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TETRAHEDRON: *ASYMMETRY*

Studies towards the total synthesis of altohyrtin A: a convergent approach to the C38–C51 carbon framework

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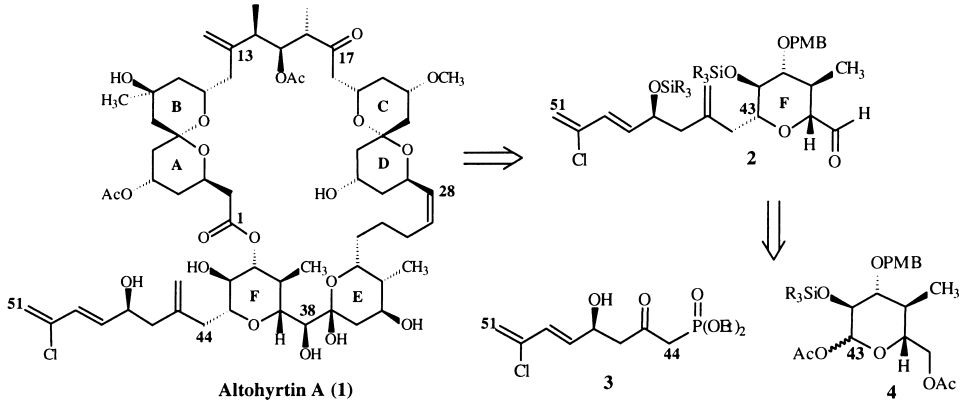
Abstract

The first pyranose-based approach to the F ring (C38–C43) of altohyrtin A **1** together with a synthetic approach to the C44–C51 chloro diene unit of **1** is described.

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] At present, the literature is replete with interesting synthetic studies that focus on the various features of the altohyrtin molecule.[2] In view of these recent developments, we wish to report our efforts towards the C38–C51 segment **2**. Disconnection at the C43–C44 bond in fragment **2** affords key advanced intermediates **3** and **4** (Scheme 1). This paper details approaches towards the C44–C51 diene **3** and C38–C43 tetrahydropyran ring **4**.



Scheme 1.

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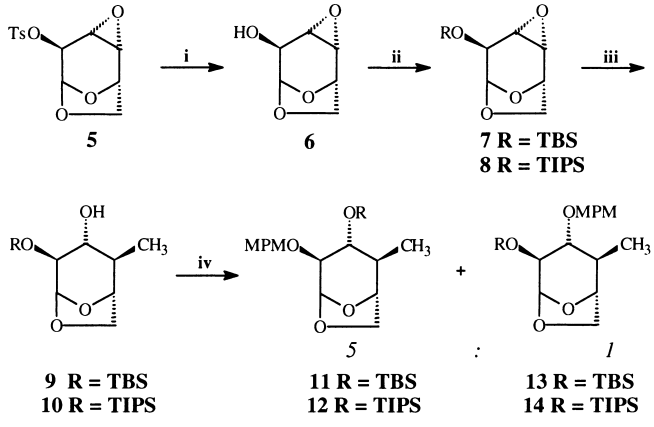
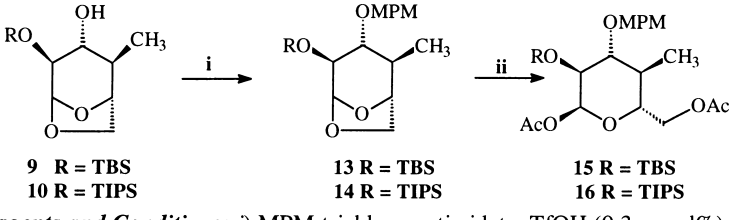
The starting material for the synthesis of lactol **4** was L-glucose which was readily converted into the epoxide **5** using known methods[3] (Scheme 2). Removal of the *p*-toluene sulfonyl group of the readily available **5** to reveal the alcohol **6** was accomplished using $Na_{(solid)}$ in liquid ammonia.[4] After protection of the alcohol as either the tertbutyldimethylsilyl (TBS) **7** or trisopropylsilyl (TIPS) ether **8**, the epoxide was cleaved in a diaxial manner to yield the 4-deoxy-4-methyl-1,6-anhydro-glucose derivatives **9** and **10**. Unexpectedly, for both of these compounds, protection of the 3-hydroxyl as its *p*-methoxybenzyl ether using NaH and MPM-Cl in DMF led instead to the 2,3-*O*,*O*-*pseudo*-diaxial migration of the silyl ether moiety.[5] The resultant isomers **11** and **13** were inseparable by flash column chromatography but the isolation of the TIPS ethers **12** and **14** allowed detailed NMR analysis which showed the undesired migrated product as the predominant isomer (ca. 5:1). Presumably, the silyl shift did not occur during the transformation of **8** to **10** (or **7** to **9**) because the magnesium oxyanion is less nucleophilic[5b] than its sodium counterpart, the entity involved in the transformation of **10** into **12** (or **9** into **11**). Happily, the desired protective group pattern was accomplished (Scheme 3) using *p*-methoxybenzyl trichloroacetimidate[6] and triflic acid (0.3 mol%).[7]



