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Approach to the Synthesis of Cladiell-11-ene-3,6,7-triol

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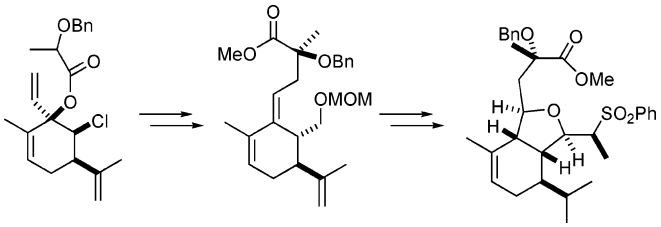
ABSTRACT



The synthesis of an advanced intermediate in the synthesis of the title compound has been achieved. Key steps include an Ireland–Claisen rearrangement to install the C7 tertiary alcohol stereocenter, an S_N2' reaction of an alkoxymethyl Cu reagent, and a diastereoselective Re-catalyzed allylic alcohol transposition.

The 2,11-cyclized cembranoids constitute a large class of marine-derived diterpenoids, some of which have been reported to possess anticancer activity in vitro.[1] Most members of this family of compounds contain a cis-fused hydroisobenzofuran bicycle (Figure 1). Since the first synthesis of deacetoxyalcyonin acetate by Overman and MacMillan in 1995,[2,3] several other members of this family have been synthesized, including ophirin B,[4] astrogorgin,[4] briarellins E and F,[5] 11-acetoxy-4-deoxyasbestinin D,[6] alcyonin, cladiell-11-ene-3,6,7-triol, and sclerophytin A.[7,8]

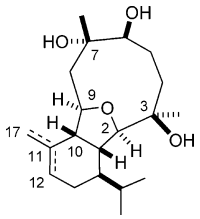


Figure 1. Cladiell-11-ene-3,6,7-triol (**1a** Δ^{11-12}). Sclerophytin A (**1b** Δ^{11-17}).

Sclerophytin A (**1b**) was reported to exhibit growth inhibitory activity toward the L1210 leukemia cell line at 1.0 ng/mL. The originally formulated structure of sclerophytin A was corrected by independent total syntheses by the Overman and Paquette groups.[7−9] Cladiell-11-ene-3,6,7-triol (**1a**) is the Δ^{11-12} isomer of sclerophytin A. Overman has demonstrated that **1a** can be photochemically converted to **1b**, so a synthesis of **1a** also constitutes a formal synthesis of **1b**.

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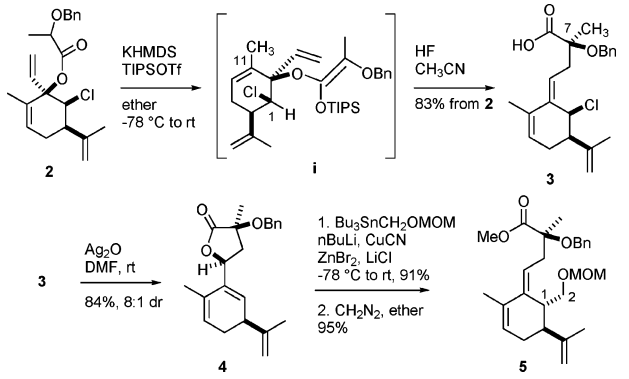
We have been interested in preparing several of the 2,11-cyclized cembranoids by total synthesis. For those targets lacking stereocenters at C7 and/or C8, we have pursued a cycloaldol approach.[10] Our approach to a cladiellene triol, which possesses a 3° alcohol stereocenter at C7, employs the Ireland−Claisen rearrangement.[11] We felt that the rearrangement could be productively employed both to establish the stereochemistry at C7 and to provide a functional handle for formation of the tetrahydrofuran ring via the C9−C10 alkene.

Treatment of ester **2** (available in three steps from (*S*)-(+)-carvone)[12] with KHMDS and TIPSOTf afforded a single stereoisomeric product **3** possessing the *Z*-alkene and the (*S*)-stereochemistry at C7 (Scheme 1). The Ireland−Claisen

Scheme 1

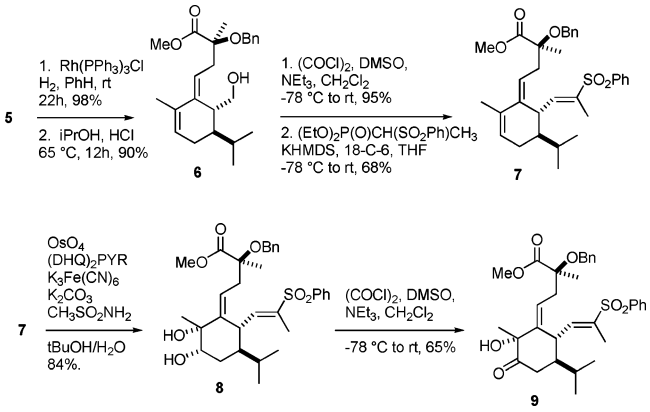


rearrangement presumably proceeded via a chairlike transition state analogous to conformer **i**, with the larger C11 substituent occupying the pseudoequatorial position. The stereochemistry of the chlorine atom at C1 was critical to the success of the Claisen rearrangement. Because the chlorine atom is situated in a pseudoaxial position with respect to the cyclohexene ring, the effective steric bulk of the C1 carbon was smaller than that of the methyl-substituted C11 carbon.[13]

