Studies Towards the Synthesis of the C29-C51 Fragment of Altohyrtin A

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Abstract: The synthesis of the highly substituted E and F pyran fragment **23** of altohyrtin A **1** from tri-*O*-benzyl-D-glucal **5** is described. The synthesis of a model compound **31** containing the altohyrtin A triene side-chain outlines the proposed strategy for the elaboration of the F pyran.

The spongipyrans are a new family of marine macrolides which exhibit an extraordinary potency as inhibitors of cancer cell growth.[1] This, along with their challenging structure, a 51-carbon chain, 42-membered lactone ring and 6 pyran rings has promoted considerable synthetic interest,[2] culminating in the elegant total synthesis of altohyrtin A (spongistatin 1) **1** by Kishi[3] and altohyrtin C by Evans.[4] We have embarked on a total synthesis of altohyrtin A, the most potent of the spongipyrans. In view of recent publications[5,6] we report here our approach to the synthesis of the highly oxygenated EF pyrans and a strategy for the introduction of the C44-C51 chlorodiene side-chain.

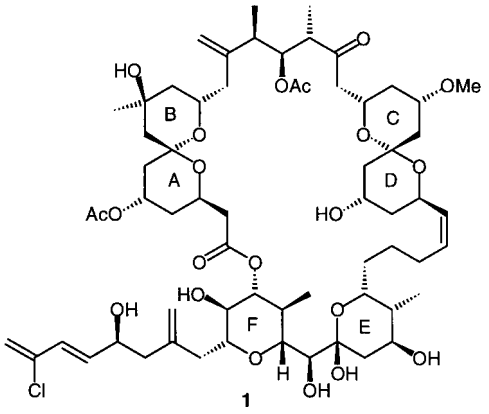
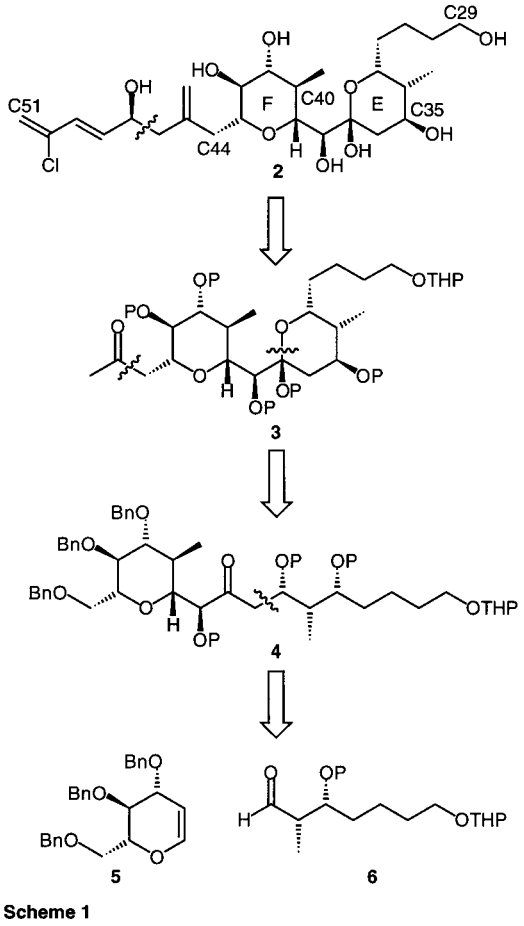


Figure 1

Scheme 1 outlines the synthesis plan. The highly substituted F pyran was to be constructed from readily available tri-*O*-benzyl-D-glucal **5** by the stereoselective introduction of C40[7] methyl group followed by *C*-glycosidation and further manipulation to install the methyl ketone. Stereocontrolled aldol reaction with the C29-C35 aldehyde **6** would provide **4** which could readily be converted to the hemi-acetal thus furnishing both the E and F pyran rings. Selective deprotection-functionalisation of the C44 benzyl group of **4** would allow access to the methyl ketone **3**. In turn **3** could be elaborated by stereocontrolled aldol coupling to furnish the chlorodiene side-chain and thus complete synthesis of the C29-C51 fragment **2**.

