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Total synthesis of altohyrtin A (spongistatin 1): an alternative synthesis of the CD-spiroacetal subunit

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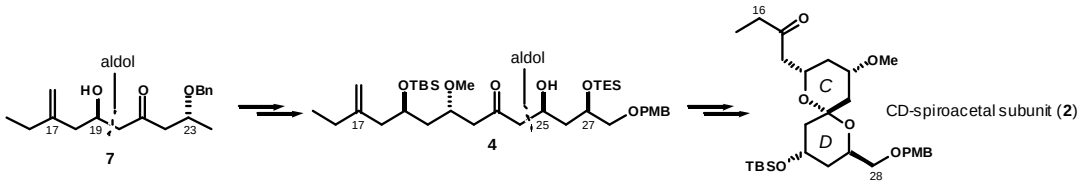
Ian Paterson* and Mark J. Coster
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.



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LETTERS

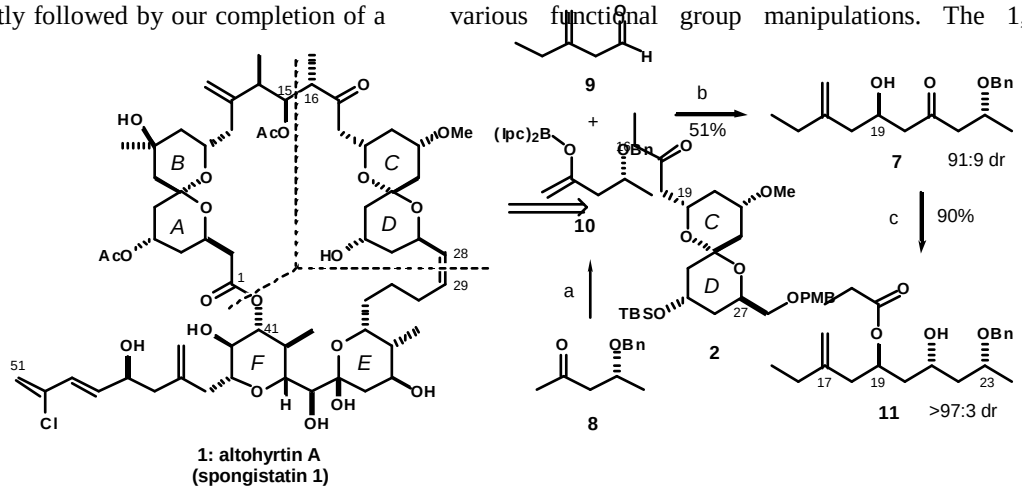
Total synthesis of altohyrtin A (spongistatin 1): an alternative synthesis of the CD-spiroacetal subunit

Ian Paterson* and Mark J. Coster

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

Abstract—The CD-spiroacetal containing C_{16}-C_{28} subunit **2**, as used in the total synthesis of the potent cytotoxic macrolide, altohyrtin A (spongistatin 1), was prepared by an alternative route using substrate-based stereocontrol in the two aldol bond constructions generating the acyclic precursor **4**.

The altohyrtins/spongistatins comprise an important family of highly cytotoxic macrolides, isolated from marine sponges.[1,2] They display exceptional growth inhibitory activity against a wide range of drug-resistant cancer cell lines, functioning by interfering with tubulin polymerisation. Their complex, highly oxygenated structures (*e.g.* **1**, Scheme 1) and potent antimitotic action, combined with an extremely meagre natural supply, have provided a strong impetus for synthetic efforts. Total syntheses of altohyrtin C (spongistatin 2) have been achieved by the Evans group[3] and more recently by the Smith group.[4] The first total synthesis of the more active, chlorinated congener, altohyrtin A/spongistatin 1 (**1**) by Kishi *et al*.,[5] was recently followed by our completion of a highly stereocontrolled synthesis, leading to useful quantities for further preclinical development.[6] With a view to further refining our total synthesis, we now report a new synthesis of the CD-spiroacetal containing subunit **2** that ~~exploits~~ substrate-based aldol stereocontrol.

