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Approaches to the C-24 to C-37 Perimeter of Altohyrtin A

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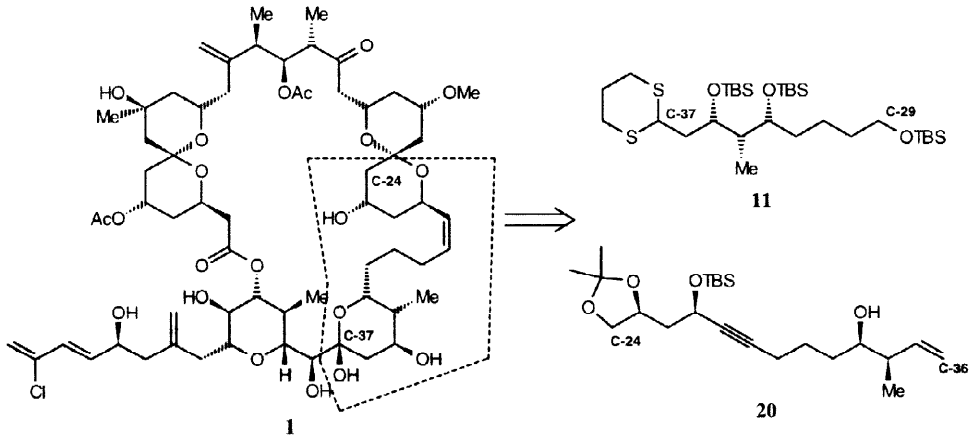
Abstract : Versatile synthetic sequences are described for the C-24 to C-37 perimeter of Altohyrtin A **1**. In addition the diastereoselectivity for the reduction of the β-alkoxy ynone system **15** using various hydride reagents is described.

There is increasing interest in the literature[1] concerning synthetic approaches towards the marine macrolide Altohyrtin A[2] since it possesses remarkable activity *in vitro* towards a broad spectrum of human cancer cell lines.



Scheme 1

Herein we report our synthetic efforts towards a versatile approach to the C-24 to C-37 perimeter. Scheme 1 shows two compounds **11** and **20** which are key building blocks in our study. The synthesis of the 2-substituted dithiane **11** is shown in Scheme 2. 5-*tert* Butyldimethylsilyloxy pentanal was readily prepared in multigramme quantities from pentane-1,5-diol by mono-protection and oxidation employing PDC. A Brown crotylation[3] to generate the homoallylic alcohol **3** proceeded in moderate yield and in 86% diastereoselectivity as judged by derivatisation to afford the *O*-acetyl mandelate esters.[4] Derivatisation to the *O*-BOC derivative **4** set the stage for a Bartlett iodocyclisation[5] as popularised by Smith *et al.*[6] The diastereoselectivity of the iodocarbonates **6**:**5** was determined as 15.6:1 by the method outlined by Smith.[6] Mild methanolic hydrolysis of the iodocarbonate **6** provided epoxide **8** and trace quantities of the diol **7**. The iodocarbonates were not isolated but transformed directly to the epoxide **8**. The epoxide was protected as the bis silyl derivative **9**. 2-Lithio-1,3-dithiane[7] was added to the epoxide **9** to give the 2-substituted dithiane **10**. Protection of the secondary alcohol gave the tris-TBS silyl ether **11**. The presence of DMPU was crucial for the successful addition of 2-lithio-1,3-dithiane to the epoxide **9**.