From the outset we were attracted by the idea of installing the C40 methyl group *via* stereoselective cyclopropanation of a glucal followed by ring-opening to introduce functionality at C39.[8,9] This would allow us to utilise a readily available carbohydrate starting material with three stereocentres already in place. Treatment of tri-*O*-benzyl-D-glucal **5** under standard Simmons-Smith conditions results in the formation of the cyclopropane from the wrong face. It is thought that the C41 oxygen directs the carbene insertion. Using a non-metal induced carbene formed from the hydrolysis of chloroform gave the desired dichlorocyclopropane **7** in good yield and excellent selectivity (Scheme 2). The selectivity arises due to the steric interaction of the bulky

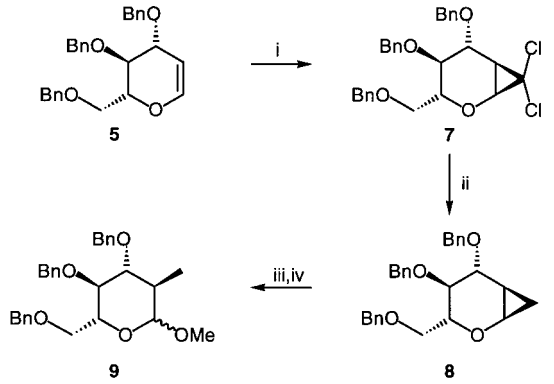


Scheme 1

chlorine atoms with the ring substituents.[8] The cyclopropane **8** was obtained from the reductive dehalogenation of **7**. All attempts to open either the dichlorocyclopropane or the analogous dehalogenated cyclopropane with carbon nucleophiles proved unsuccessful. Cyclopropane **8** could be opened with methanol and *N*-iodosuccinimide to furnish, after reduction of the iodide, the anomeric methoxide **9** in 82% (for 2 steps).[9]

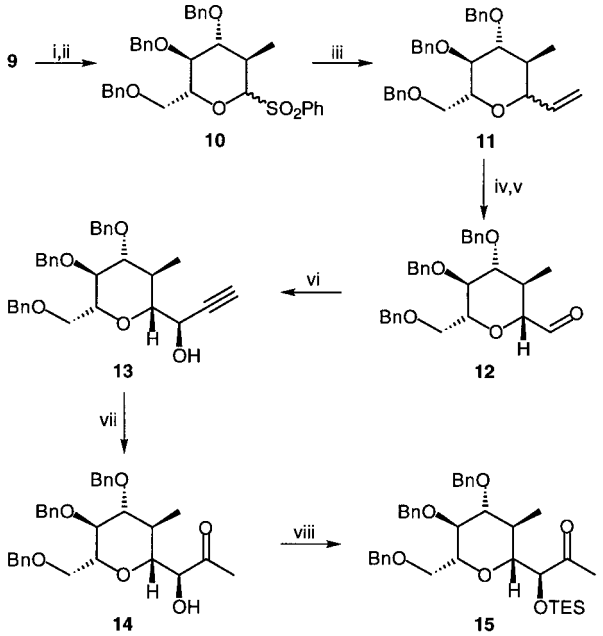
Formation of the anomeric methoxide **9** provided an opportunity to exploit methodology already developed within our group.[10] We have previously shown that anomeric sulfones can be readily synthesised, easily handled and are reactive, versatile reagents in glycosidation and *C*-glycosidation reactions. Conversion of **9** to the sulfone **10** by standard manipulation was followed by displacement with a vinyl zinc reagent to give **11** as an inconsequential mixture of anomers in good yield (Scheme 3).

The C38 alkene **11** was then converted to the methyl ketone **15** by a short sequence of manipulations (Scheme 3). Ozonolysis, followed by silica catalysed epimerisation gave the desired anomeric aldehyde almost exclusively. Stereoselective addition of acetylene magnesium bromide in toluene furnished a mixture of C38 alcohols, favouring the desired *R* configuration **13**. The selectivity was due to chelation of the Grignard reagent with the ring oxygen. The stereochemistry was confirmed by comparison of the Mosher's esters. It is possible to recycle



Scheme 2. *Reagents and conditions*:
i. PhH, 50% NaOH(aq), Et_3NBnCl, $CHCl_3$, rt 5 h, 91%; ii. Bu_3SnH, AIBN, PhH, reflux o/n, 78%; iii. MeOH, NIS, rt 48 h; iv. Bu_3SnH, AIBN, 82% (2 steps)