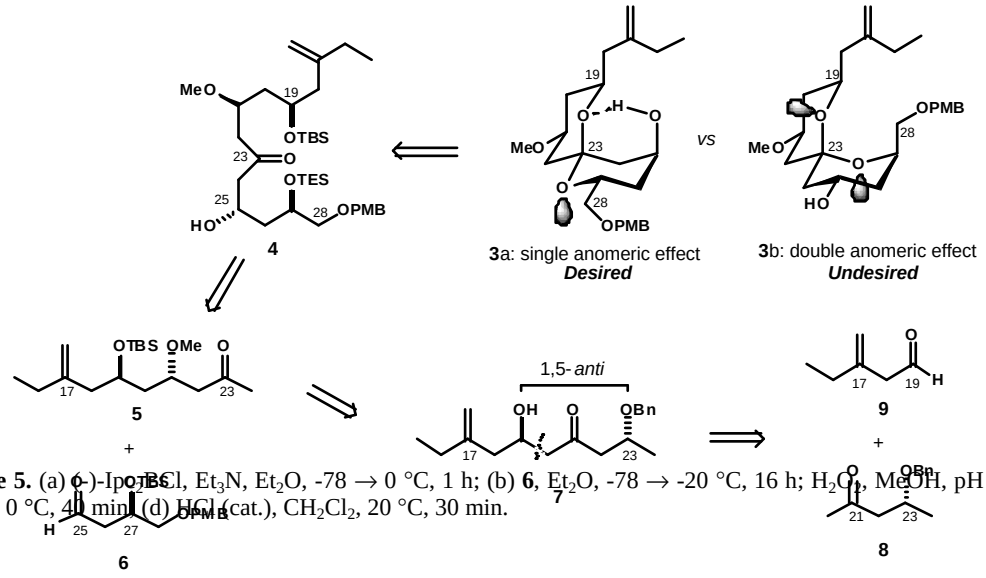


Scheme 1.

The CD-spiroacetal of the altohyrtins/spongistatins benefits from only a single anomeric effect, necessitating care in initially establishing the C23 acetal centre correctly and subsequently avoiding unwanted epimerisation.[7] Accordingly, our revised retrosynthetic analysis for **2** involved formation of the precursor **3a**, incorporating a C17-methylene, from ketone **4** by removal of the silyl protecting groups and concomitant spiroacetal formation (Scheme 2). The aldol coupling of ketone **5** with aldehyde **6** to give the required acyclic precursor **4** would depend on substrate-based stereoinduction in setting up the C25 stereocentre, as demonstrated in an analogous system.[6c] Ketone **5** would arise from **7** by 1,3-*anti* reduction and various functional group manipulations. The 1,5-*anti* relationship between the oxygen functionality in **7** suggested a boron-mediated aldol reaction[8] between the β-alkoxyketone **8** and β,γ-unsaturated aldehyde **9**, where substrate-based induction would again be employed productively.

Keywords: altohyrtin; spongistatin; boron aldol; cytotoxic; remote stereoinduction.

* Corresponding author. Fax: +44-1223-336362; e-mail: ip100@cus.cam.ac.uk.



Scheme 5. (a) (+)-Ipc$_2$BCl, Et$_3$N, Et$_2$O, -78 → 0 °C, 1 h; (b) **6**, Et$_2$O, -78 → -20 °C, 16 h; H$_2$O$_2$, MeOH, pH 7 buffer, 20 °C, 1 h; (c) HF$_{(aq)}$, MeCN, 0 °C, 40 min; (d) HCl (cat.), CH$_2$Cl$_2$, 20 °C, 30 min.

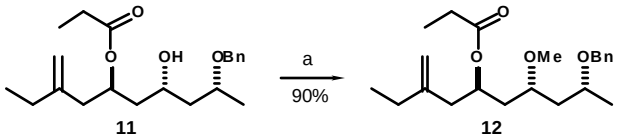
Scheme 2. Retrosynthetic analysis.

