Tetrahedron Letters 51 (2010) 6232–6235

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of a tricyclic core of rameswaralide

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ARTICLE INFO

Article history:
Received 31 August 2010
Revised 8 September 2010
Accepted 13 September 2010
Available online 13 October 2010

Keywords:
Ruthenium
Cycloaddition
The fused bicyclic system
Reductive radical cyclization
Total synthesis

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, 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 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]

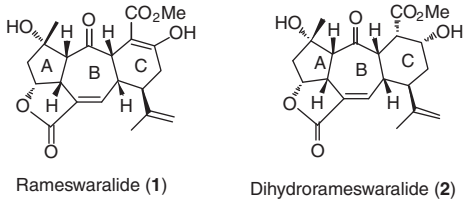

Figure 1. Structure of rameswaralide (**1**) and its derivative (**2**).

Synthesis of the 5,7-fused bicyclic compound **6** commenced with a known β-hydroxy ketone **8** (Scheme 1).[5c,d] Stereoselective

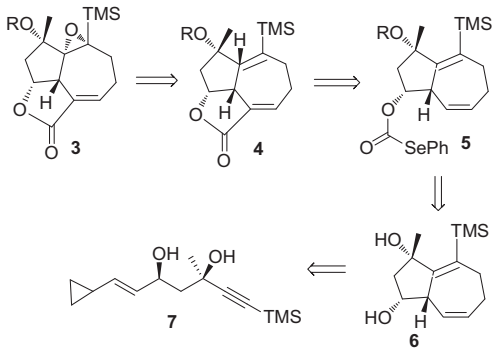

Figure 2. Retrosynthetic analysis of tricyclic core **3**.

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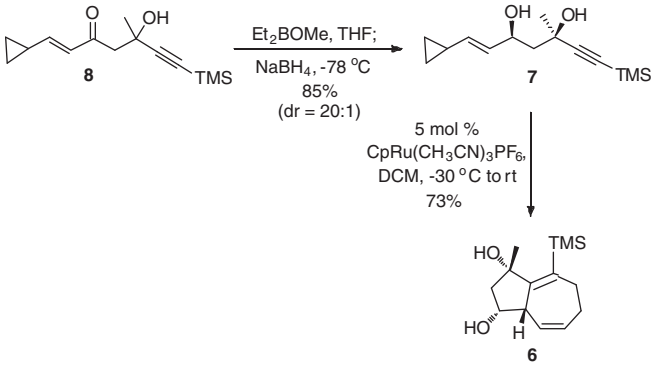
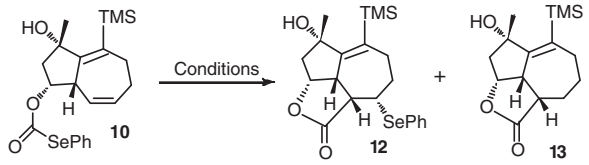
doi:10.1016/j.tetlet.2010.09.042



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)

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]

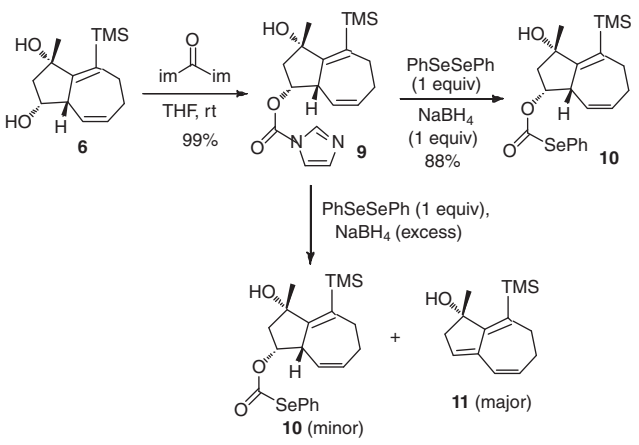
With 5,7-bicyclic compound **6** in hand, our attention turned to development of the conditions for forming the five-membered α,β-unsaturated lactone found within the tricyclic skeleton **4** (Fig. 2). One possible approach to forming the γ-lactone while retaining the alkene functionality involves an 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).

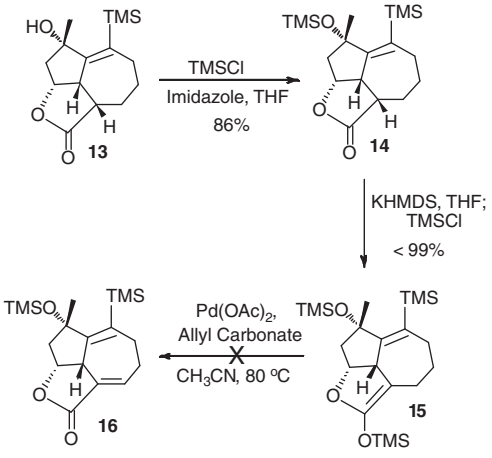
To prepare the required five-membered α,β-unsaturated lactone, the reported Tsuji method of reacting a silyl enol ether with allyl methyl carbonate was explored.[10] To avoid any difficulties associated with the formation of α,β-unsaturated lactone, the tertiary hydroxyl group within **13** was protected 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) enabled to selectively oxidize phenylthiol **17** to the desired phenyl sulfoxide **19** in 65% yield along with 12% of sulfone **20** (Scheme 4).