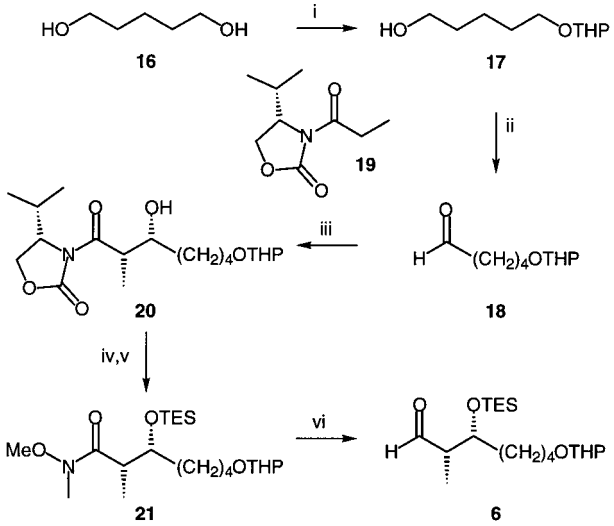
the undesired *S* diastereoisomer *via* Mitsunobu inversion. The alkyne **13** could be hydrolysed in good yield with mercury oxide and sulfuric acid to give the α-hydroxy ketone **14**. Finally, protection of the C38 alcohol as the triethyl silyl ether gave **15** in good yield. The efficiency of the route has been demonstrated by the synthesis of multigram quantities of the methyl ketone **15**.



Scheme 3. *Reagents and conditions*:
i. $PhSSiMe_3$, TMSOTf, DCM, 0°C-rt o/n, 95%; ii. mCPBA, DCM, 0°C-rt 4 h, 94%; iii. $CH_2CHMgBr$, $ZnCl_2$, THF, DCM, rt o/n, 80%; iv. O_3, DCM, PPh_3, -78°C 10 min; v. SiO_2, DCM, rt o/n, 65% (2 steps); vi. CHCMgBr, THF, toluene, -78°C-rt 6 h, 71% (5:1); vii. HgO, H_2O, H_2SO_4, acetone, rt 1 h, 90%; viii. TESOTf, Hünig's base, DCM, -78°C-rt 30 min, 89%

The C29-C35 aldehyde **6** was readily formed from pentanediol **16** in six steps (Scheme 4). Monoprotection as the tetrahydropyranyl ether, followed by oxidation with tetra-*n*-propylammonium perruthenate (TPAP)[11] gave aldehyde **18**. Stereoselective aldol coupling with the Evans auxiliary[12] **19** gave the desired *syn* alcohol **20** which was converted to the protected C29-C35 aldehyde **6** *via* transamination, protection as the triethyl silyl ether and reductive cleavage of the amide.

With both fragments **6** and **15** in-hand the aldol coupling was investigated. Initial studies investigated the use of lithium enolates. The reaction was found to proceed with moderate yield but high selectivity (6:1). Attempts to determine the stereochemistry at C35 *via* Mosher's ester's were inconclusive. Instead the configuration was established by n.O.e. studies of the correspondent hemi-acetal obtained by deprotection of the two TES groups with HF/pyridine. It was shown that the major product **22** had the wrong configuration.



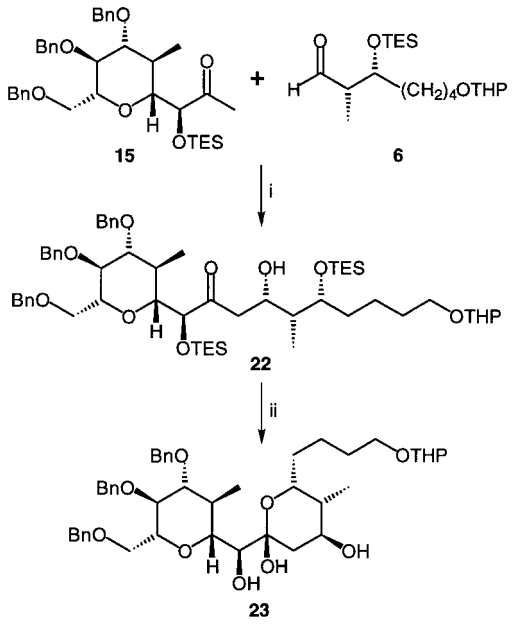
Scheme 4. *Reagents and conditions*:
i. DHP, Dowex 50W X2, 30°C 3 h, 89%; ii. TPAP, NMO, DCM, rt 1h, 75%; iii. **19**, Bu_2BOTf, iPr_2NH, -20°C 3h, 75%; iv. MeO(Me)NH.HCl, DCM, Me_3Al, 0°C-rt 3h, 77%; v. 2,6-lutidine, TESOTf, DCM, -20°C 3 h, 64%; vi. DIBAL-H, THF, -78°C 2 h, 69%

