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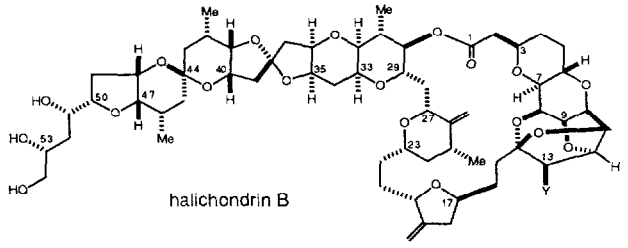
Synthetic Studies towards Halichondrins: Synthesis of the C.27-C.38 Segment

Thomas D. Aicher, Keith R. Buszek, Francis G. Fang, Craig J. Forsyth, Sun Ho Jung, Yoshito Kishi*, Paul M. Scola

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, U.S.A.

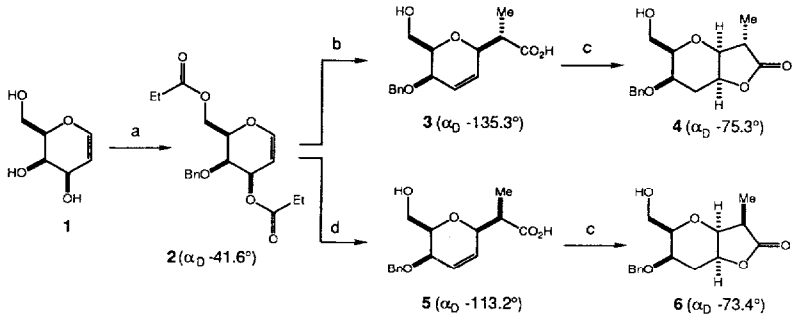
Abstract: *An efficient synthesis of the C.27-C.38 segment of halichondrins is accomplished, using the Ireland-Claisen rearrangement, Ni(II)/Cr(II)-mediated coupling and Michael reactions as the key steps.*

Halichondrins are a class of polyether macrolides isolated originally from a marine sponge *Halichondria okadai* Kadota.[1,2] Halichondrins, epecially halichondrin B and homohalichondrin B, exhibit an extraordinary *in vitro* and *in vivo* antitumor activity. However, the very limited supply of halichondrins from natural sources has prevented further evaluation of their potential clinical application thus far.[2] Their intriguing and challenging structural features, coupled with this fact, encouraged synthetic efforts towards this class of natural products.[3,4] In this paper, we report an efficient synthesis of the C.27-C.38 segment of the halichondrins.



We noticed that the Ireland-Claisen rearrangement[5] of D-galactose glycal was exceptionally well suited for the synthesis of the C.30-C.37 portion of halichondrins, where the C.3 stereochemistry of D-galactose should dictate the C.32 stereochemistry[6] of halichondrins and the stereochemistry of the silyl enolether generated from the C.3 propionate of D-galactose glycal in the presence of HMPA should dictate the C.31 stereochemistry of halichondrins.[7] We recognized a possibility to use the 3,4,6-*O*-tripropionate of the glycal for the Ireland-Claisen rearrangement, which could eliminate three steps required for differentiation of the hydroxyl groups. Experimentally, however, the relative rates for the first and second Ireland-Claisen rearrangements were found to be similar. Therefore, we needed to selectively protect the C.4 hydroxyl group of the glycal. The Ireland-Claisen rearrangement was carried out under standard conditions to yield the expected product in approximately 8:1 stereoselectivity (Scheme 1). This mixture was then subjected to an iodolactonization, followed by reductive removal of the iodine, to give the γ-lactone 4 (mp 119-120 °C). The minor stereoisomer of the Ireland-Claisen

