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

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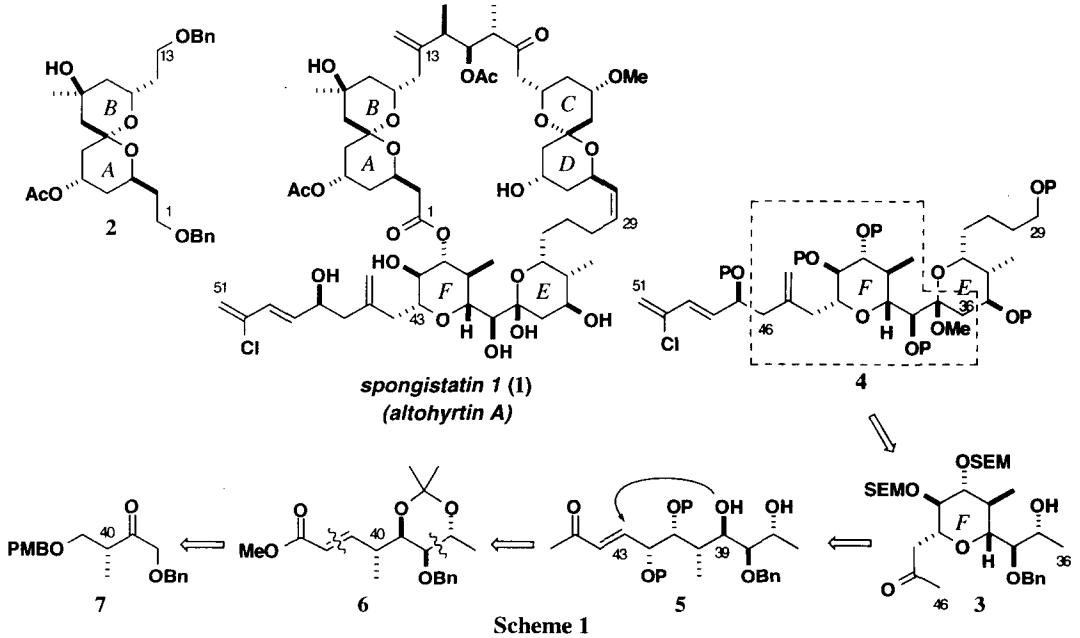
Abstract: The C_{36}–C_{46} subunit **3**, containing the F ring of spongistatin 1 (**1**), was prepared in 12 steps from ketone (*R*)-**7**. Key steps include: (*i*) the boron-mediated *anti* aldol reaction, **7** → **9**; (*ii*) the Sharpless AD, **6** → **13**; and (*iii*) an intramolecular hetero-Michael addition, followed by base-promoted equilibration to give **3**. © 1997 Elsevier Science Ltd.

The spongistatins[1-3] and altohyrtins[4] are a recently isolated group of marine macrolides, which display remarkable potency as antimitotic agents. Their structures (*e.g.*, **1** in **Scheme 1**) all feature a 42-membered macrolide ring built up of AB and CD spiroacetal units and E and F tetrahydropyranyl rings.[1-5] The spongistatins are reported to show especially powerful growth inhibitory activity *in vitro* against multi-drug resistant cancer cells and are believed to function by inhibiting tubulin polymerisation.[3]



Scheme 1

Due to their extremely meagre natural supply, synthetic efforts towards the spongistatins/altohyrtins are required to firmly establish the structures.[6] As part of studies in this area,[7,8] we have previously described[7a] the synthesis of the AB-spiroacetal subunit **2** of spongistatin 1 (altohyrtin A). We now report a stereocontrolled synthesis of the C_{36}–C_{46} segment **3**, representing a fully functionalised core for the lower half **4**.[6]

