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Synthetic Studies of the Ionophore Antibiotic Zincophorin. 2. Iterative Sigmatropic Construction of the C_1-C_{11} Subunit

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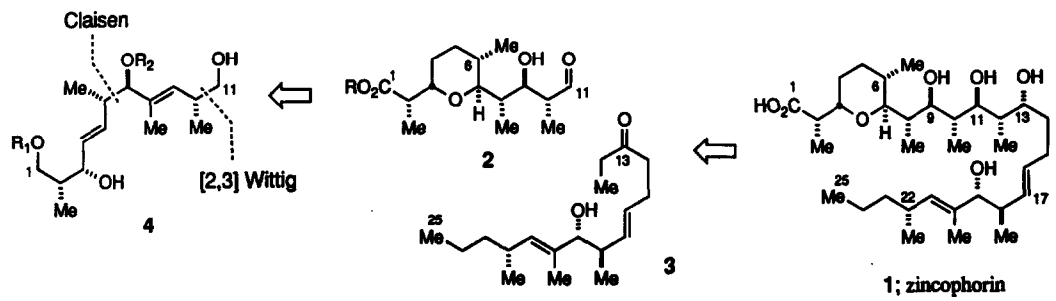
Summary: Advanced intermediates **22** and **23**, *representing the C_1-C_{11} subunit of the ionophore zincophorin, have been prepared by a scheme incorporating sequential glycolate Claisen and [2,3] Wittig rearrangements to establish the key structural and stereochemical elements of the title compound.*

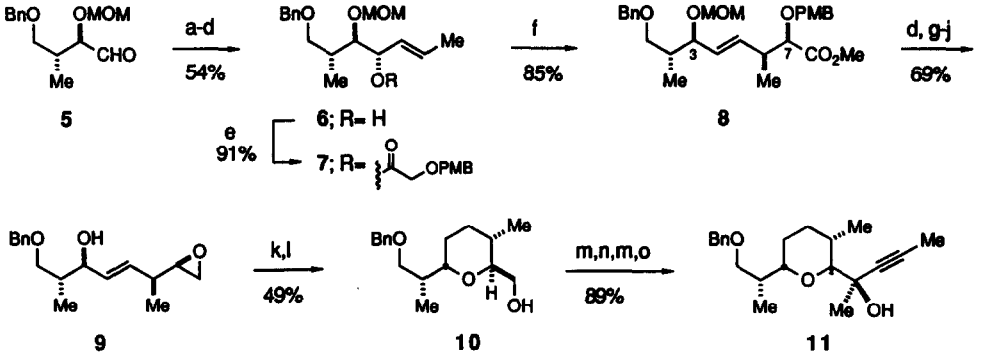
Zincophorin, **1**, an antibiotic isolated from fermentations of *Streptomyces griseus*, exhibits remarkable ionophoric properties, including the ability to selectively sequester divalent cations.[1] Danishefsky and co-workers have recently described an elegant total synthesis of zincophorin, based on the stereocontrolled Julia coupling of advanced intermediates corresponding to the C_1-C_{16} and C_{17}-C_{25} fragments of **1**.[2] Our interest in the application of diastereoselective sigmatropic reactions to the synthesis of polyketide-derived natural products[3] led us to consider an alternative approach to zincophorin, in which the coupling of intermediates **2** and **3**, corresponding to the C_1-C_{11} and C_{12}-C_{25} subunits respectively, would establish the key structural and stereochemical elements of the parent ionophore. Recently we reported the asymmetric preparation of **3**,[4] wherein the carbon skeleton of the target ketone was developed by an iterative sigmatropic sequence consisting of a diastereoselective [2,3] Wittig rearrangement of a tertiary allylic ether[5] and a subsequent orthoester Claisen rearrangement. Our analysis of the C_1-C_{11} subunit of zincophorin suggested that a conceptually similar scheme, involving sequential enolate Claisen and [2,3] Wittig rearrangements, could be employed for the construction of intermediate **2**. We now record the successful realization of this strategy, culminating in the synthesis of a C_1-C_{11} precursor to zincophorin.



