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Reprint of: Synthesis of a tricyclic core of rameswaralide ☆

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ABSTRACT

A tricyclic core containing a 5,7-fused bicyclic unit of rameswaralide was prepared starting from a 1,6-enyne. The synthetic sequence involved (i) ruthenium-catalyzed [5+2]-cycloaddition of 1,6-enyne, (ii) an acyl radical based approach to construct the lactone, and (iii) a regioselective installation of the conjugated double bond by a concomitant sulfenylation–dehydrosulfenylation sequence.

Rameswaralide (**1**), a novel diterpene with a tetracyclic ring skeleton, was isolated from the soft coral *Sinularia dissecta* near the Mandapam coast of India in 1998 (Figure 1).[1] Its relative stereochemistry was determined by analysis of ^{1}H NMR coupling constants and NOESY correlations. The structure of **1** was further confirmed by selective reduction of the enolic group with $NaBH_4$ to form the corresponding dihydrorameswaralide (**2**). It was reported that rameswaralide (**1**), and its derivatives, could function as effective anti-inflammatory agents for the treatment of a variety of inflammatory disorders, including arthritis, psoriasis, and inflammatory bowel disease.[2]

Rameswaralide (**1**) is a highly oxygenated natural product containing a variety of functional groups, including a tertiary hydroxyl group, a carbonyl moiety, a fully enolized β-ketoester, a γ-lactone, and an isopropylidene group (Fig. 1). Furthermore, it contains *cis*-fusions at the AB- and BC-ring junctions. Due to its complex features and biological importance, rameswaralide (**1**) is a good target for total synthesis. To date, the total synthesis of **1** has not been reported, but several reported approaches have appeared.[3] Herein, we report the synthesis of the tricyclic core **3** containing a 5,7-fused bicyclic (AB-ring) unit of rameswaralide (**1**) (Fig. 2).

Retrosynthetically, the tricyclic compound **3** (Fig. 2) could be accessed from chemoselective epoxidation of vinylsilane **4**. In turn,

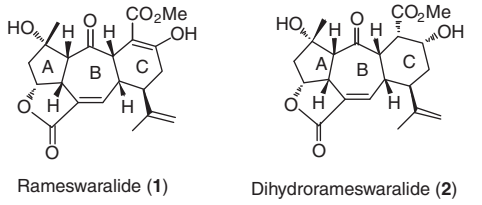

Figure 1. Structure of rameswaralide (**1**) and its derivative (**2**).

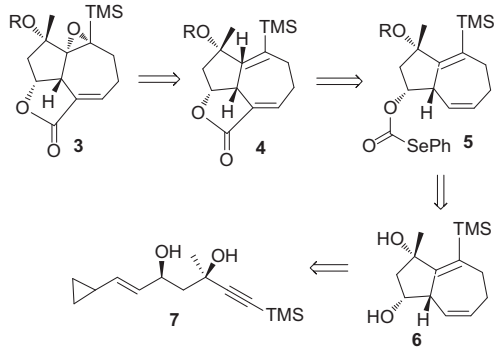

Figure 2. Retrosynthetic analysis of tricyclic core **3**.

the five-membered γ-lactone in **4** could be derived from the alkoxycarbonyl radical cyclization of acylselenium **5** onto the exocyclic *cis*-disubstituted olefin with retention of the alkene

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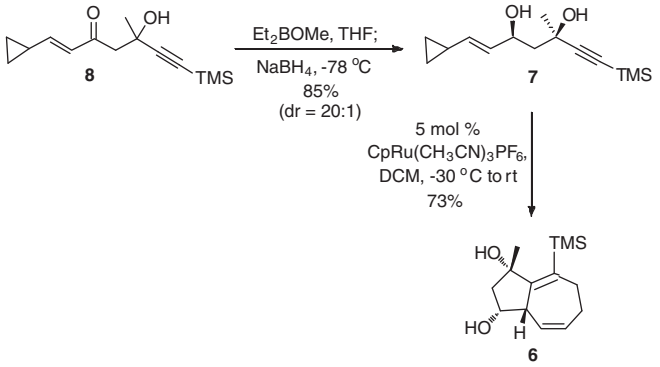
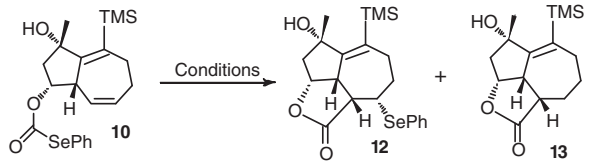


Scheme 1. Formation of the 5,7-fused bicyclic compound **6**.

Table 1
Atom transfer/reductive radical cyclization



Entry	Conditions	Results
1	Et_3B, O_2, PhH, rt, 24 h	No reaction
2	Et_3B, O_2, $Yb(OTf)_3$, PhH	Decomposition
3	$Bu_3SnSnBu_3$, *hv*, PhH, 80 °C	No reaction
4	$Me_3SnSnMe_3$, *hv*, PhH, 80 °C	No reaction
5	40 mol % Bu_3SnH, 20 mol % AIBN PhH, 80 °C, 24 h	**12** (30% yield)
6	120 mol % Bu_3SnH, 20 mol % AIBN PhH, 80 °C, 12 h	**12** (86% yield)

functionality.[4] The 5,7-fused bicyclic skeleton **6** could be formed by ruthenium-catalyzed [5+2] intramolecular cycloaddition of the 1,6-enyne **7** developed in these laboratories.[5,6]