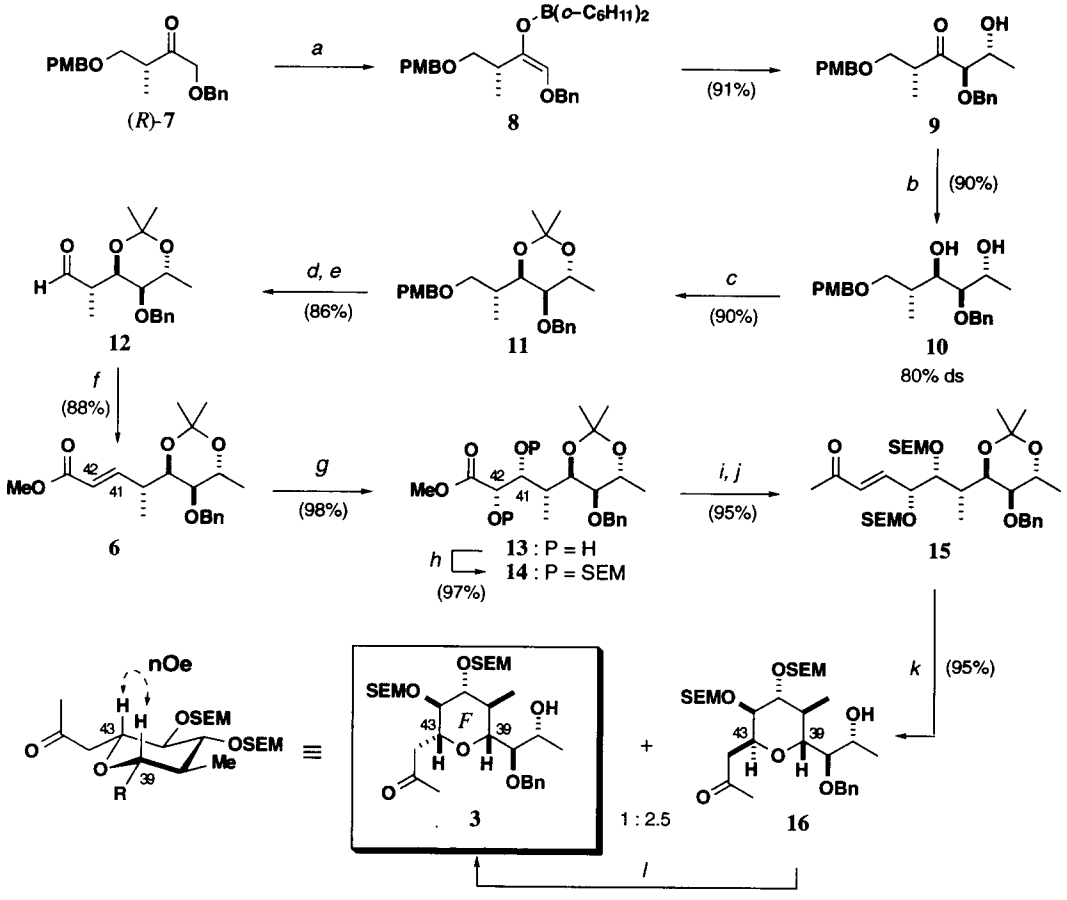
As shown in the retrosynthetic analysis in **Scheme 1**, our strategy for the construction of the highly substituted F ring was based on an intramolecular hetero-Michael addition of the C_{39}-OH, as in **5** → **3**. In this enone cyclisation, the required C_{43} stereocentre was expected to result from the thermodynamic preference for the ketone group to adopt an equatorial position in the tetrahydropyran ring (NB: all other substituents are equatorial). We planned that the required precursor **5** would be assembled, in turn, from the *anti-syn-anti* stereotetrad **6**, which should be accessible using suitable asymmetric aldol methodology from the ketone **7**. Our synthesis of the F-ring subunit **3**, which proceeded along these lines, is summarised in **Scheme 2** and outlined below.[9]