The synthesis began with the regioselective enolisation of methyl ketone **8**,[9] using (+)-Ipc$_2$BCl and Et$_3$N,[10] to give enol borinate **10** *in situ* (Scheme 3).[11] Reaction of **10** with aldehyde **9**,[12] followed by oxidative workup, provided the 1,5-*anti* aldol adduct **7** as the predominant diastereomer (91:9 dr), in 51% yield (unoptimised).[13] The stereogenicity at C$_{19}$ and degree of diastereoselectivity were determined by ^{1}H NMR analysis of the (*R*)- and (*S*)-MTPA esters,[14] and conform to the levels of 1,5-*anti* selectivity generally observed for aldol reactions of this type.[8] Gratifyingly, no isomerisation of aldehyde **9** to the α,β-unsaturated isomer was observed under the reaction conditions, illustrating the mild nature of the boron mediated aldol reaction.[15]

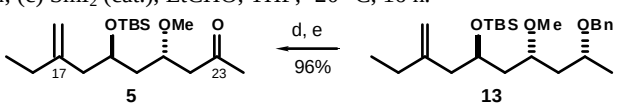
The Evans-Tishchenko reduction[16] was chosen as the most appropriate method for conversion of β-hydroxyketone **7** to the mono-protected 1,3-*anti* diol **11**. Preliminary experiments utilising benzaldehyde as the hydride source were slow and low yielding. However, the use of propionaldehyde and catalytic SmI$_2$ proved efficient, allowing for the production of **11** in good yield (90%) and with an excellent level of 1,3-stereoinduction (>97:3 dr).

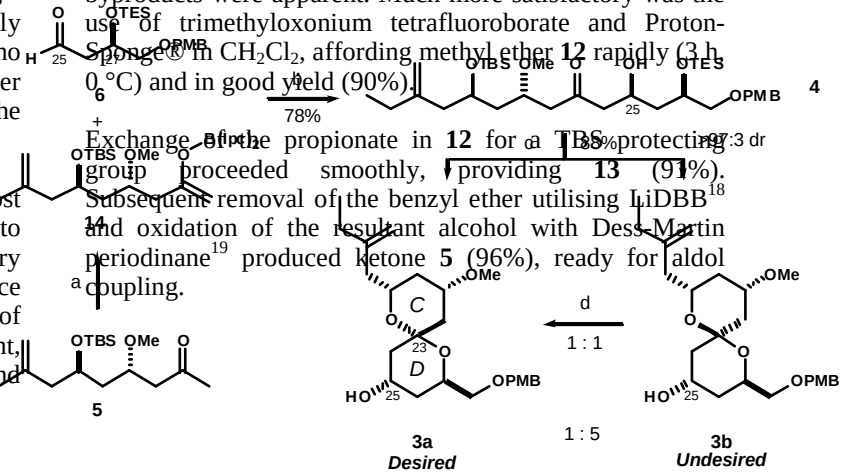
Methylation of alcohol **11** required the use of very mild, near neutral conditions (Scheme 4).[17] Subjection of **11** to MeOTf and 2,6-di-*tert*-butylpyridine in refluxing CH$_2$Cl$_2$ proved successful, although the yield was moderate (65%), reaction times were prolonged (16 h) and unwanted byproducts were apparent. Much more satisfactory was the use of trimethyloxonium tetrafluoroborate and Proton-Sponge® in CH$_2$Cl$_2$, affording methyl ether **12** rapidly (3 h, 0 °C) and in good yield (90%).

Exchange of the propionate in **12** for a TBS protecting group proceeded smoothly, providing **13** (91%). Subsequent removal of the benzyl ether utilising LiDBB[18] and oxidation of the resultant alcohol with Dess-Martin periodinane[19] produced ketone **5** (96%), ready for aldol coupling.



Scheme 3. (a) (+)-Ipc$_2$BCl, Et$_3$N, Et$_2$O, -78 → 0 °C, 1 h; (b) **9**, Et$_2$O, -78 → -20 °C, 90 min; H$_2$O$_2$, MeOH, pH 7 buffer, 20 °C, 1 h; (c) SmI$_2$ (cat.), EtCHO, THF, -20 °C, 16 h.