Use of chiral boron enolates was then investigated. Treatment of the methyl ketone **15** with (-)-DIPCl and triethylamine followed by addition of the aldehyde gave the desired diastereoisomer exclusively **22** (Scheme 5).[13] Deprotection and concomitant cyclisation gave the hemi-acetal **23** in excellent yield. Further manipulation of **23** will allow us the introduction of the labile conjugated diene side chain (C45-C51) and complete the synthesis of **2**. The primary C44 benzyl group can be selectively removed utilising either ferric chloride or acetic anhydride with iodine. These strategies are currently under investigation.

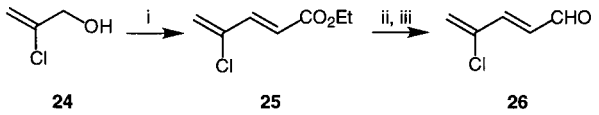
As outlined before (Scheme 1), we envisioned that this labile side chain (C45-C51) could be introduced through a aldol coupling between a methyl ketone at C45 and aldehyde **26**. In order to test the feasibility of this approach it was decided to undertake preliminary studies on a model ketone **28** that could be synthesised from the readily available glucose derivative **27**[14] that mimics the F-pyran moiety in Altohyrtin A.

Aldehyde **26** was synthesised *via* a one-pot Swern-Horner-Wadsworth-Emmons olefination[15] from the commercially available alcohol **24**. Thus, oxidation of **24** and treatment of the resulting aldehyde *in situ* with triethyl phosphonoacetate-K^{t}BuO gave **25** (100% *E*) in 33-36% combined yield from **24**.[16] Reduction of **25** with DIBAL and Swern oxidation of the resulting alcohol led to **26**[17] in 51% combined yield as a very unstable oil that could be stored under Ar at -60 °C for several days without loss of purity.

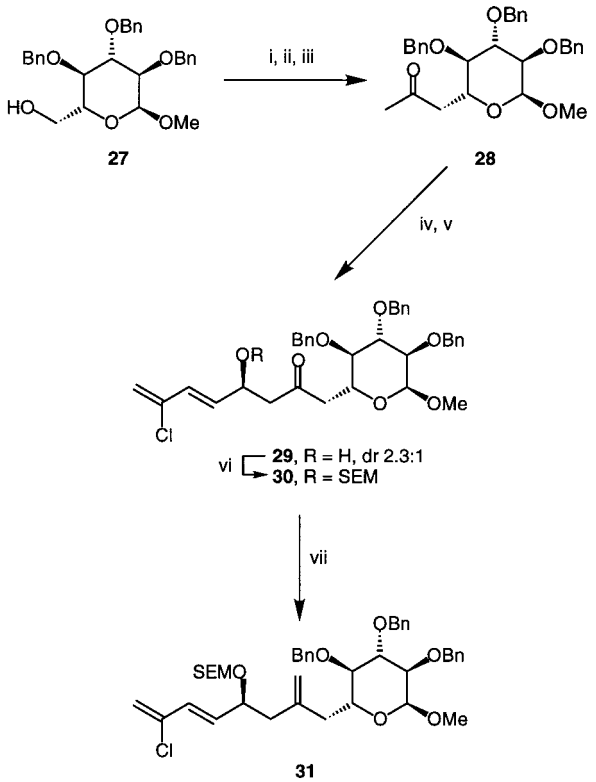
Methyl ketone **28** was obtained from **27** following a three steps sequence. Treatment of **27** with Tf_2O[18] led to the corresponding very stable triflate in 94% yield. Reaction with 2-lithio-2-methyl-1,3-dithiane (88-94 %),[18,19] and deprotection of the resulting dithiane with MeI-$CaCO_3$ (87-91%) gave the desired ketone **28**. The use of a sealed tube in



Scheme 5. *Reagents and conditions*:
i. (-)-DIP-Cl, Et_2O, Et_3N, **6**, -78˚C 3 h -20˚C 14 h, 30% (90% wrt SM); ii. HF/Pyr, THF, rt 36 h, 85%