Reagents and Conditions: *i)* Na (solid), NH_3/DME, -78°C, 87%.. *ii*) a)TBDMS-Cl, DMF. imid., 12 h, 50°C, 81%; or b) TIPS-OTf, 2,6-lutidine, DCM, 3h, 0°C, 96%; *iii)* CH_3MgCl, CuI (cat), THF, -42°C to +40°C, overnight, 78-87%. *iv)* NaH, MPM-Cl, tetrabutyl-ammonium iodide, DMF, 0°C-rt, 69-84%.

Scheme 2.



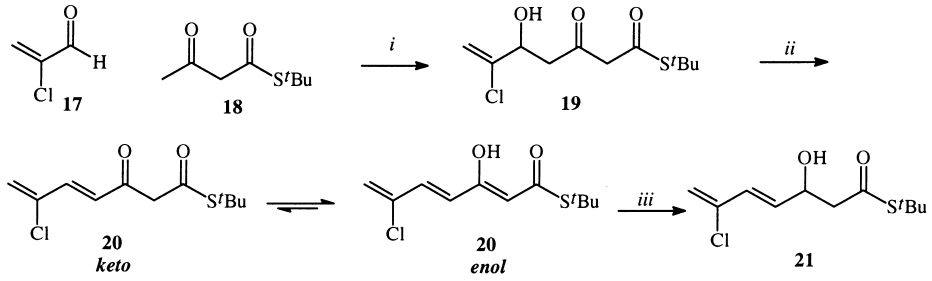
Reagents and Conditions: *i*) MPM-trichloroacetimidate, TfOH (0.3 mmol%), 0 °C to r.t., 5 h, 73, 91%; *ii)* Ac_2O, TES-OTf (5 mol%), -78 °C to –55 °C, 1.5 h, 87, 94%.

Scheme 3.

The use of protic acids to hydrolyse the 1,6-acetal group resulted in the concomitant hydrolysis of the ether linkages at C2 and C3 (sugar numbering). The methodology described by Fraser-Reid[8] also gave rise to silyl and even benzyl ether hydrolysis, but lowering the reaction temperature (−55 to −60°C) resulted in the clean hydrolysis of the 1,6-acetal group in compounds **13** and **14** to give the desired diacetates **15** and **16**, respectively, in excellent yields (87, 94%). The simple anomeric deacetylation

using benzylamine as described by Wong[9] should readily afford the corresponding lactol for coupling to the phosphonate **3**.

The starting point for the synthesis of the C43–C51 segment **3** was 2-chloro-2-propenal **17**, which was prepared by a modified method of Shostakovskii[10] in 40% yield over two steps from propenal. The dianion of β-keto ester **18**,[11] generated by sequential treatment of the ketoester with sodium hydride (1.6 equiv.) and *n*-butyl lithium (1.2 equiv.) was condensed with aldehyde **17** to provide alcohol **19** in 53% yield (Scheme 4).



Reagents and Conditions: *i)* NaH, 30 min, 0 °C, *n*-BuLi, -20°C, 30 min, **17** in THF, r.t., 1h.; *ii*) CH_2Cl_2, pyridine, 0°C, CH_3SO_2Cl, 5 °C, 59 %; *iii*) $NaBH_4$, abs EtOH, 0°C to r.t., 69 %.

Scheme 4.

Making the methyl sulfonate of the C47 alcohol group in compound **19** gave the required derivative which underwent instantaneous elimination to afford the chloro diene **20** (59%), exclusively exhibiting the *E*-configuration at the newly formed double bond ($J_{H48–H49}$ 15 Hz). Interestingly, the diene **20** exists in both tautomeric forms with a ratio of 91:9 with preference for the *enol* form. Reduction of ketone **20** gave the desired alcohol **21** in 69% yield. The *S-tert* butyl ester **21** should undergo condensation with lithium diethyl methylphosphonate, based on a procedure described by Heathcock[12] to furnish target compound **3**.

In conclusion, we have described the first successful pyranose-based route to the F ring of altohyrtin A and have demonstrated the first steps of a method for the preparation of the halogen-containing side chain of this natural product.

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