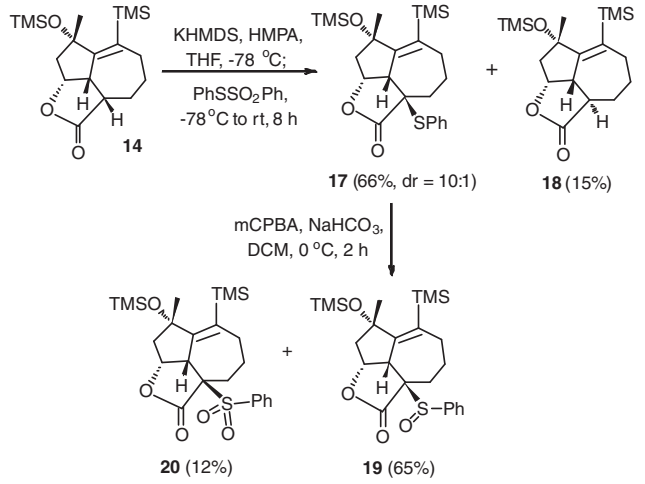
Elimination of phenyl sulfoxide **19** posed a challenge because the phenyl sulfoxide group could abstract either the methine or the methylene hydrogen to form endocyclic α,β-unsaturated lactone **21** and/or exocyclic α,β-unsaturated lactone **22**, respectively (Scheme 5). Treatment of **19** in toluene at 90 °C for 6 h only



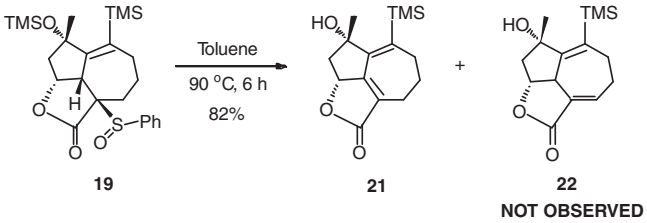
Scheme 2. Synthesis of acylselenium **10**.



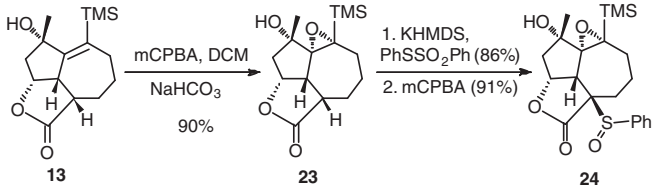
Scheme 3. Attempted formation of α,β-unsaturated lactone.



Scheme 4. Formation of phenyl sulfoxide **19**.



Scheme 5. Attempted elimination of sulfoxide **19**.

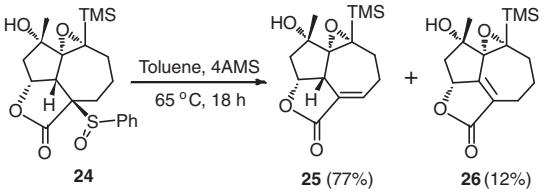


Scheme 6. Epoxidation of endocyclic olefin.

resulted in the undesired conjugated diene **21** (Scheme 5) with the concomitant deprotection of the TMS group of tertiary alcohol. The desired γ-lactone **22** was not observed in the elimination reaction.

Several factors can be attributed to favoring this regioselectivity. The first is the minimizing of the carbonyl group dipole and sulfoxide group dipole interaction, which will favor formation of the endocyclic regioisomer.[11a] Second is the allylic nature of the bridgehead hydrogen, whose abstraction leads to lactone **21** (Scheme 5). Converting the double bond to the corresponding epoxide **23** (Scheme 6) attenuates both factors to some extent. In addition, it dramatically increases the steric hindrance for abstraction of the bridgehead hydrogen. We speculate that the combination of these effects might be enough to shift the regioselectivity. As expected, the endocyclic olefin of lactone **13** (Scheme 6) was smoothly converted to epoxide **23** in 90% yield as a single diastereomer with mCPBA. Sulfenylation of **23** with $PhSSO_2Ph$, followed by mCPBA oxidation of the resulting intermediate sulfide, provided sulfoxide **24** (Scheme 6).

Gratifyingly, the treatment of sulfoxide **24** in toluene at 65 °C for 18 h provided the desired exocyclic α,β-unsaturated lactone **25** in 77% yield (Scheme 7), along with 12% yield of the undesired endocyclic γ-lactone **26**. Increasing the reaction temperature to



Scheme 7. Formation of exocyclic α,β-unsaturated lactone.

90 °C led to increased amounts of the undesired regioisomer **26** (**25:26** 69%:22%).

In summary, we have described an efficient approach to the synthesis of the tricyclic core containing the AB-ring moiety of rameswaralide (**1**), highlighted by a challenging formation of the 5,7-fused bicyclic skeleton and α,β-unsaturated five-membered lactone. The ruthenium-catalyzed [5+2]-cycloaddition reaction was employed to construct the 5,7-fused bicyclic system with excellent diastereoselectivity. Use of reductive radical cyclization followed by an oxidation/elimination approach was utilized to form the exocyclic α,β-unsaturated five-membered lactone with good regioselectivity. Efforts to apply these strategies toward the enantioselective total synthesis of rameswaralide (**1**) are ongoing.

Acknowledgments

We thank the National Institutes of Health, General Medical Sciences GM 033049, for their generous support of our research programs. H.M.N. was supported by an NIH postdoctoral fellowship. Mass spectra were provided by the Mass Spectrometry Regional Center of University of California—San Francisco, supported by the NIH Division of Research Resources.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.042.

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