Scheme 6. *Reagents and Conditions:*
i. ClCOCOCl, DMSO, Et_2O, Et_3N, -78 °C to rt, then $(EtO)_2POCH_2CO_2Et$, K^{t}BuO,Et_2O- DMSO, -78 °C to rt, 33-36% (100% *E*); ii. DIBAL, DCM, -78 °C to -30 ˚C; iii. ClCOCOCl, DMSO, DCM, Et_3N, 51% from **25**



Scheme 7. *Reagents and Conditions:*
i. Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, DCM, -40 ˚C to rt, 94%; ii. 2-methyl-1,3-dithiane (240 mol%), nBuLi (200 mol%),THF, -78 °C to -20 °C, then HMPA and triflate, -78 ˚C, 2 h, 88-94%; iii. MeI (1000 mol%), $CaCO_3$, CH_3CN-H_2O, sealed tube, 55-60 ˚C, 8 h, 87-91%; iv. (+)-DIP-Cl (175 mol%), Et_3N (200 mol%), Et_2O, 0 °C, 30 min, then **26** (200 mol%), -78 °C to -20 °C, 14 h; v. H_2O_2, MeOH, pH = 7 buffer, 3 h, 63% (dr 2.3:1); vi. SEMCl, iPr_2EtN, DCM, rt, 76%; vii. $TiCl_4{\cdot}CH_2Br_2{\cdot}Zn$ (350 mol%), DCM-THF, rt, 2 h, 63%

the deprotection step avoided the sequential additions of MeI as reported before.[20]

Once **26** and **28** were in hand, the boron mediated aldol reaction [(+)-DIP-Cl, Et_3N][21] gave the desired coupling product **29** (diastereomeric ratio 2.3:1 by HPLC) in a 63% yield. The configuration of the new stereogenic centre in the major isomer was established by reaction with (*R*)- and (*S*)-methoxyphenylacetic acids (DCC, DMAP, DCM) to give the corresponding diastereomeric esters, both in 67% yield. Application of the Trost-Mosher method[22] for the determination of the absolute configuration of secondary alcohols, to these diastereomeric esters, confirmed the predicted configuration at C47.

From **29** only the methylenation step was required to complete the synthesis of this model of the C44-C51 side chain of Altohyrtin A. Several methods are described in the literature to achieve such transformation, but due to the expected high instability of the C47 hydroxy group, the mild Oshima-Lombardo reagent was chosen.[23] Protection of the free hydroxy group in **29** as SEM[24] led to **30** in 76% yield. When **30** was treated with 350 mol% of a stock solution of the Oshima-Lombardo reagent ($TiCl_4{\cdot}CH_2Br_2{\cdot}Zn$)[25] the methylenated product **31**[26] was obtained in 63% yield.[6]

In conclusion, we have developed a synthesis of the C29-C44 fragment and the C44-C51 side chain of Altohyrtin A using pyranoside **27** as a model system for the latter strategy. Studies towards the incorporation of this side chain to the C29-C44 fragment already synthesised **23** are currently being carried out in our laboratory.

Acknowledgements

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13. **23:** ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.34-7.21 (15H, m), 5.04 (1H, brs), 4.90 (1H, d, J 11.0 Hz), 4.82 (1H, d, J 11.0 Hz), 4.67 (1H, d, J 11.0 Hz), 4.56 (1H, brs), 4.52 (1H, d, J 11.0 Hz), 4.49 (1H, d, J 12.0 Hz), 4.44 (1H, d, J 12.0 Hz), 4.19 (1H, brd, J 9.0 Hz), 4.10 (1H, brd, J 7.5 Hz), 3.86 (1H, m), 3.77 (1H, m), 3.73-3.70 (2H, m), 3.66 (1H, d, J 10.0 Hz), 3.53 (1H, t, J 8.5 Hz), 3.49-3.43 (2H, m), 3.36-3.33 (3H, m), 3.28 (1H, brt, J 9.5 Hz), 2.24 (1H, d, J 12.0 Hz), 2.14-2.09 (2H, m), 1.81-1.75 (1H, m), 1.72-1.66 (2H, m), 1.65-1.59 (2H, m), 1.58-1.40 (6H, m), 1.33-1.24 (3H, m), 0.99 (3H, d, J 6.5 Hz), 0.82 (3H, d, J 7.0 Hz).
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