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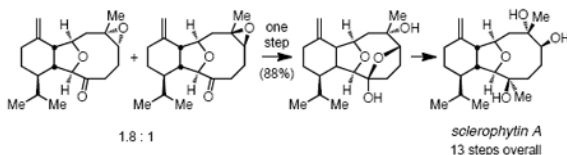
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Enantioselective Synthesis of (-)-Sclerophytin A by a Stereoconvergent Epoxide Hydrolysis

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Abstract



The cytotoxic natural product (-)-sclerophytin A was constructed in 13 steps from geranial. Highlights from the synthesis are a stereoselective Oshima-Utimoto reaction, a Shibata-Baba indium-promoted radical cyclization, and a novel stereoconvergent epoxide hydrolysis.

The oxygenated cembrane diterpenes are a large class of natural products comprising cladiellins, briarellins, asbestinins, and sarcodictyins. Their intricate chemical structures have captivated many in the synthetic chemistry community, with recent successes in the crafting of polyanthellin A1, asbestinins2, briarellins E and F3, vigulariol4, and astrogorgin5 being highly notable recent achievements.⁶ In addition to intriguing structures, these compounds also tend to possess potent biological activity. Amongst the cladiellins, sclerophytin A (Scheme 1) is a particularly striking compound; it was isolated from the marine soft coral *Sclerophyllum capitalis* and found to exhibit remarkable potency against mouse leukemia cells (cytotoxic at 1 ng/ml versus L1210 cell line), yet its original structural formulation was incorrect.⁷⁻⁸ Total syntheses by the Paquette and Overman groups established the correct formulation of sclerophytin A to be that depicted in Scheme 1.⁹ As a means to examine the utility of the stereoselective Oshima-Utimoto reaction¹⁰ in chemical synthesis, we've been attracted to the target sclerophytin A and its structural relatives.¹¹ Herein, we describe a short enantioselective route to ketone **1** (Scheme 1), a key intermediate in a prior synthesis of vigulariol,^{4b} and show that **1** can be readily converted to sclerophytin A by a three step sequence involving a novel stereoconverging epoxide hydrolysis.

In terms of retrosynthetic analysis (Scheme 1), we considered that ketone **1** might arise by ring-closing olefin metathesis of triene **2** and that **2** might be obtained from intermediate **3** by a 6-*exo-trig* radical cyclization of an appropriately modified derivative. The Oshima-Utimoto reaction of the allylic alcohol embedded in **4**, if it occurs without interference from the adjacent alkenes, was proposed to convert **4** to cyclic acetal **3**, stereoselectively. Notably, appropriately functionalized substrate **4** is readily available in a single step from geranial.

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Supporting Information Available: Characterization and procedures. This material is available free of charge through the internet at <http://pubs.acs.org>.

To begin the synthesis, allylic alcohol (*E*)-**4** was prepared in 92% yield and 98% enantiomeric excess by Brown methallylation¹² of geranial and was then subjected to the Oshima-Utimoto reaction. This sequence delivered **3** as a mixture of epimers in 62% yield (Scheme 2). Subsequent Jones oxidation of the Oshima-Utimoto product **3** to the derived lactone revealed >20:1 *anti:syn* (C4:C5) stereoselection from the Oshima-Utimoto reaction.¹³ After α -iodination to give **5**, we examined the tin-free radical reactions pioneered by Shibata and Baba for reductive radical-mediated transformation.¹⁴ Thus, treatment of **5** with InCl_3 and NaBH_4 delivered the reductive radical cyclization product in 56% yield. The intermediate lactone was subsequently reduced with DIBAL-H affording lactol **6** in 85% yield. Of note, the radical ring closure proceeded with excellent stereoselectivity (>10:1; relative configuration established by x-ray analysis, see Scheme 2), presumably a consequence of reaction through transition structure **TS-1**. Also of note is that the In-promoted radical reaction proceeded in comparable efficiency as optimized tin-based reaction conditions ($\text{Ph}_3\text{SnH/AIBN}$).