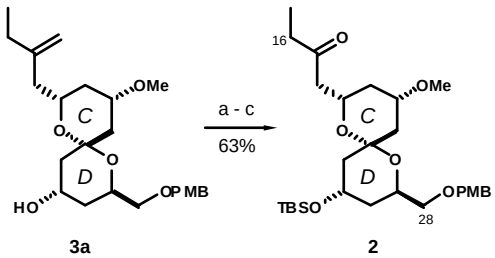
Scheme 4. (a) Me$_3$OBF$_4$, Proton-Sponge®, CH$_2$Cl$_2$, 0 °C, 3 h; (b) K$_2$CO$_3$, MeOH, 20 °C, 16 h; (c) TBSCl, Im, DMF, 20 °C, 16 h; (d) LiDBB, THF, -78 °C, 1 h; (e) Dess-Martin periodinane, pyr, CH$_2$Cl$_2$, 20 °C, 40 min.

The boron-mediated aldol reaction of aldehyde **6** with ketone **5** was well precedented from our previously published route to the CD-spiroacetal subunit **2**.[6c] In the event, treatment of ketone **5** with (-)-Ipc_2BCl and Et_3N led to regioselective enolisation to give enol borinate **14** *in situ* (Scheme 5). Reaction of this with aldehyde **6**, followed by oxidative workup, gave the linear C_{16}-C_{28} fragment **4**[13] (78% yield) as the only identifiable diastereomer (>97:3 dr). Notably, this boron-mediated aldol reaction exploits triple asymmetric induction, where the influence of all three chiral components (aldehyde, ketone and boron reagent) are matched.

Treatment of **4** with aqueous HF in acetonitrile led to the smooth formation of spiroacetals **3a** and **3b** (1:5, 88% yield). Under anhydrous acid conditions (HCl, CH_2Cl_2) the spiroacetals equilibrated to a *ca*. 1:1 mixture, and were readily separable by flash chromatography (43% of the desired isomer **3a** and 33% of **3b**). The undesired isomer **3b** could then be re-equilibrated to give more of **3a**.

With CD-spiroacetal **3a** in hand, bearing the correct stereochemistry at the anomeric centre (C_{23}), conversion to the required subunit **2** was straightforward. Protection of **3a** as the corresponding TBS ether was achieved with TBSOTf and 2,6-lutidine (Scheme 6). Dihydroxylation with catalytic OsO_4 and NMO as co-oxidant, followed by sodium periodate cleavage of the resultant diol, provided the desired CD-spiroacetal subunit **2** (63%, three steps), identical in all respects with material provided by our earlier route.[6c]

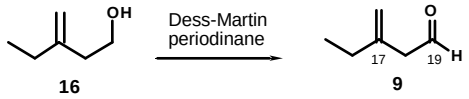
In conclusion, the CD-spiroacetal containing C_{16}-C_{28} subunit **2** was prepared in this new route in 11.8% yield over 13 steps from ketone **8**. The synthesis presented here further illustrates the utility of the boron-mediated aldol reaction for the stereoselective construction of polyacetate subunits.[20] Combined with the highly stereoselective and hydroxyl discriminating Evans-Tishchenko reduction, this provides a powerful tool for the synthesis of polyketide natural products. Additionally, the use of sensitive β,γ-unsaturated aldehydes in the boron-mediated aldol reaction has been shown to be effective.



Scheme 6. (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 1 h; (b) OsO_4 (cat.), NMO, Me_2CO/H_2O, 20 °C, 6 h; (c) $NaIO_4$, MeOH/pH 7 buffer, 20 °C, 1 h.

Acknowledgements

We thank the EPSRC (GR/L41646), Cambridge Commonwealth Trust and AstraZeneca for support and Dr Anne Butlin (AstraZeneca) for helpful discussions.



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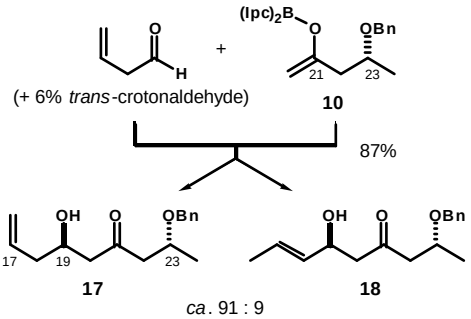

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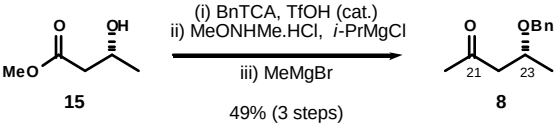

15 49% (3 steps) **8**