Addition of propynyl lithium to the readily available **(2R,3R)-5**[6] afforded a 3:1 mixture of diastereomeric alcohols, which was subjected to MnO_2 oxidation, chelation-controlled reduction and $LiAlH_4$ reduction of the alkynyl group to give the E allylic alcohol **6** ($[\alpha]_D$= -2.7°, c=0.75, $CHCl_3$) as a single diastereomer.[7] Acylation of **6** afforded the *p*-methoxybenzyl-protected glycolate **7**, which underwent enolate Claisen rearrangement[3a,b] to yield, as the only isolated product, ester **8** ($[\alpha]_D$= +21.8°, c= 0.74, $CHCl_3$). Construction of the tetrahydropyranyl nucleus was achieved using a scheme previously employed by Nicolaou for the synthesis of indanomycin.[8] Ester **8** was transformed to epoxide **9** ($[\alpha]_D$= -51.4°, c= 0.33, $CDCl_3$), whereupon hydrogenation of the C_4-C_5 olefin and acid-catalyzed cyclization gave tetrahydropyranyl alcohol **10** ($[\alpha]_D$=

+28.0°, c= 4.62, $CDCl_3$). In anticipation of a final sigmatropic rearrangement to complete the carbon framework of our C_1-C_{11} target, tertiary alcohol **11** was prepared from **10** by a four-step sequence consisting of 1) perruthenate oxidation of **10** to the aldehyde, 2) addition of propynyl Grignard reagent, 3) reoxidation of the resulting propargyl alcohol and 4) chelation-controlled addition of methyl Grignard reagent.

Scheme 1



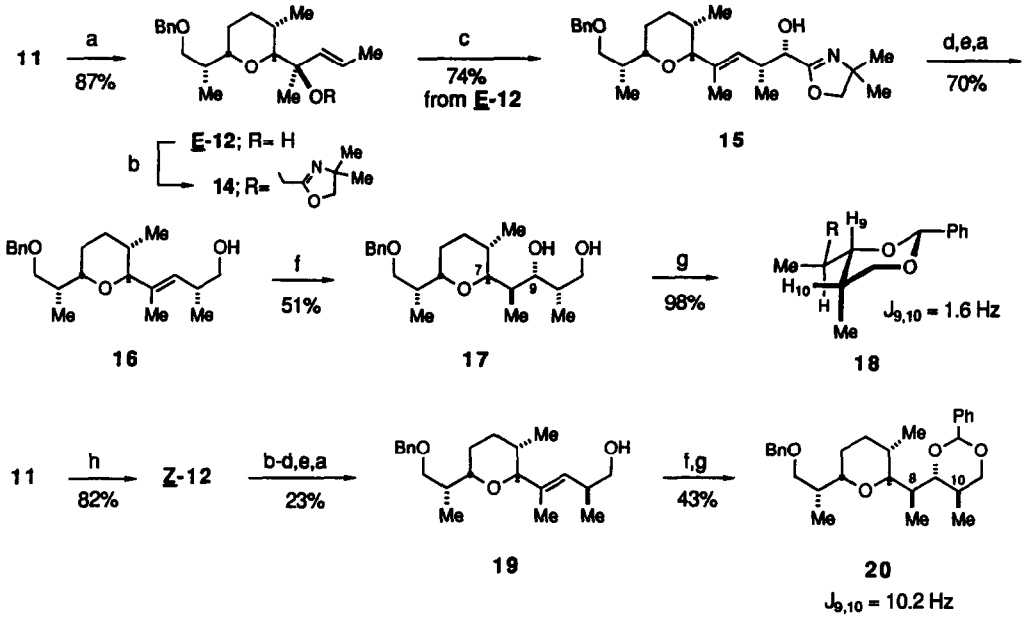
(a) MeCC-Li, THF; (b) MnO_2, CH_2Cl_2; (c) $ZnCl_2$, $NaBH_4$, Et_2O; (d) $LiAlH_4$, THF, 0->25°C; (e) *p*-$MeOC_6H_4CH_2OCH_2CO_2H$, DCC; (f) i) LDA, $(Me)_3SiCl$, THF, -78->0°C, ii) aq NH_4Cl, iii) CH_2N_2, Et_2O; (g) TsCl, pyridine; (h) aq HCl, THF; (i) $Ce(NH_4)_2(NO_3)_6$, MeCN; (j) NaOMe, MeOH; (k) Pd/C, H_2, EtOAc; (l) CSA, CH_2Cl_2; (m) TPAP, NMO, CH_2Cl_2; (n) MeCC-MgBr, THF; (o) MeMgBr, THF, -78°C.