With the success of the Ireland−Claisen rearrangement, 15 of the 20 carbons of the carbon framework were in place. It was at this point that we chose to install the C1−C2 bond. Rather than attempting a direct displacement of the β-Cl substituent, we sought to employ a Cu-mediated S_N2' ring opening of the allylic lactone using an alkoxy Cu nucleophile.[14] S_N2' reactions of alkoxyalkyl Cu nucleophiles are not well precedented, although earlier work by Fuchs,[15] Taylor,[16] and Dieter[17] suggested that such a transformation would be plausible.[18] The success of this approach was predicated on an initial syn-selective S_N2' reaction of allylic chloride **3** to lactone **4**.[19] In the event, a Ag-mediated S_N2' cyclization proceeded in a syn fashion to afford the corresponding lactone in an 8:1 dr favoring β isomer **4**. To our satisfaction, Cu-mediated anti S_N2' reaction of an alkoxymethyl nucleophile proceeded in excellent yield on scale to afford a single stereoisomeric product. Zn(II) salts ($ZnCl_2$ or $ZnBr_2$) proved to be critical to the success of the transformation; no substitution occurred in the absence of the Zn salt.[20]

At this stage in the synthesis, we hoped to close the tetrahydrofuran ring via an electrophilic cyclization of the C2 hydroxy group onto the C9−C10 alkene. The isopropenyl alkene was hydrogenated to avoid competing cyclizations to give diene **6** after cleavage of the MOM protecting group (Scheme 2). Although the electrophilic cyclization approach

Scheme 2



met with some limited success when ICl was employed, the yields proved to be too low to be synthetically useful. Other electrophilic reagents (Br_2, I_2, $Pb(OAc)_4/ZnBr_2$, NBS, $Hg(O_2CCF_3)_2$, etc.) gave poor yields and/or undesired side products.

We next considered reversing the sense of ring closure so that the C2−O bond would be established in the tetrahydrofuran ring-forming step rather than the C9−O bond. To this end, Swern oxidation of alcohol **6** and Horner−Wadsworth−Emmons Wittig reaction afforded *E*-sulfone **7**. Sharpless dihydroxylation of triene **7** gave C11−C12 α-diol **8**.

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On the basis of the Sharpless mnemonic, the $(DHQ)_2PYR$ ligand could in principle give either the observed product or the C9−C10 β-diol (Figure 2).[21] We postulate that the

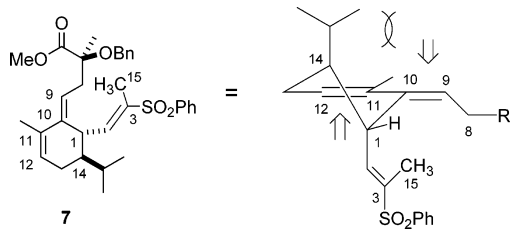


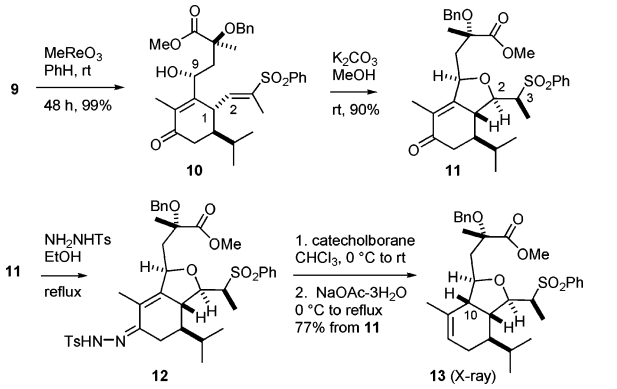
Figure 2. Regioselectivity of the dihydroxylation of triene **7**.

observed regioselectivity is a result of 2-fold allylic strain.[22] A molecular mechanics conformational search of a substructure of triene **7** (R = H) indicated that conformations within ca. 3 kcal/mol of the global minimum have the C1 alkenyl and C14 isopropyl substituents disposed pseudoaxially to avoid allylic strain between the C1 substituent and the C8 carbon. Similarly, the C2−C3 alkene is oriented so as to place the C15 methyl syn to the allylic hydrogen at C1. As a consequence, the effective size of the C1 alkene substituent is significantly smaller than the C14 isopropyl substituent. The 1,3-diaxial interactions between the ligated OsO_4 would therefore be smaller for α attack at C11−C12 than for β attack at C9−C10.

Oxidation of the C12 hydroxy group of diol **8** gave ketone **9**. $MeReO_3$-catalyzed allylic alcohol transposition[23] of unconjugated enone **9** afforded conjugated enone **10** (Scheme 3). The concerted nature of the transposition was evident by the retention of stereochemistry at the C9 stereocenter in the rearranged product. The stereochemistry at C9 of hydroxy ester **10** was supported by NOESY analysis of the derived lactone and was later confirmed by X-ray crystallographic analysis (vide infra).

The tetrahydrofuran ring was then formed by base-mediated cyclization of unsaturated sulfone **10**. Addition of

Scheme 3



the C9 alkoxide would be restricted to the *re* face of the vinyl sulfone due to allylic strain (cf. Figure 2), resulting in the β stereochemistry at C2 in isobenzofuran **11**. Fortuitously, the isolated product possessed the (*S*)-stereochemistry at C3, although it is of no consequence for the synthesis per se. The requisite cis ring fusion stereochemistry of the bicycle was set by axially selective reduction of tosylhydrazone **12** and in situ allylic diazene rearrangement.[10a,24]

X-ray crystallographic analysis of sulfone **13** revealed that all six stereocenters that are present in cladiellene triol (and sclerophytin A) were of the desired configuration. Addition of the C4−C5 fragment and cyclization of the oxonane ring remain. Further efforts toward these goals will be reported in due course.

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Note Added after ASAP Publication. In the Figure 1 caption, Δ^{11-17} was incorrectly listed as Δ^{11-18} in the version published ASAP July 29, 2006. The corrected version was published ASAP July 31, 2006.

Supporting Information Available: Characterization data for compounds **3**−**11** and **13**. CIF file for compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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