A Method for Constructing the C2−C12 Dispiroacetal Moiety of Altohyrtin A

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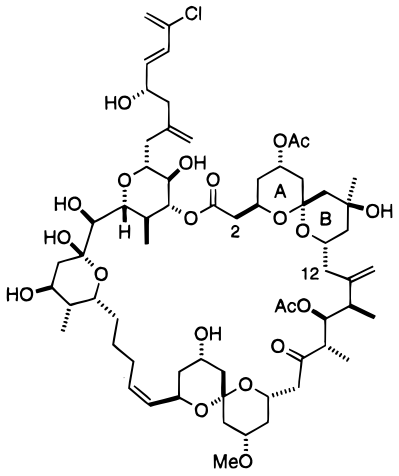
Several novel, marine-derived, macrocyclic lactones with identical or similar skeletal structures, including the altohyrtins,[1,2] the spongistatins,[3] and cinachyrolide A,[4] have recently been isolated and shown to be extremely potent cancer cell growth inhibitors. In screens against the U.S. National Cancer Institute's 60 human cancer cell lines, many of these compounds displayed high cytotoxicity toward a subset of chemoresistant tumor types. Of these compounds, altohyrtin A (**1**) is the only compound for which the absolute stereochemistry has been reported. In light of the high activity of this compound in conjunction with its paucity, studies are being directed toward a total synthesis of **1**.



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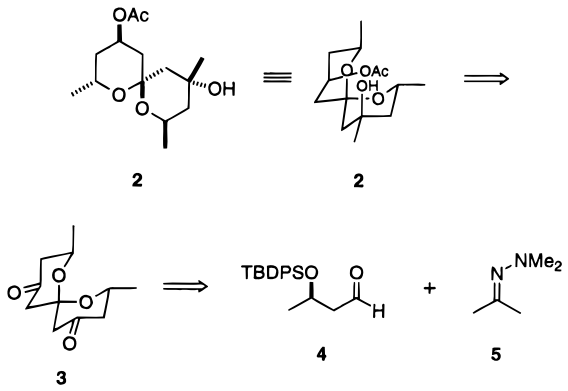
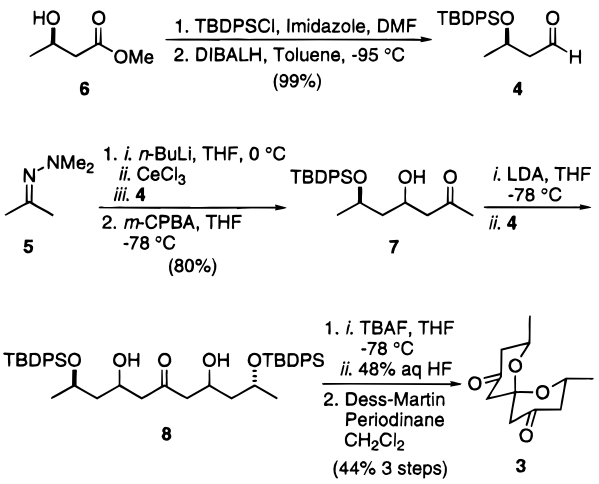
In our research aimed at this target, we were interested in synthesizing the spiroketal **2**, which is a model for the C2−C12, A−B spiroketal fragment of altohyrtin A (**1**). We envisioned spiroketal **2** (Scheme 1) as being derived from the C_2-symmetric diketone **3**, which upon further disconnection revealed the readily-available aldehyde **4** and acetone dimethylhydrazone (DMH),[5] **5**, as possible starting materials. Although spiroketal **2** possesses the opposite stereochemistry reported for the corresponding fragment of **1**, either enantiomer of aldehyde **4** is equally accessible using the same procedure.

The three-step synthesis of the aldehyde **4** (Scheme 2) began by catalytic, asymmetric hydrogenation of commercially-available methyl acetoacetate using a procedure of Kitamura and Noyori *et al.*[6] in which the hydroxy ester **6** was obtained in excellent yield and purity (>97% ee). Both enantiomers of ester **6** are commercially available, yet very expensive ($40/1 g from Aldrich Chemical Co., Inc.). Therefore, multigram quantities of **6** were obtained more cost efficiently using the Noyori protocol. Silyl protection of the secondary hydroxyl as the *tert*-butyldiphenylsilyl (TBDPS) ether followed by careful DIBALH reduction of the ester provided aldehyde **4** in nearly quantitative yield. Condensation of aldehyde **4** with the lithium anion of hydrazone **5** gave the desired hydrazone product, which was used crude due to instability. Several hydrazone cleavage conditions were explored but resulted in unsatisfactory yields of ketone **7**, including sodium periodate[7,8] (46%), ozone[9,10] (48%), and silica gel[11] (50−60%). The optimum cleavage conditions were found to be *m*-CPBA[12] in THF at −78 °C, which provided ketone **7** more conveniently and in a reproducible two-step yield of 59%. On the basis of spectroscopic analysis of isolated byproducts, the deprotonation followed by β-elimination of aldehyde **4** prior to anion addition was suspected to be the cause of this moderate yield. The problem was solved by transmetalation of the