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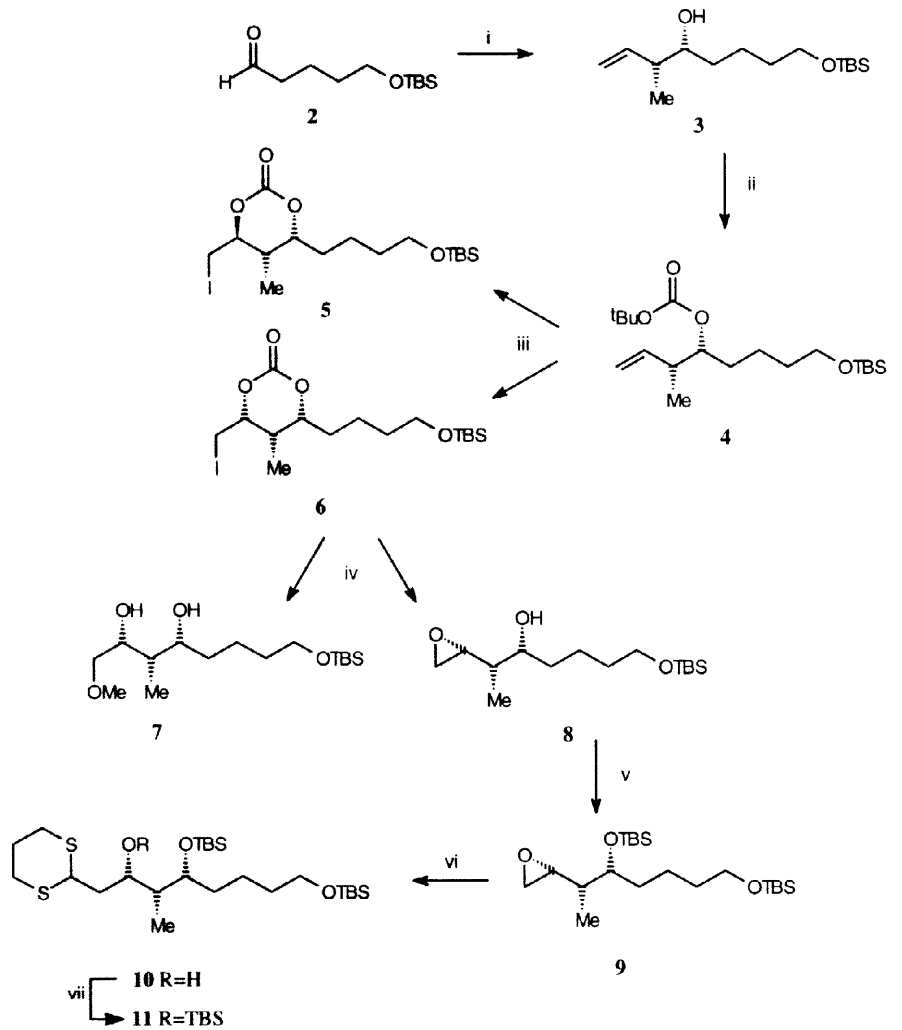
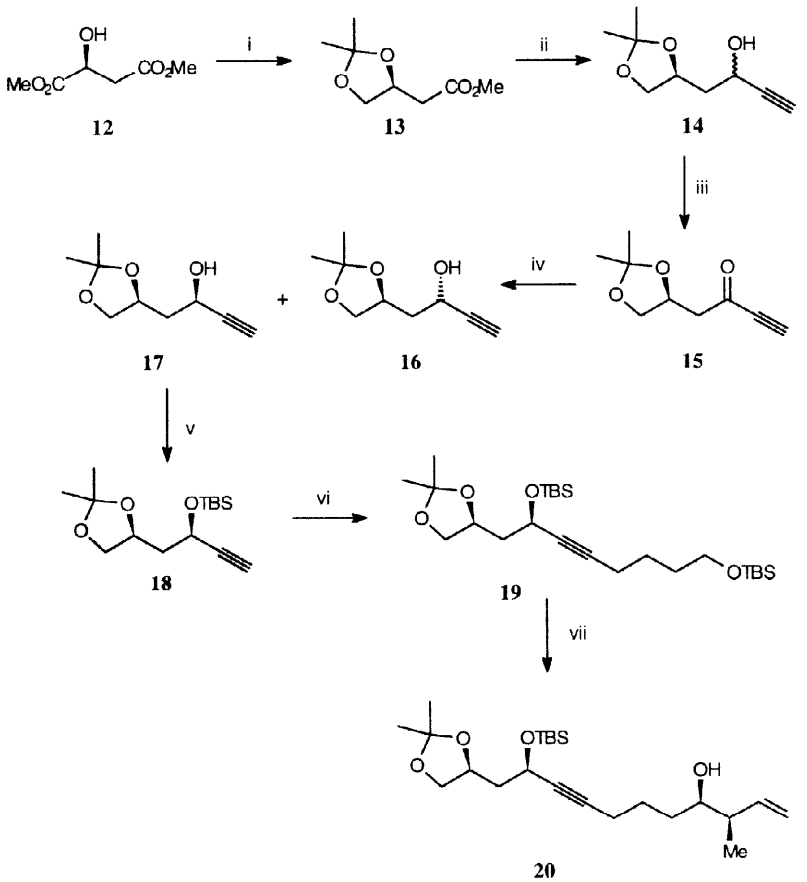