Conversion of **6** to ketone **1** was accomplished in four straightforward synthesis steps (Scheme 3). First the alcohol was acylated and then displaced with cyanide under the aegis of scandium triflate (\rightarrow **7**). Addition of butenylmagnesium bromide, followed by aqueous work-up, delivered ketone **8** which was converted to ketone **1** by ring-closing metathesis.¹⁵

Conversion of ketone **1** to sclerophytin A requires *trans* dioxygenation of the trisubstituted alkene. It was considered that this might be accomplished by hydrolytic ring opening of an intermediate epoxide. As depicted in Scheme 4, peracid epoxidation occurs regioselectively but without stereocontrol, and therefore provides a mixture of both α -**9** and β -**9**. While epoxidation of the tertiary alcohol **10** (derived from **1** by addition of MeMgBr) could be accomplished stereoselectively as ascertained by Clark,^{4b} spontaneous cyclization to vigulariol could not be avoided (efforts to protect alcohol **10** were futile). Examination of the x-ray structure of epoxy ketone α -**9** (see Scheme 4), however, inspired a solution. The structural feature of consequence is a near linear alignment (160°) of the carbonyl oxygen, C6 of the epoxide (eunicellin numbering), and the epoxide oxygen. While the carbonyl oxygen and C6 are separated by 3.68 Å in α -**9**, it was reasoned that proximity would be increased, perhaps facilitating intramolecular oxirane rupture, upon conversion of the carbonyl to the tetrahedral hydrate. This reactivity would be unique to stereoisomer α -**9** and would lead to oxygenation of the alkene in a manner that is stereochemically-appropriate to the target.

In the event, treatment of a 1.8:1 mixture of α -**9** and β -**9** with aqueous LiOH at room temperature resulted in rapid hydrolysis of α -**9** to give **11** (Scheme 5). That an intramolecular advantage may operate in this hydrolytic epoxide opening is supported by three lines of evidence: first, NMR and x-ray analysis (Scheme 5) of the product shows that it exists as the stable hemiketal **11**; second, analogous ring-opening of 1-methylcyclohexene oxide under the same reaction conditions occurs in <5% conversion; third, β -**9** is unreactive under these conditions and could be recovered from the reaction mixture. While resolution of α -**9** and β -**9** is an attractive feature of the basic reaction conditions, it was considered that β -**9** might also be converted to the target under acidic conditions where the regiochemical preference for epoxide opening would be opposite to that observed with LiOH. Ultimately, it was found that this stereoconvergent epoxide hydrolysis could be accomplished in a single-pot process. First, the mixture of α -**9** and β -**9** was subjected to LiOH until TLC analysis indicated complete consumption of α -**9**, then the mixture was neutralized with KHSO_4 , diluted with CH_3CN , and treated with $\text{Sc}(\text{OTf})_3$. Under these conditions, the product hemiketal **11** was isolated in 88% yield as a single product stereoisomer. Finally, subjecting of **11** to MeMgCl delivered sclerophytin A in excellent yield and in agreement with characterization data.^{7·9f}

In conclusion, we have described an enantioselective synthesis of (-)-sclerophytin A that occurs in 13 steps from geranial. The versatility of radical reactions and the Oshima-Utimoto reaction suggests that the synthesis strategy described herein may be transferable to a number of other eunicellin-derived natural products and these will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