Scheme 1



Scheme 2



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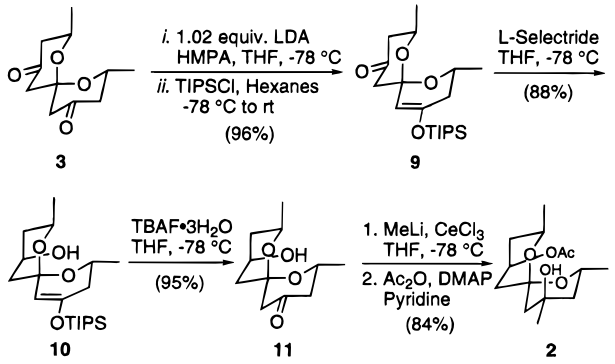
Scheme 3



lithium anion with cerium trichloride prior to addition, which resulted in an improved two-step yield of 80%. Although cerium anions have been shown to be less basic than the corresponding lithium anions,[13] the generation of the cerium anion of a hydrazone is to the best of our knowledge novel.

The remaining carbons of the diketone skeleton were installed by a second condensation in which the β-hydroxy ketone **7** was treated with 2.1 equiv of LDA followed by the addition of another equivalent of aldehyde **4**. Purification of the three diastereomers of ketone **8** was not possible at this point; therefore, the crude material was deprotected with tetrabutylammonium fluoride (TBAF) in THF and ketalized by the addition of 48% aqueous HF. Purification of the ketalized diol mixture was also unsuccessful. However, the silicon byproducts were removed through extractive procedures, and the resulting crude diols were oxidized with Dess–Martin periodinane[14] to afford the desired diketone **3** in a 44% yield over the three steps. Purification of the diketone **3** resulted in loss of product due to its instablity to silica gel. The three-step yield could considerably improve in the application of this chemistry to the synthesis of the altohyrtin system, since the requisite compounds would be presumably less polar, potentially resulting in greater ease of purification.

Transformation of the diketone **3** into the model spiroketal **2** is shown in Scheme 3. Masking one carbonyl of the C_2-symmetric diketone **3** as a silyl enol ether allowed for the efficient differentiation of the two carbonyls. The selective monosilyl enol ether formation was successfully performed with 1.02 equiv of LDA in HMPA/THF followed by addition of TIPSCl in hexanes to provide silyl enol ether **9** in 96% yield as a 6:1 mixture of regioisomers. The TIPS enol ether was found to be superior to the corresponding TBS enol ether, which in the subsequent steps was prone to decomposition, resulting in ring-opening of the spiroketal by cleavage of the silyl group and β-elimination. Reduction of ketone **9** with L-Selectride in THF gave the desired axial alcohol **10** in 88% yield. Silyl cleavage with TBAF·$3H_2O$ in THF at −78 °C unmasked the remaining carbonyl moiety to afford the hydroxy ketone **11** in 95% yield. Methylcerium addition to **11** provided the desired tertiary, axial alcohol in 91% yield. The stereochemistry of this addition was confirmed by X-ray crystallographic analysis of the 4-nitrobenzoate derivative (Figure 1).[15] Selective acylation of the secondary hydroxyl with acetic anhydride and DMAP in pyridine completed the synthesis of the spiroketal **2** with a 92% yield.

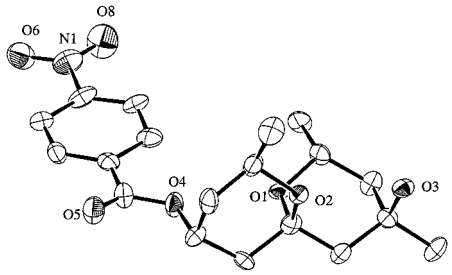


Figure 1. ORTEP representation of the 4-nitrobenzoate derivative of the methyl-addition product of **11**.

In summary, a synthesis of the desired model (**2**) has been accomplished in a 23% overall yield for 13 steps starting from commercially-available methyl acetoacetate. The application of the chemistry developed for the model to the synthesis of the C2–C12, A–B spiroketal of altohyrtin A (**1**) is currently being investigated. The synthesis of a C_2-symmetric intermediate, analogous to diketone **3**, and its subsequent desymmetrization is being explored. An advantage of this synthesis is that either enantiomer would be accessible in the event that the absolute stereochemistry was incorrectly assigned or should the enantiomer of the A–B spiroketal fragment exist in any of the other related natural products.

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Supporting Information Available: Experimental procedures and spectral data for all compounds (9 pages).

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(15) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.