Final elements of the C_1-C_{11} carbon framework were introduced by means of the [2,3] Wittig rearrangement of tertiary allylic ether **14** (Scheme 2). The requisite E olefin of **14** was established by $LiAlH_4$ reduction of propargyl alcohol **11**, whereupon alkylation of **E-12** with chloromethyloxazoline **13** afforded the desired [2,3] Wittig substrate. Earlier reports have demonstrated that the [2,3] Wittig rearrangement of α-alkoxy, tertiary allylic ethers is generally accompanied by excellent simple and induced diastereoselection;[3c,5] however, the stereochemical consequences for heterocyclic substrates remain unexplored. We were gratified to observe that treatment of **14** with base resulted in smooth [2,3] rearrangement, yielding a single product, oxazoline **15**.[9] Reductive cleavage of the oxazoline yielded the corresponding diol, which was further transformed to alcohol **16** ($[\alpha]_D$= +46.4°, c= 0.85, $CDCl_3$) by periodate oxidation and hydride reduction of the resulting aldehyde.[10]

To install the final stereochemical elements of our projected C_1-C_{11} intermediate we examined procedures for effecting the stereocontrolled hydration of olefin **16**. Reaction of **16** with BH_3-THF proceeded cleanly to give diol **17** ($[\alpha]_D$= 10.0°, c= 0.05, $CDCl_3$), a diastereofacial selectivity opposite to that required for installation of the C_8-C_9 stereochemistry of zincophorin. ^1H NMR analysis of the derived benzylidene **18** reveals a 1.6 Hz coupling between the C_9 and C_{10} protons, indicative of an axial-equatorial relationship which can only be accommodated by a *syn* orientation of C_9 and C_{10} substituents. In retrospect, the stereochemistry of hydroboration for **16** is consistent with both the Kishi-Houk[11] and Still[12] models for allylic stereocontrol in the hydroboration of trisubstituted acyclic olefins. Of considerable interest was the hydroboration of the C_{10} epimer **19**, for which the Still and Kishi-Houk models predict disparate stereochemical consequences. Hydroboration of **19**, prepared from **Z-12** by a sequence similar to that employed for **16**, afforded a single diol, which was transformed to benzylidene **20**. The H_9-H_{10} coupling constant (10.2 Hz) requires an *anti* relationship between the C_9 and C_{10} substituents of **20**; thus, the stereochemical outcome for hydroboration of both **16** and **19** is consistent with Still's model, suggesting that the tetrahydropyranyl system and specifically the C_7 configuration, is the dominant stereocontrol element.[12] The hydroboration of **19** stands in contrast to recent studies from our

laboratories involving similarly functionalized acyclic substrates,[13] for which hydroboration is directed by the allylic center appended to the less-substituted olefinic carbon, as predicted by the Kishi-Houk models.