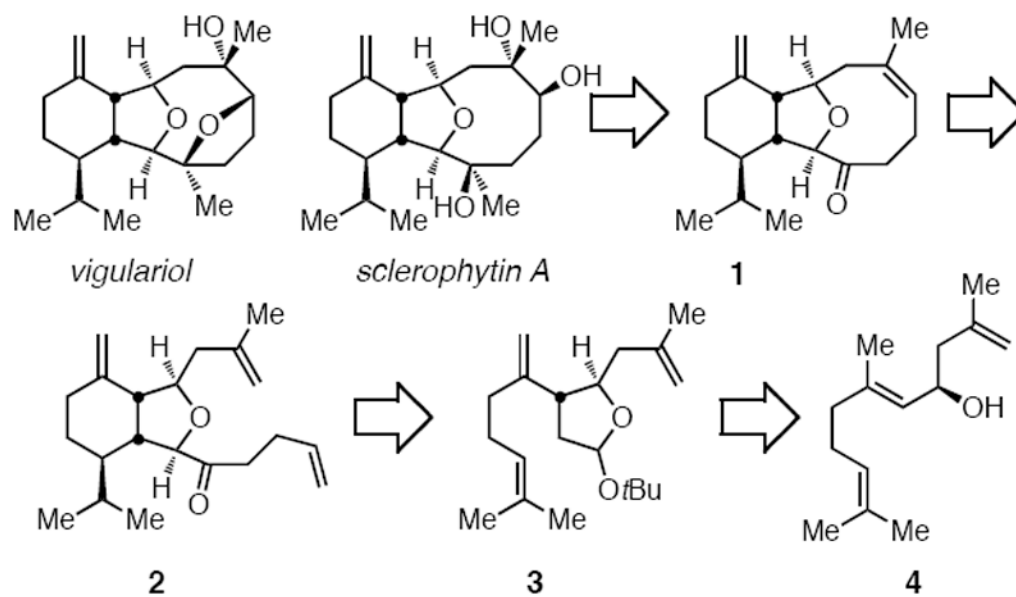
Acknowledgments

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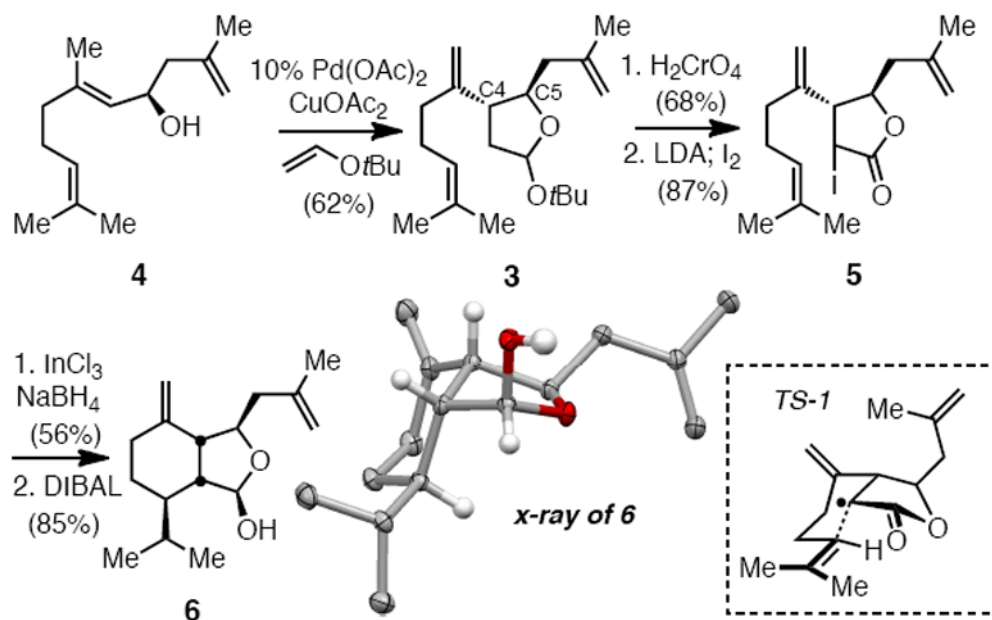
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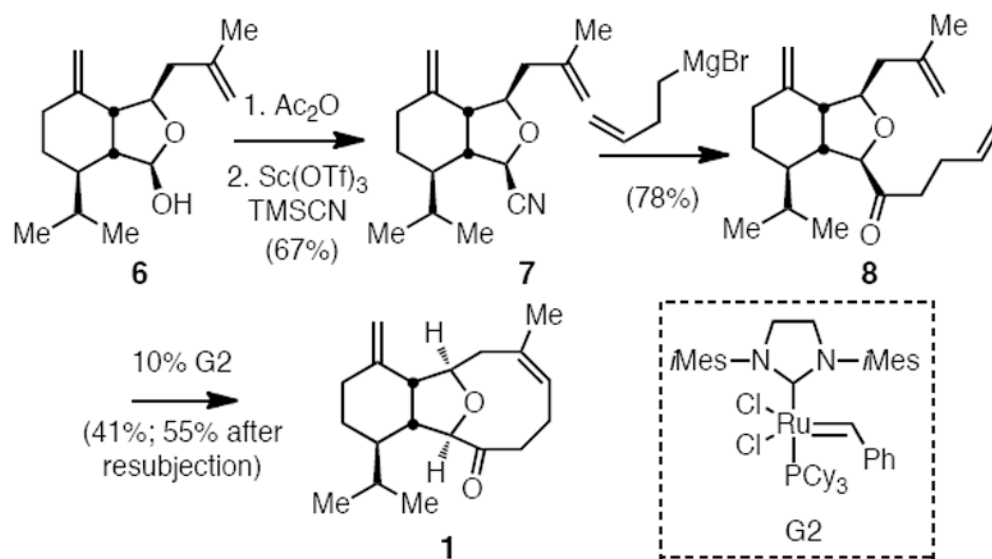
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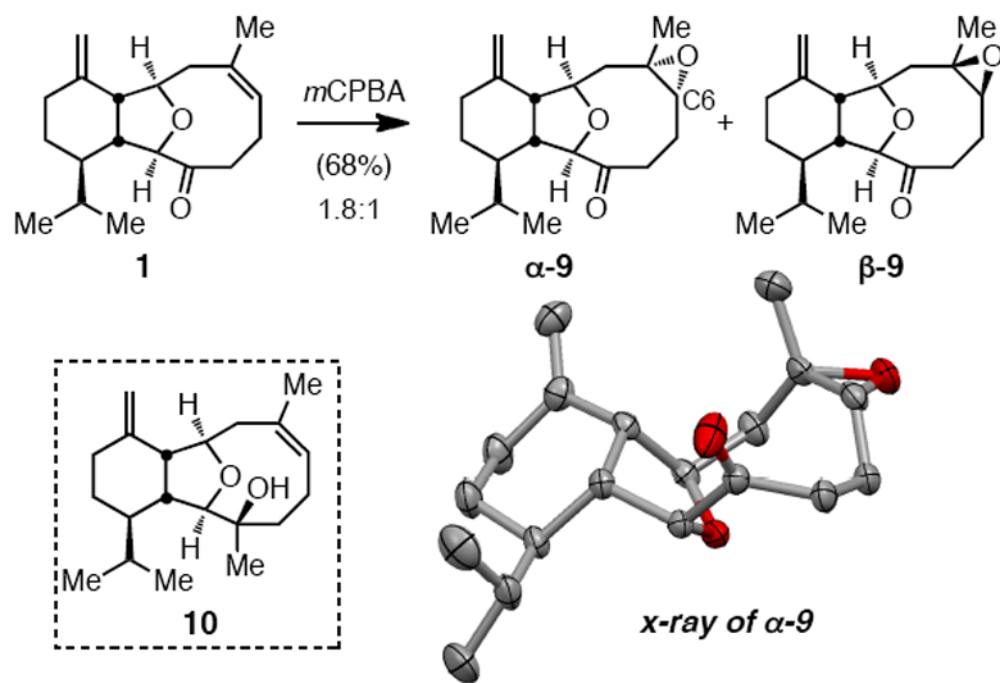
Scheme 1.



