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A Novel Fluoride Induced Cyclisation Reaction

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Abstract: Intrinsic diastereoselection in the OsO_4 dihydroxylation of **8** gave a 12:1 mixture of stereoisomers which could be reversed to a 1:8 selectivity by the use of Sharpless AD technology. The acetonides **9** and **10** could be elaborated to ene ester systems **12** and **14** respectively. Both **12** and **14** underwent a peculiar cyclisation reaction to furnish the 5,5-fused ring systems **13** and **15**. © 1998 Elsevier Science Ltd. All rights reserved.

During our synthetic studies towards the total synthesis of the marine macrolide Altohyrtin A[1] **1** (also known as Spongistatin 1[2]), we sought a versatile synthon for the C37-C45 fragment **2** as shown in Figure 1.

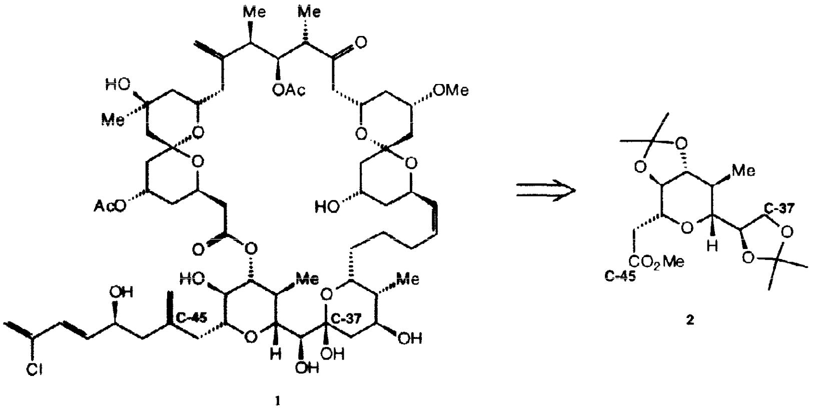
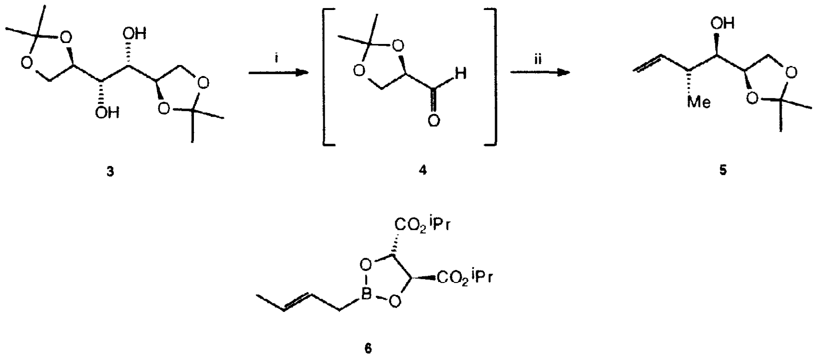


Figure 1

The synthesis of **2** initially followed chemistry developed by Roush,[3,4] whereby D-glyceraldehyde acetonide[5] **4** (produced by oxidative cleavage of D-mannitol diacetonide using sodium metaperiodate in THF) and the chiral (*E*)-crotylboronate (*S*,*S*)-**6** were combined with essentially complete diastereoselectivity to produce the homoallylic alcohol **5**.



i) $NaIO_4$, THF ii) **6**, toluene 4Å molecular sieves (29% overall)

Scheme 1

The homoallylic alcohol **5** was protected as its TBS silyl ether **7** and elaborated to furnish the *trans* α,β unsaturated ester **8** by ozonolysis followed by Wittig reaction with the

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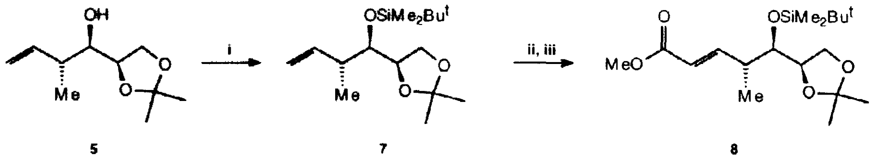
stabilised reagent $Ph_3P{=}CHCO_2Me$. The intermediate aldehyde was not isolated since it was unstable to purification by flash column chromatography.

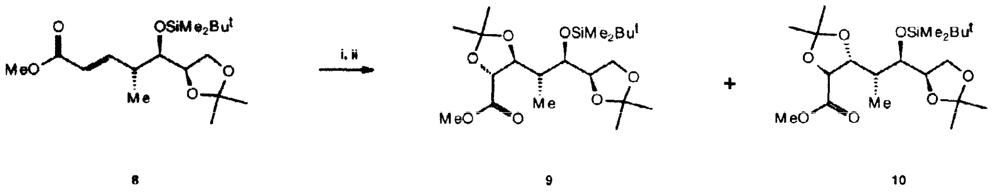


i) $Me_2{}^tBuSiCl$, imidazole, DMF, room temperature, 96%, ii) a) O_3, MeOH / CH_2Cl_2, -78°C, b) Me_2S, iii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, reflux, 80% over 2 steps.

Scheme 2

The ene ester **8** contains three chiral centres and we surmised that the larger δ ($OSiMe_2{}^tBu$) substituent would direct the dihydroxylation in preference to the smaller γ (Me) substituent, thus generating the *cis* diol with the correct stereochemistry for conversion into synthon **2**. However, dihydroxylation using catalytic OsO_4 (0.5 mol%) and NMO as co-oxidant gave a 12:1 ratio of the *cis* diol resulting from approach of the oxidant from the ostensibly more crowded face. The absolute stereochemistry was assigned on the basis of a derived compound (*vide infra*).