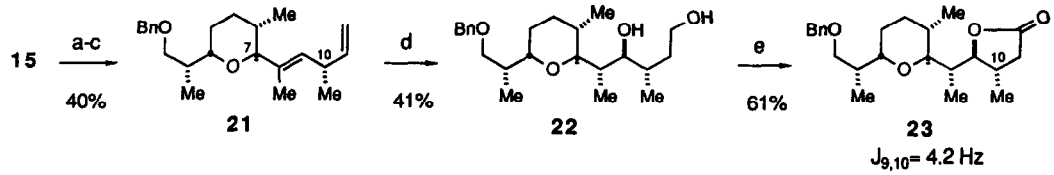
Scheme 2



(a) $LiAlH_4$, THF; (b) 2-chloromethyl-4,5-dihydro-4,4-dimethyloxazole (13), KH, DME; (c) *n*-BuLi, THF, -78°; (d) CF_3CO_2H (1 eq), H_2O (1 eq), THF, then $LiAlH_4$; (e) $NaIO_4$, acetone-H_2O; (f) BH_3-THF, 25°, then H_2O_2, aq NaOH; (g) C_6H_5CHO, CSA, C_6H_6; (h) Pd-Pb/$CaCO_3$, H_2, MeOH.

In an effort to employ the C_{10} stereochemistry of **16** to direct the facial selectivity of additions to the C_8-C_9 olefin, we next examined strategies for intramolecular reagent delivery (Scheme 3). Attempts to effect intramolecular hydrosilation[14] of **16** were unsuccessful and led to recovered starting material. To access a system for effecting intramolecular delivery[15] of a hydroborating reagent, diene **21** ($[\alpha]_D$= 31.0°, c= 0.100, $CDCl_3$) was prepared in three steps from **15**. Treatment of **21** with mono- and dialkylboranes resulted only in hydroboration of the terminal olefin; however, reaction with BH_3-THF afforded diol **22** ($[\alpha]_D$= 20.0°, c= 0.200, $CDCl_3$), possessing the desired C_8-C_9 configuration of zincophorin. The stereochemistry of **22** was established by the oxidation to lactone **23** ($[\alpha]_D$= 16.7°, c= 0.090, $CDCl_3$); the H_9-H_{10} coupling constant (4.2 Hz) for **23** is consistent with a *trans*-substituted butyrolactone,[16] confirming an *anti* relationship of C_9 and C_{10} substituents.

Scheme 3



(a) CF_3CO_2H (1 eq), H_2O (1 eq), THF, then $LiAlH_4$; (b) $NaIO_4$, acetone-H_2O; (c) $Ph_3P{=}CH_2$, THF; (d) BH_3·THF, 0->25°C then H_2O_2, aq NaOH; (e) Ag_2CO_3-Celite, PhH.

The construction of zincophorin intermediates **22** and **23** via sequential enolate Claisen and [2,3] Wittig rearrangements demonstrates the synthetic utility of a stereorational, iterative sigmatropic strategy which can be extended to a host of other polyketide-derived targets. The advanced precursors to the C_1-C_{11} subunit of **1** described herein can be transformed into derivatives of aldehyde **2**, and suggest previously unconsidered opportunities for final assembly of zincophorin, including the potential for lactone **23** to serve as the nucleophilic component in condensations with electrophilic C_{12}-C_{25} subunits to establish the C_{11}-C_{12} bond of the ionophore.

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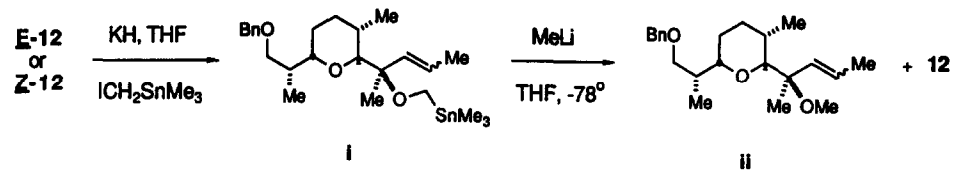

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