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TETRAHEDRON: *ASYMMETRY*

A second generation pyranose-based approach to the F ring (C38–C45) of altohyrtin A

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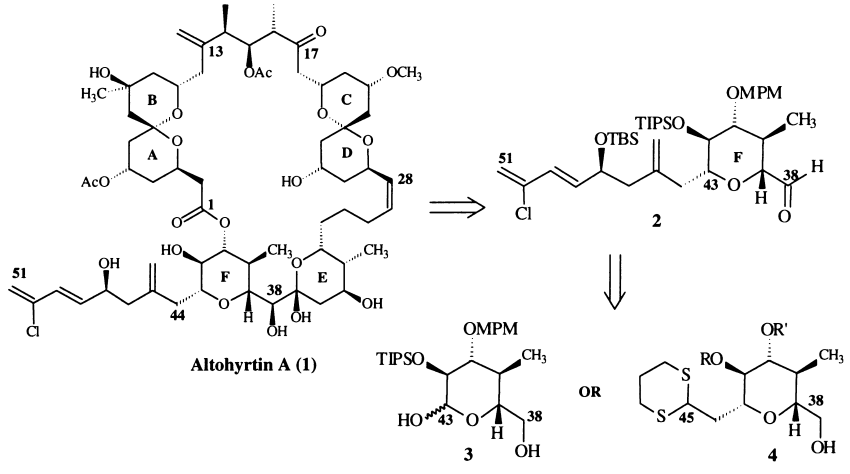
Abstract

A second generation approach to the F ring, fragment C38–C45, of altohyrtin A (**1**) is described herein. The C43–C44 *C*-glycosidic linkage was prepared and subsequently functionalised with a thioketal moiety. © 1999 Elsevier Science Ltd. All rights reserved.

Altohyrtin A **1** (spongistatin 1), isolated from the marine sponge *Hyrtios altum*, has been shown to display potent cytotoxic activity against a variety of human cancer cell lines.[1] The recent synthetic interest[2] is testament to its appeal. In a recent report,[3] we described the first pyranose-based approach to the F ring (C38–C43) of altohyrtin A **1**. This strategy aimed to create the β-*C*-glycoside at C44 by utilising a Horner–Emmons coupling to the lactol **3** (Scheme 1).[4]



Scheme 1.

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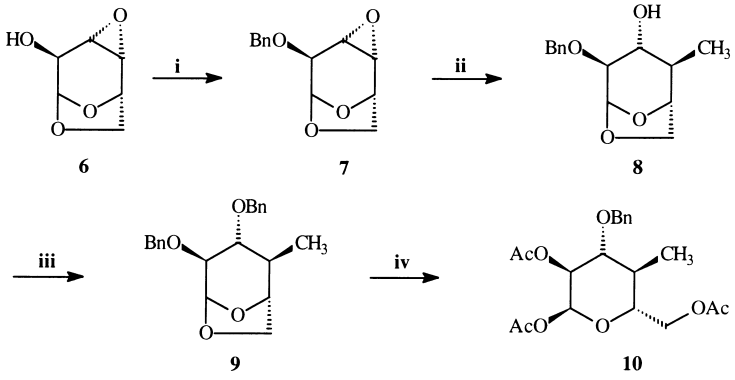
We describe a second generation approach with a disconnection which creates a C38–C45 fragment **4** and allows for more facile homologation of the exocyclic diene chain.

The epoxy alcohol **6** was protected as its benzyl ether **7** (Scheme 2) under standard conditions. The epoxide was opened using the lower order cuprate $(CH_3)_2CuMgI$, providing **8** in 73% yield. After benzylation to furnish **9**, attempts were made to hydrolyse the 1,6-anhydrobridge under the conditions developed in our labs previously.[3]



Scheme 2. Reagents and conditions: (i) THF, DMF, NaH, BnBr, tetrabutylammonium iodide, 0°C to rt, 3.5 h, 80%; (ii) THF, CuI, CH_3MgCl, 2 h, −42°C, rt, 14 h, 73%; (iii) as (i), 16 h, 83%; (iv) Ac_2O, −78°C, TES-OTf, −78°C to −5°C, 30 min, 83%

However, the acetal group of compound **9** was stable to acetic anhydride and triethylsilyl triflate until the temperature of the reaction was raised to −5°C. At this temperature, the 2-*O*-benzyl ether, which is thought to have stabilised the 1,6-acetal, was concomitantly hydrolysed along with the 1,5-acetal ring to yield the triester **10**. This observation is consistent with that of Wong who reported the hydrolysis of a primary benzyl ether under similar conditions (trimethylallylsilane, TMS-OTf).[5] These acetolysis conditions conveniently provided the required differential protection of the C40 and C41 hydroxyl groups. Differential protection of these alcohols is of critical importance for later stage couplings to C1 of althohyrtin A and was attained with much greater difficulty in our previous efforts.[3]

The triester **10** was treated with allyltrimethylsilane and $BF_3 \cdot OEt_2$ at 0°C for 41 h to yield the allyl α-*C*-glycoside **12** (Scheme 3) in high yield.[6] Ozonolysis of the olefin in sodium methoxide[7] provided the ester **13** as a 7:4 mixture favouring the α-anomer. After protective group manipulation to give compound **14** and subsequent functional group interchange, the thioketal **15** was isolated in 12% overall yield from compound **10**.

Studies investigating the further elaboration of compound **15** will be reported in due course.

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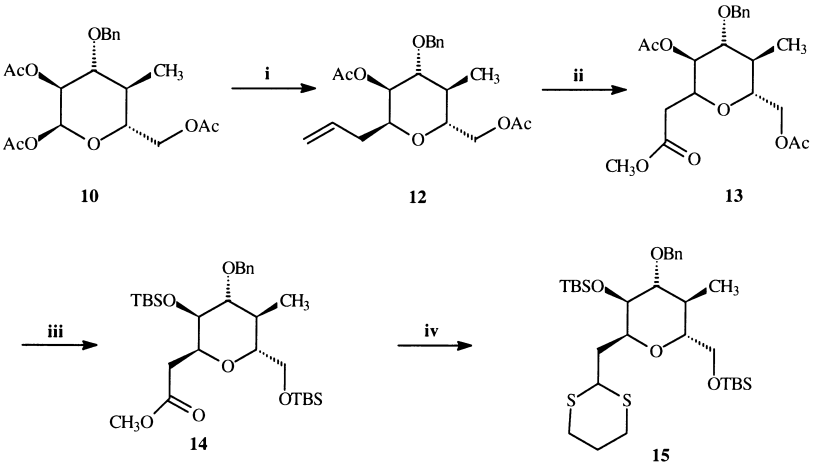

Scheme 3. Reagents and conditions: (i) allyl-TMS, $BF_3 \cdot OEt_2$, CH_3CN, 0°C, 41 h, 90% yield; (ii) DCM, −78°C, 2.5 M NaOMe, O_3, 5 h, 74%; (iii) a. THF/MeOH, 0°C, K_2CO_3, 1.5 h; b. TBS-OTf, DCM, 0°C, 1.5 h, rt, 3.5 h, 85%; (iv) a. DCM, −80°C, DIBAL-H, 20 min; b. 1,3-propanedithiol, DCM, 0°C, $BF_3 \cdot OEt_2$, 20 min, 21%

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