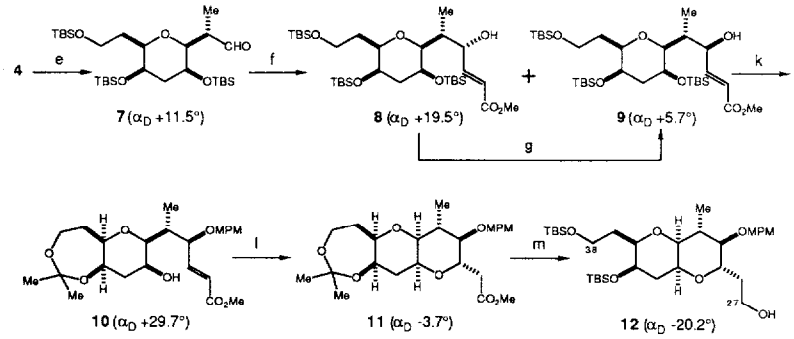
rearrangment was removed either by chromatography at the stage of iodo-γ-lactone or by recrystallization at the γ-lactone stage. As expected,[7] the Ireland-Claisen rearrangement of the silyl enolether generated in the absence of HMPA yielded **5** as the major product (with stereoselectivity = 5:1), which was converted into the γ-lactone **6** (mp 142-3 °C). It is intriguing to note that this substance perfectly matches the C.45-C.52 portion of the norhalichondrins.



Scheme 1. Reagents and Reaction Conditions
(a) 1. TBSCl/imidazole/DMF/RT. 2. BnBr/NaH/THF-DMF (10:1)/0 °C→RT. 3. TBAF/THF/RT. 4. $(EtCO)_2O/Et_3N/CH_2Cl_2$/RT. (b) 1. LiHMDS/TBSCl/HMPA-THF (1:9)/-78 °C→0 °C, followed by reflux/C_6H_6. 2. 1N NaOH/H_2O-THF (1:1)/RT. (c) 1. I_2-KI/sat. $NaHCO_3$/RT, followed by silica gel chromatography (EtOAc-hexanes). 2. *n*-Bu_3SnH/AIBN/reflux/C_6H_6. (d) 1. LDA/THF/-78 °C, followed by TBSCl quench then reflux/C_6H_6. 2. same as step b.2.

Using routine synthetic reactions, the γ-lactone **4** was converted into the aldehyde **7**. The C.29-C.30 bond formation between the aldehyde and the β-position of acrylate was efficiently realized by the Ni(II)/Cr(II)-mediated reaction[8], to form γ-hydroxy-*trans*-acrylates in 90-95% yield (Scheme 2). This example demonstrates the uniqueness of this coupling reaction. However, it also shows its current limitation; the product formed was approximately a 2:1 mixture of the two possible diastereomers, favoring the desired stereoisomer. There is a distinct possibility that the stereochemical outcome of this coupling reaction could be controlled by using a suitable ligand. We have made some efforts along this line but have met with only limited success thus far. The minor, undesired alcohol was subjected to the Mitsunobu procedure[9] to invert the stereochemistry.

After protection of the allylic alcohol as a *p*-methoxyphenylmethyl (MPM) group, deprotection of the silyl groups, and protection of two out of the three resultant alcohols as an acetonide, the Ni(II)/Cr(II)-coupling product was subjected to a Michael reaction in the presence of $(n\text{-}Bu)_4NF$ (TBAF) in THF at room temperature, to furnish the desired cyclized product with better than 20:1 stereoselectivity. It is interesting to note that the Michael reaction of the corresponding triol initially yielded the desired diastereomer as the major product but it rapidly isomerized to the undesired diastereomer. Using routine synthetic reactions, this Michael product was transformed into the C.27-C.38 segment **12**[10].



Scheme 2. Reagents and Reaction Conditions
(e) 1. DIBAL/THF/-78 °C. 2. *p*-TsOH/MeOH/RT. 3. $Tf_2O/Py/CH_2Cl_2$/RT, followed by treatment with NaCN/DMF/RT 4. DIBAL/CH_2Cl_2/-78 °C, followed by reduction with $NaBH_4$/MeOH/0 °C. 5. $H_2/Pd(OH)_2$ on C/MeOH/RT. 6. EtSH/BF_3•Et_2O/CH_2Cl_2/RT. 7. TBSOTf/Et_3N/CH_2Cl_2/RT. 8. $I_2/NaHCO_3/H_2O$-acetone. (f) 1. **7** + *trans*-ICH=$CHCO_2Me$[16]/$NiCl_2$(1.0%)-$CrCl_2$/THF/RT, followed by silica gel chromatographic separation (EtOAc-hexanes). (g) 1. PPh_3/*p*-NO_2-$PhCO_2H/Et_2O$-toluene (2:1)/RT, followed by EtO_2CN=NCO_2Et treatment. 2. K_2CO_3/MeOH/RT. (k) 1. MPMOC(=NH)CCl_3/BF_3•Et_2O/CH_2Cl_2/0 °C. 2. HF•Py/MeCN/RT. 3. $MeC(OMe)_2Me$/PPTS/CH_2Cl_2/RT. (i) 1. TBAF (Aldrich)/THF/RT. (m) 1. PPTS/MeOH/RT. 2. TBSOTf/Et_3N/CH_2Cl_2/RT. 3. LAH/Et_2O/0 °C.