The starting ketone (*R*)-**7** was prepared from (*R*)-methyl-3-hydroxy-2-methylpropionate, as previously reported for the enantiomeric series.[10a] By using the (*E*)-selective enolisation conditions already employed with a number of α-chiral alkoxymethyl ketones,[10] a boron-mediated aldol reaction[11] with acetaldehyde was performed under substrate control. Thus, treatment of ketone (*R*)-**7** with (*c*-$C_6H_{11})_2BCl$ (Et_3N, Et_2O, –78 °C) generated the boron enolate **8**, which on addition of acetaldehyde gave the 1,2-*anti*-2,4-*anti* adduct **9** with >97% diastereoselectivity (91% yield). Hydroxyl-directed reduction[12] of **9** using $Me_4N{\bullet}BH(OAc)_3$ then gave the required stereotetrad **10**, obtained as the major isomer with 80% diastereoselectivity.[13] Next, acetonide formation gave **11**, where ^{13}C NMR analysis[14] was used to confirm the 1,3-*anti* diol reduction stereochemistry. Removal of the *para*-methoxybenzyl (PMB) group using DDQ[15] followed by Swern oxidation gave the aldehyde **12** (86%), which was chain extended by a HWE olefination,[16] with $(MeO)_2POCH_2CO_2Me$ ($^iPr_2NEt$, LiCl, MeCN), to give exclusively the (*E*)-alkene **6** in 88% yield.

The C_{41} and C_{42} stereocentres were then introduced into alkene **6** using the Sharpless asymmetric dihydroxylation.[17] This reagent-controlled reaction was carried out in aqueous ^{t}BuOH using freshly prepared, enriched AD-mix-β [$(DHQD)_2PHAL$ (4 mol%), $K_2OsO_2(OH)_4$ (1 mol%), $K_3Fe(CN)_6$, K_2CO_3][17b] with added $MeSO_2NH_2$, providing the diol **13** in 98% yield with excellent stereoselectivity (>97% ds). The resulting hydroxyl groups were then protected as their β-(trimethylsilyl)ethoxymethyl (SEM) ethers[18] to give **14** in 97% yield. After reduction of ester **14** into the corresponding aldehyde using DIBAL (–100 °C, CH_2Cl_2), conversion into the methyl ketone **15** was carried out by means of a HWE olefination with $(MeO)_2POCH_2COMe$ mediated by activated $Ba(OH)_2$ (aq. THF, 20 °C).[19] Notably, these mild reaction conditions provided the required (*E*)-enone **15** in high yield (96%) without any detectable epimerisation.

At this stage, we were ready to explore the selectivity in the hetero-Michael reaction triggered by removal of the acetonide from **15**. Under acidic conditions, the generated diol cyclised *in situ* to give the epimeric tetrahydropyrans **16** and **3** as a 2.5 : 1 mixture, with the *minor* component having the desired C_{43} configuration. A wide range of bases (*e.g.*, NaOMe, KO^{t}Bu, DBU) and reaction conditions were screened for equilibration of this mixture. Eventually, we found that by treatment of the mixture of ketones **16** and **3** with Triton methoxide[20] (THF, 0 °C, 1 h), the required isomer **3** could be obtained in 70% overall yield. The stereochemistry of **3** was confirmed using a combination of 2D NMR techniques.[9] In particular, a strong nOe was observed between the axial protons at the C_{39} and C_{43} positions of the tetrahydropyran ring.

In summary, this synthesis of the C_{36}–C_{46} subunit **3** of spongistatin 1 (altohyrtin A), incorporating the F ring, proceeds in 12 steps (28% yield) from the chiral ketone (*R*)-**7**. We have also used this route to prepare the enantiomer of **3** by starting with (*S*)-**7** and employing AD-mix-α.[6] Studies directed towards the synthesis of the CD spiroacetal and the E ring of spongistatin 1 (**1**) are currently underway.