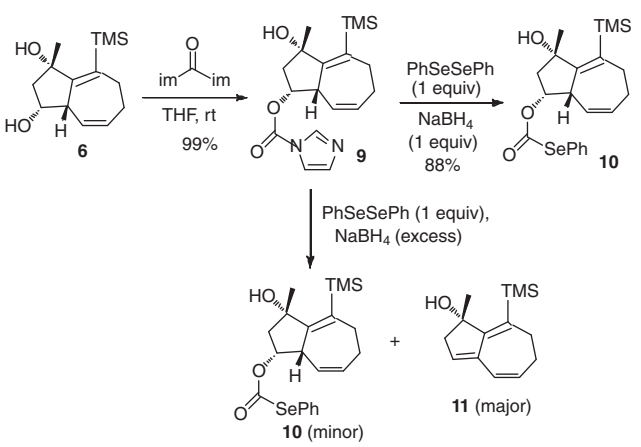
Synthesis of the 5,7-fused bicyclic compound **6** commenced with a known β-hydroxy ketone **8** (Scheme 1).[5c,d] Stereoselective reduction of **8** to the corresponding *syn* 1,3-diol **7** was realized using Et_2BOMe as a chelating reagent and $NaBH_4$ as a hydride source.[7] The diol **7** was obtained in 85% yield and with excellent diastereoselectivity (dr = 20:1). The relative stereochemistry of compound **7** was assigned by using Rychnovsky's method for determining the stereochemistry of the 1,3-diol acetonides.[8] Subjection of 1,6-enyne **7**–5 mol % of $CpRu(CH_3CN)_3PF_6$ in CH_2Cl_2 for 3 h provided the desired hydroazulene product **6** (Scheme 1) in 73% yield as a single diastereomer. The stereochemistry of compound **6** has been determined by X-ray crystallography.[5c,d]

With 5,7-bicyclic compound **6** in hand, our attention turned to development of the conditions for forming the five-membered α,β-unsaturated lactone found within the tricyclic skeleton **4** (Fig. 2). One possible approach to forming the γ-lactone while retaining the alkene functionality involves an atom transfer radical cyclization of acylselenium precursor **10** (Scheme 2) onto the disubstituted *cis*-olefin.[4] Accordingly, chemoselective acylation of diol **6** with 1,1′-carbonyl-diimidazole provided acylimidazole **9** in 99% yield. Treatment of **9** with a reagent combination of PhSeSePh and $NaBH_4$ afforded acylselenium **10** in 88% yield (Scheme 2). It is important that an equimolar amount of PhSeSePh and $NaBH_4$ must be used in the reaction to ensure high conversion in forming the desired product **10**. If an excess amount of $NaBH_4$ was employed in the reaction, an undesired elimination product **11** (Scheme 2) was formed as the major product.

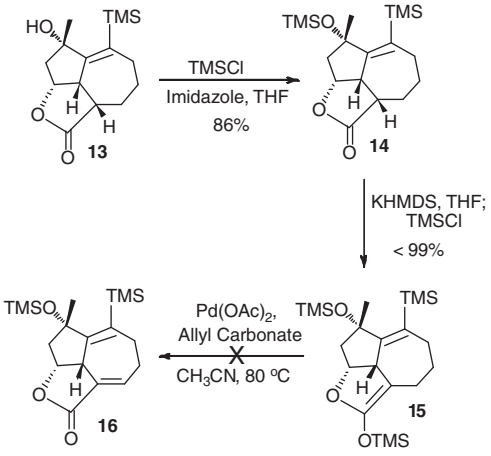
Having successfully synthesized radical precursor **10**, a variety of atom transfer radical cyclization conditions were attempted (Table 1, entries 1–4).[9] Unfortunately, these conditions did not provide the desired tricyclic product **12**, and only resulted in decomposition or recovery of the starting material **10**. On the other hand, when a substoichiometric amount of Bu_3SnH (40 mol %) was employed in the reaction, a reductive radical product **13** was isolated in 30% yield (entry 5). Use of stoichiometric amount of Bu_3SnH (1.2 equiv) and AIBN (0.2 equiv) as the radical initiator provided tricyclic product **13** in 88% yield as a single diastereomer (entry 6).

To prepare the required five-membered α,β-unsaturated lactone, the reported Tsuji method of reacting a silyl enol ether with allyl methyl carbonate was explored.[10] To avoid any difficulties associated with the formation of α,β-unsaturated lactone, the tertiary hydroxyl group within **13** was protected as silyl ether **14** (Scheme 3). Subsequent treatment of **14** with KHMDS at −78 °C, followed by trapping the enolate intermediate with TMSCl, provided silyl enol ether **15**. Reaction of **15** with $Pd(OAc)_2$ and allyl methyl carbonate in THF at 80 °C for 18 h did not yield the desired α,β-unsaturated lactone **16**.

An unsuccessful attempt at transforming the silyl enol ether **15** into the corresponding γ-lactone **16** prompted us to explore the introduction of the conjugated double bond by a concomitant sulfenylation–dehydrosulfenylation approach (Scheme 4).[11] When $PhSSO_2Ph$ was employed as the electrophilic reagent, sulfide **17** was obtained in 66% yield along with the undesired epimer **18** (Scheme 4). Chemoselective oxidation of the phenyl sulfide functionality in **17** was investigated next. The use of mCBPA (1.1 equiv)



Scheme 2. Synthesis of acylselenium **10**.



Scheme 3. Attempted formation of α,β-unsaturated lactone.