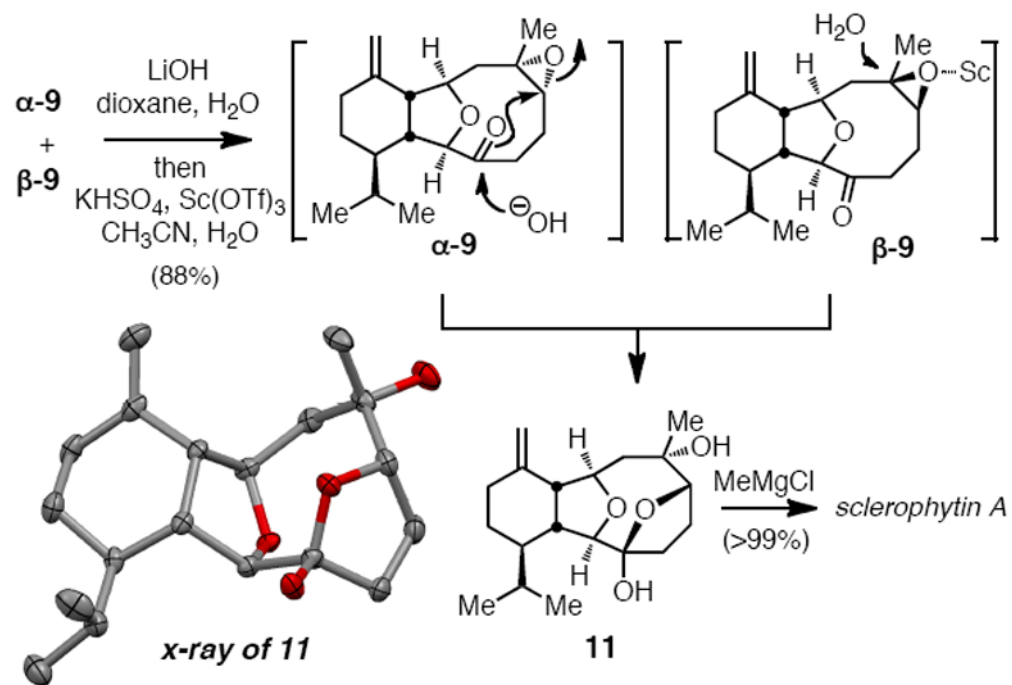
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.