Scheme 2: (*a*) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, -78 °C, 3 h; MeCHO, -78 → -20 °C, 16 h; (*b*) $Me_4N{\bullet}HB(OAc)_3$, AcOH, MeCN, -30 → 20 °C, 23 h; (*c*) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 20 °C, 24 h; (*d*) DDQ, CH_2Cl_2, H_2O, 20 °C, 1 h; (*e*) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 1 h; Et_3N, -25 °C, 1 h; (*f*) $(MeO)_2POCH_2CO_2Me$, *i*-Pr_2NEt, LiCl, MeCN, 20 °C, 17 h; (*g*) AD-mix-β [$(DHQD)_2PHAL$ (4 mol%), $K_2OsO_2(OH)_4$ (1 mol%), $K_3Fe(CN)_6$, K_2CO_3], $MeSO_2NH_2$, *t*-BuOH, H_2O, 20 °C, 17 h; (*h*) $Me_3Si(CH_2)_2OCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, 40 °C, 24 h; (*i*) DIBAL, CH_2Cl_2, -100 °C, 1 h; (*j*) $Ba(OH)_2{\bullet}H_2O$, $(MeO)_2POCH_2COMe$, THF, H_2O, 20 °C, 22 h; (*k*) AcOH, THF, H_2O (9:1:1), 20 °C, 19 h; (*l*) $BnNMe_3OMe$ (40% wt. soln. in MeOH), THF, 0 °C, 1 h.

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5. Cinachyrolide A is assumed to be structurally identical to spongistatin 4. Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.

6. Although the absolute configuration at all 24 stereogenic centres in altohyrtin A (≡ spongistatin 1) has been proposed as shown in structure **1** by Kobayashi and Kitagawa (ref 4c,d), this assignment is partially in conflict with the relative stereochemistry proposed independently by the Pettit and Fusetani groups. While we have tentatively accepted structure **1** as a starting point, it is essential to build enough flexibility into the synthetic route in case of later revision of the stereochemical assignment. In particular, access to the enantiomeric relationship for the boxed region in **4** may be required.

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8. For a review on marine macrolide synthesis, see: Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

9. All new compounds gave spectroscopic data in agreement with the assigned structures. NMR data for **3** : ^{1}H NMR δ (500 MHz, $CDCl_3$) 7.35 - 7.24 (5H, m, ArH), 4.88 (1H, d, J = 6.7 Hz, $OC\underline{H}_aH_bO$), 4.80 (1H, d, J = 6.4 Hz, $OC\underline{H}_aH_bO$), 4.78 (1H, d, J = 6.7 Hz, $OCH_a\underline{H}_bO$), 4.75 (1H, d, J = 6.4 Hz, $OCH_a\underline{H}_bO$), 4.71 (1H, d, J = 11.4 Hz, $C\underline{H}_aH_bPh$), 4.54 (1H, d, J = 11.4 Hz, $CH_a\underline{H}_bPh$), 4.02 (1H, app qn, J = 6.4 Hz, $C\underline{H}OH$), 3.83 - 3.75 (1H, m, $OC\underline{H}_aH_bCH_2SiMe_3$), 3.74 - 3.67 (1H, m, $OCH_a\underline{H}_bCH_2SiMe_3$), 3.66 -3.61 (1H, m, 43-CH), 3.59 - 3.44 (3H, m, $OC\underline{H}_2CH_2SiMe_3$, 39-CH), 3.32 (1H, dd, J = 6.4, 2.2 Hz, $C\underline{H}OBn$), 3.29 - 3.20 (2H, m, 41-CH, 42-CH), 3.00 (1H, br d, J = 18.2 Hz, 44-$C\underline{H}_aH_b$), 2.74 (1H, dd, J = 18.2, 10.3 Hz, 44-$CH_a\underline{H}_b$), 2.14 (3H, s, 46-CH_3), 2.12 - 2.02 (1H, m, 40-$C\underline{H}Me$), 1.30 (3H, d, J = 6.4 Hz, 36-CH_3), 1.01 - 0.86 (4H, m, 2 x $C\underline{H}_2SiMe_3$), 0.89 (3H, d, J = 6.5 Hz, 40-$CH\underline{Me}$), 0.02 (18H, s, 2 x $SiMe_3$); ^{13}C NMR δ (400 MHz, $CDCl_3$) 207.5, 138.0, 128.4, 128.1, 127.8, 96.9, 85.8, 81.4, 81.2, 80.7, 74.7, 72.9, 66.7, 66.2, 66.1, 45.0, 37.4, 30.6, 20.4, 18.2, 18.0, 12.7, -1.4, -1.5; HRMS (CI^+) calcd for $C_{31}H_{60}NO_8Si_2$ $(M + NH_4)^+$ 630.3858, found 630.3860.

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