The C.27-C.38 segment **12** was also synthesized from methyl L-glucopyranoside (Scheme 3). Using the literature method known for its antipode[11], methyl L-glucopyranoside[12] was converted into the methylated compound **13**, which was transformed to the tetraacetate, then subjected to *C*-glycosidation with CH_2=CHCH(OAc)TMS[13], to yield the expected β-*C*-glycoside **15** selectively[14]. This substance was then converted to the C.27-C.38 segment, which was proven to be identical with the substance obtained *via* the Ireland-Claisen rearrangement route. Primarily because of the non-stereoselectivity or the disfavored stereoselectivity observed for steps p.1 and q.1, the overall efficiency of this route was far less than that from the Ireland-Claisen rearrangement, yet this route, coupled with the Ireland-Claisen rearrangement route, provided firm evidence to assign the stereochemistry of the C.27-C.38 segment **12**. Namely, the Ireland-Claisen rearrangement route utilized the three chiral centers of D-galactose glycal to produce the γ-lactone **4**. Thus, the stereochemistry at the C.32, C.33, C.35 and C.36 positions can be assigned as shown without any doubt. On the other hand, the *C*-glycosidation route utilized the four stereocenters of methyl L-glucopyranoside to produce the *C*-allyl product **15**. Thus the C.29, C.30, C.31, C.32 and C.33 stereocenters of this substance can be assigned as shown. The fact that both routes gave the same product established the stereochemistry of the C.27-C.38 segment unambiguously.

The C.27-C.38 segment thus synthesized has recently been successfully utilized for the total syntheses of the halichondrin **B** series.[15]

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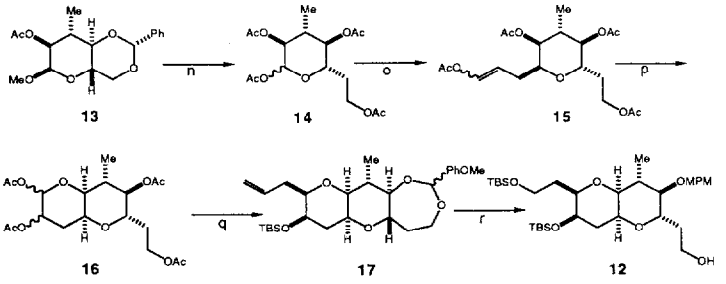

Scheme 3. Reagents and Reaction Conditions
(n) 1. NBS/CCl_4/$BaCO_3$/77 °C. 2. NaCN/DMSO/70 °C. 3. DIBAL/CH_2Cl_2/-78 °C, followed by reduction with $NaBH_4$/MeOH/0 °C. 4. $Ac_2O/BF_3{\cdot}Et_2O$/RT. (o) 1. CH_2=CHCH(OAc)TMS[13]/$BF_3{\cdot}Et_2O$-TMSOTf/MeCN/0 °C→RT, yielding a 1:1 E:Z mixture. (p) 1. OsO_4/NMO/H_2O-acetone (1:9)/RT[17], yielding a 1:1 mixture of C.35 alcohols. 2. K_2CO_3/MeOH/RT. 3. $Ac_2O/HClO_4$/RT. (q) 1. CH_2=$CHCH_2TMS/BF_3{\cdot}Et_2O$-TMSOTf/MeCN/0 °C→RT, yielding a ca. 10:1 C.36 diastereomeric mixture, favoring the undesired product. 2. O_3/CH_2Cl_2/MeOH then Me_2S/-78 °C→RT. 3. $NaBH_4$/MeOH/0 °C. 4. TBSCl/imidazole/CH_2Cl_2/RT. 5. NaOMe/MeOH/RT. 6. *p*-MeOPhCH$(OMe)_2$/PPTS/CH_2Cl_2/RT. 7. TBSCl/imidazole/CH_2Cl_2/RT. (r) DIBAL/toluene/-78 °C.

References and Footnotes

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