For ease of purification the crude diols were not isolated but transformed[6] directly to the acetonides **9** and **10**, which could be separated by flash column chromatography.

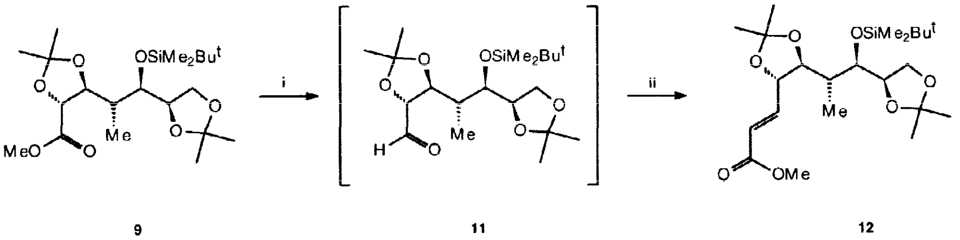


i) OsO_4 (*cat*), NMO, 8:1 acetone / water, ii) $(MeO)_2CMe_2$, acetone, TsOH, 80%.

Ratio **9**:**10** of 12:1

Scheme 3

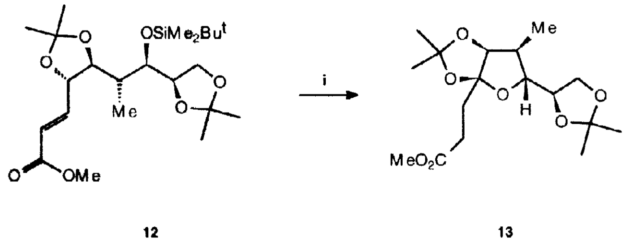
The ester **9** was reduced to the aldehyde **11** using DIBALH. This crude aldehyde was subjected to reaction with the Wittig reagent $Ph_3P{=}CHCO_2Me$, and the ene ester **12** was isolated in 59% yield over the two steps.



i) DIBALH, CH_2Cl_2, -78°C, ii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, reflux, 59% over 2 steps.

Scheme 4

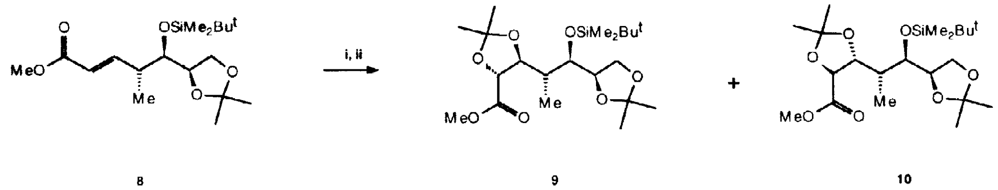
Following deprotection of **12**, intramolecular cyclisation of the resultant oxyanion onto the unsaturated ester **12** was expected to take place to generate the double β C-glycoside synthon **2**. Although this type of cyclisation is well known in the literature,[7,8,9] treatment of **12** with KF / TBAF in THF gave the 5,5 fused bicycle **13** depicted in Scheme 5 as the sole product in moderate yield. The stereochemistry was determined by a series of nOe enhancement experiments, and these studies indicated the stereochemical consequence of dihydroxylation of compound **8**.



i) KF, TBAF, THF, 45%

Scheme 5

In an attempt better to control the stereochemistry of the dihydroxylation reaction the Sharpless AD-mix formulations[10] were examined. Dihydroxylation using the commercially available AD-mix β proved slow, as is usual for ene ester systems.[10,11,12] However by increasing the proportion of $(DHQD)_2PHAL$ to 10 mol%, the amount of OsO_4 to 10 mol%, using 3 equivalents of $K_3Fe(CN)_6$ and K_2CO_3 and finally adding 3 equivalents of $MeSO_2NH_2$ overnight conversion of ene ester **8** took place to furnish a mixture of diols with an impressive reversal of diastereoselectivity resulting in an 8:1 ratio in favour of compound **10** (Scheme 6).

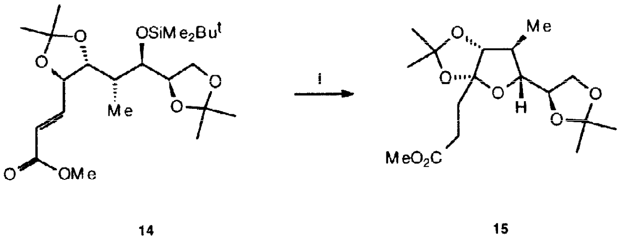


i) $(DHQD)_2PHAL$ (10 mol%), OsO_4 (10 mol%), $K_3Fe(CN)_6$ (3 eq), K_2CO_3 (3 eq) $MeSO_2NH_2$ (3 eq), 1:1 ^{t}BuOH / water, ii) $(MeO)_2CMe_2$, acetone, TsOH, 66%.

Ratio **9**:**10** of 1:8

Scheme 6

The ester **10** was elaborated to the ene ester **14** using similar transformations as depicted in Scheme 4 (57% overall yield). On treatment of compound **14** with TBAF in THF at room temperature cyclisation ensued to give the 5,5-fused bicyclic compound **15** in 30% yield.



i) TBAF, THF, 30%

Scheme 7

At present we surmise that the isopropylidene moiety is responsible for preventing the ene esters **12** and **14** undergoing internal oxyanion conjugate Michael addition reactions. We are currently investigating the employment of alternative protecting groups, and will report these results in due course. Other work is being undertaken to elucidate the mechanism of this surprising cyclisation reaction.

Acknowledgements

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