mixture (taking care to avoid competing decomposition) gave an equimolar mixture of **7a** and **8a**. HPLC separation and re-equilibration of the wrong isomer **8a** allowed for good conversion into the *desired* spiroacetal **7a**. Subsequent manipulation of the terminal alkene in the derived TBS ether **7b** then gave the ethyl ketone **3**,[6] corresponding to the spongistatin $C_{16}$–$C_{28}$ subunit required for aldol coupling with subunit **2**.



**Scheme 4**: (*a*) $H_2C{=}C(Et)CH_2SiMe_3$, $TiCl_4$, $CH_2Cl_2$, −100 °C, 20 min; (*b*) TIPSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C, 2 h; (*c*) CSA, MeOH, $CH_2Cl_2$, 20 °C, 3.5 h; (*d*) Dess-Martin periodinane, $CH_2Cl_2$, 20 °C, 30 min; (*e*) $(c\text{-}C_6H_{11})_2BCl$, $Et_3N$, $Et_2O$, 0 °C, 30 min; **19**, −78 → −20 °C, 21 h; $H_2O_2$, MeOH/pH 7 buffer; (*f*) DDQ, $CH_2Cl_2$, pH7 buffer, 20 °C, 1 h; (*g*) PPTS, $CD_2Cl_2$, 20 °C, 7 d; (*h*) TMSOTf, $CH_2Cl_2$, −78 °C, 15 min; (*i*) DBU, $CH_2Cl_2$, 20 °C, 16 h.

A complementary strategy for the stepwise construction of the required CD-spiroacetal system was also investigated (**Scheme 4**). Here we planned to append the C-ring to the D-ring by a hetero-Michael cyclisation

under kinetic control, as in **15** → **16**, where axial attack might be favoured. The required cyclisation substrate **17** was now assembled by a $C_{23}$–$C_{24}$ aldol coupling between the methyl ketone **18** and the aldehyde **19**. Under conditions of chelation control ($TiCl_4$, $CH_2Cl_2$, 0.01 M, –100 °C), addition of $H_2C{=}C(Et)CH_2SiMe_3$ to the aldehyde **11** gave the 1,3-*anti* isomer **20** in 79% yield with 96% ds. After TIPS protection to form **21**, the $C_{23}$ aldehyde **19** was obtained by selective silyl deprotection and oxidation (81%). A stereocontrolled aldol reaction between the methyl ketone **18**[10a] (99% ee) and the aldehyde **19** (85% ee), where remote asymmetric induction dominates[10] from the $C_{27}$-stereocentre in the intermediate boron enolate **22**, then provided the stereochemically homogeneous 1,5-*anti* adduct **23** in 72% yield with 84% ds. Following Dess-Martin oxidation[11] to generate the β-diketone **17**, PMB deprotection and acid-promoted cyclisation gave the dihydropyranone **24**, where the D-ring was now in place.

We were now ready to explore the selectivity of spiroacetalisation, *i.e.* **24** → **16** *vs* **25**. Notably, HF•pyridine treatment of **24** gave only the *undesired* spiroacetal **25**, where presumably acetal equilibration occurred under the reaction conditions. However, we were able to isolate the intermediate alcohol **15** by using TMSOTf ($CH_2Cl_2$, –78 °C, 15 min) for desilylation. Under mild, basic conditions[12] (DBU, $CH_2Cl_2$), **15** slowly underwent a hetero-Michael reaction to install the C-ring, leading now to a small preference (60 : 40) for formation of the *desired*, less stable,[13] spiroacetal **16** over **25**. In both cases, extensive NOE studies allowed unambiguous assignment of the spiroacetal stereochemistry.

In summary, we have synthesised the desired CD-spiroacetal subunit **3** in 17 steps from the aldehyde **9**. An alternative route was also developed around a hetero-Michael reaction leading to **16**, but this requires a further improvement in stereoselectivity to be the method of choice. With the required $C_1$–$C_{15}$ aldehyde **2** already in hand,[4a] studies are now underway to achieve a selective aldol coupling of these two segments.

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6. All new compounds gave spectroscopic data in agreement with the assigned structures. **3** had: $^1$H NMR δ (500 MHz, $CDCl_3$) 7.25 (1H, d, *J* = 8.5 Hz, aromatic), 6.86 (2H, d, *J* = 8.5 Hz, aromatic), 4.52-4.51 (3H, m, $OC\underline{H}_2Ar$ and $H_{27}$), 4.11 (1H, m, $H_{25}$), 3.93 (1H, m, $H_{19}$), 3.80 (3H, s, $ArOC\underline{H}_3$), 3.51-3.45 (3H, m, $H_{28AB}$ and $H_{21}$), 3.32 (3H, s, $OC\underline{H}_3$), 2.84 (1H, dd, *J* = 3.7, 17.1 Hz, $H_{18A}$), 2.66 (1H, dd, *J* = 8.9, 17.1 Hz, $H_{18B}$), 2.40 (2H, q, *J* = 7.3 Hz, $H_{16AB}$), 2.21 (1H, m, $H_{20A}$), 2.13 (1H, dd, *J* = 3.4, 14.3 Hz, $H_{24A}$), 2.03 (1H, dd, *J* = 3.8, 11.5 Hz, $H_{22A}$), 1.68 (1H, dt, *J* = 3.6, 13.7 Hz, $H_{26A}$), 1.59 (1H, m, $H_{26B}$), 1.50 (1H, dd, *J* = 3.7, 14.3 Hz, $H_{24B}$), 1.36 (1H, t, *J* = 11.5 Hz, $H_{22B}$), 1.04 (1H, m, $H_{20B}$), 1.01 (3H, t, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 0.85 (9H, s, $SiC(C\underline{H}_3)_3$), 0.03 (3H, s, $SiC\underline{H}_3$), 0.01 (3H, s, $SiC\underline{H}_3$); $^{13}$C NMR δ (100 MHz, $CDCl_3$) 209.3, 159.1, 130.5, 129.2, 113.7, 98.4, 73.9, 72.9, 72.6, 66.6, 65.1, 64.3, 55.6, 55.3, 48.6, 43.2, 37.0, 36.9, 35.5, 35.1, 25.9, 18.1, 7.7, –4.91, –4.95.
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10. For high levels of 1,5-*anti* stereoinduction in related cases, see: (a) Paterson, I.; Gibson. K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585. (b) Evans, D. A.; Coleman, P. J.; Cote, B. *J. Org. Chem.* **1997**, *62*, 788.
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12. In contrast, stronger bases, *e.g.* KO$^t$Bu, led to formation of the undesired spiroacetal **25**.
13. Molecular modelling (MM2) of related systems suggested that **25** was substantially lower in energy (14.6 kJ mol$^{-1}$) than **16**.

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