Scheme 2

Reagents and Conditions : i) (*Z*)-$CH_3CH{=}CHCH_2B(Ipc)_2$, THF, -78°C, (60%), ii) a) *n*-BuLi, Et_2O, -78°C; b) BOC-ON, THF, -78°C to r.t., (60%); iii) IBr, toluene, -80°C to -85°C, iv) K_2CO_3, MeOH, 6 hours; v) TBSOTf, imidazole, DMF, 0°C to r.t., (100%); vi) 2-lithio-1,3-dithiane, THF, DMPU, -78°C to r.t., (75%); vii) TBSOTf, imidazole, DMF, r.t., (100%).

The synthesis of the alkyne **20** is shown in Scheme 3. Selective reduction of *S*-malic acid dimethyl ester[8] and acetonide protection of the resulting diol gave **13** in good yield and on multigramme scale. DIBALH reduction of **13** furnished the intermediate aldehyde and subsequent addition of ethynyl magnesium bromide gave a 1:1 mixture of diastereomers **14**[9]. Dess Martin periodinane mediated oxidation[10] of the mixture of alcohols **14** gave the ynone **15** which was subjected to a variety of hydride reducing agents to generate a mixture of propargylic alcohols **16** and **17**. The results are summarised in Table 1. No selectivity was observed with $NaBH_4$ or L-Selectride® but good selectivity of the *syn* alcohol product could be obtained when LiI and $LiAlH_4$[11] at -100°C, $Zn(BH_4)_2$[12] at 0°C or $Zn(BH_4)_2$ at -30°C was used. The best selectivity and yield for formation of **17** was observed when the Corey (*R*)-oxaborilidine[13] was used at -30°C. Protection of the alcohols **16** and **17** as their TBS ethers enabled separation by flash column chromatography. n-BuLi mediated deprotonation of the

alkyne **18** followed by alkylation using $ICH_2CH_2CH_2CH_2OTBS$ (prepared in 2 steps from butan-1,4-diol by monoprotection followed by functional group manipulation of the free alcohol to the iodide[14]) gave **19** in good yield. Chemoselective desilylation of the primary TBS ether followed by a Dess Martin oxidation of the primary alcohol to the aldehyde and subsequent Brown crotylation[3] gave the advanced intermediate **20**. Derivatisation of the homoallylic alcohol to the *O*-acetyl mandelate ester[4] enabled the enantiomeric excess of the crotylation reaction to be established as >95%.



Scheme 3

Reagents and Conditions : i) a) $BH_3.SMe_2$ complex, THF, $NaBH_4$, (84%), b) acetone, *p*-TsOH (cat.), anhydrous $CuSO_4$, (75%); ii) a) DIBALH, CH_2Cl_2, -78°C, (87%), b) BrMgC≡CH, THF, -40°C to -10°C (69%); iii) Dess Martin Periodinane, CH_2Cl_2, r.t., (92%); iv) Reducing agent (see table 1) v) TBSCl, imidazole., DMF, 0°C to rt, (91%); vi) a) *n*-BuLi, -40°C THF:DMPU (6:1), b) $ICH_2CH_2CH_2CH_2OTBS$, (88%); vii) a) $(HF)_n.py$, THF, r.t., (72%), b) Dess Martin Periodinane, CH_2Cl_2, (88%), c) (*Z*)-$CH_3CH{=}CHCH_2B(Ipc)_2$, THF, -78°C, (59%).

Reagent	Temperature °C	Yield %	Ratio *Syn:Anti*
$NaBH_4$	0	78	50:50
L-Selectride®	-78	84	50:50
LiI, $LiAlH_4$[11]	-100	52	81:19
$Zn(BH_4)_2$[12]	0	75	84:16
$Zn(BH_4)_2$[12]	-30	87	88:12
(*R*)-Oxaborilidine[13]	-30	89	95:5

Table 1

In conclusion, we have demonstrated versatile syntheses of two key building blocks which can be used in the construction of the marine macrolide Altohyrtin A. Synthetic efforts are now in place to elaborate compound **20** and to couple the dithiane intermediate **11**; the results of these studies will be reported elsewhere.

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