

Iodocyclization and Prins-Type Macrocyclization: An Efficient Formal Synthesis of Leucascandrolide A

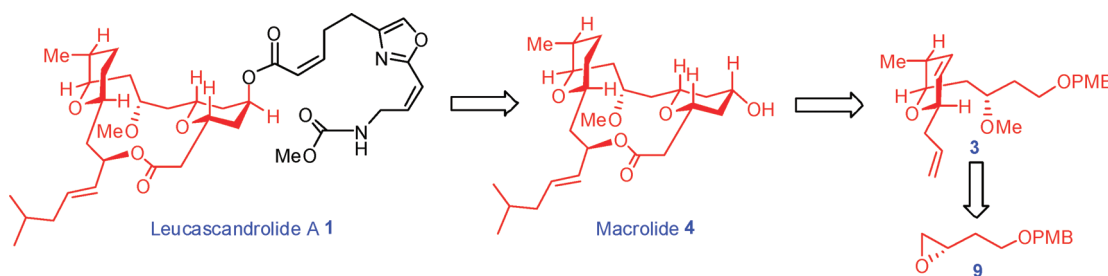
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ABSTRACT



The formal total synthesis of leucascandrolide A has been achieved in 20 steps from a known epoxide with an overall yield of 11.5% following a recently developed strategy for the construction of *trans*-2,6-disubstituted-3,4-dihydropyrans and a Lewis acid catalyzed intramolecular Prins-cyclization of an aldehydic homoallylic alcohol to generate the tetrahydropyran ring with three stereogenic centers and macrocycle concomitantly.

In 1996, Pietra and co-workers identified a new genus of calcareous sponges *Leucascandra caveolata* obtained from the northeastern coast of New Caledonia Coral Sea, which resulted in the discovery of a highly complex natural product designated as leucascandrolide A (**1**) (Figure 1).¹ This macrolide exhibits high in vitro cytotoxicity against human KB and P388 tumor cell lines displaying IC₅₀ values of 0.05 and 0.25 $\mu\text{g/mL}$, respectively. The natural product also possesses potent antifungal ability against *Candida albicans*, pathogenic yeast that attacks AIDs patients and other immunocompromised individuals. Additionally, following hydrolysis of the C5 ester linkage, biological testing of the 18-membered macrocyclic core and the separated side chain demonstrated that the macrocyclic domain is solely responsible for the cytotoxicity, while the oxazole-containing unsaturated side chain appears to be responsible for the antifungal activity.

The highly oxygenated 18-membered macrolide (**1**) has eight stereogenic centers and three alkenes and also features two trisubstituted tetrahydropyran rings, one of these having an unusual oxazole-containing side chain axially appended at C5. A subsequent report indicates that leucascandrolide A is no longer available from its initial natural source.² It has been proposed that leucascandrolide A and its cometabolite leucascandrolide B are products of opportunistic microbial colonization of the

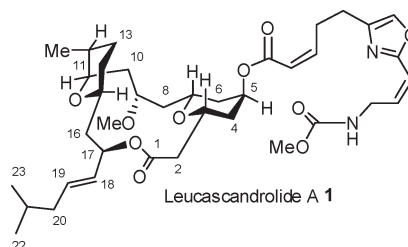


Figure 1. Structure of Leucascandrolide A (**1**).

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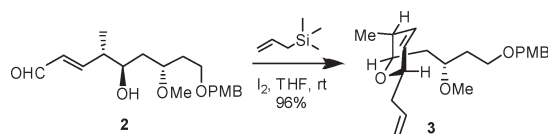
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sponge, as evidenced by the large amounts of dead tissue in the initial harvest of *Leucascandra caveolata*. Currently, there is no natural source of leucascandrolide A. Based on its impressive biological activity, inaccessibility from natural sources, and structural complexity associated with ample synthetic challenges, the construction of leucascandrolide A has spurred considerable synthetic interest, resulting in several total and formal syntheses.^{3–5}

In this article, we present a unique synthetic solution for the leucascandrolide problem featuring a concise, convergent, and highly stereoselective approach to this complex natural product. Our interest for **1** arose from studies in which we demonstrated that the critical *trans*-2,6-disubstituted tetrahydropyran relevant to the C11–C15 fragment would be prepared following a recently developed iodocyclization of δ -hydroxy α,β -unsaturated aldehyde with allyltrimethyl silane in the presence of molecular iodine (Scheme 1).⁶ The second most important reaction was to apply a Prins-type macrocyclization which has recently emerged as a successful strategy in the synthesis of polyketide derived complex natural products.⁷

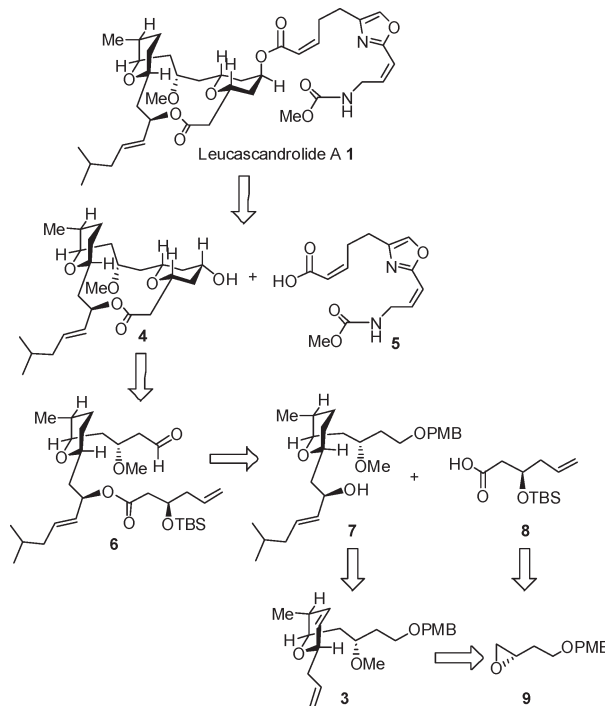
Scheme 1. Iodocyclization Protocol for the Synthesis of **3**



Our retrosynthetic analysis for the total synthesis of leucascandrolide A is illustrated in Scheme 2. Leucascandrolide A (**1**) would be derived from the macrolactone **4** by attachment of the oxazole containing side chain at the C5

hydroxyl under the Mitsunobu protocol. The alcohol fragment **4** could be obtained through a late stage Prins-cyclization (Scheme 2). The C11–C15 pyran of **7** could be prepared following our recently reported protocol. The δ -hydroxy α,β -unsaturated aldehyde **2** precursor for the iodocyclization reaction as well as the acid fragment **8** could be obtained starting from a known chiral epoxide **9**.

Scheme 2. Retrosynthetic Analysis of Leucascandrolide A (**1**)



The application of allylation on δ -hydroxy α,β -unsaturated aldehyde **2** with allyltrimethyl silane in the presence of molecular iodine following our protocol⁶ facilitated an eight-step preparation of the *trans*-2,6-disubstituted dihydropyran **3** as the only product (Scheme 3). The preparation of **2** commenced with the conversion of the epoxide **9**⁸ into a homoallyl alcohol through the copper(I)-catalyzed⁹ addition of a vinyl Grignard reagent followed by cross-metathesis with Hoveyda–Grubbs¹⁰ catalyst affording the α,β -unsaturated aldehyde. It was then subjected to

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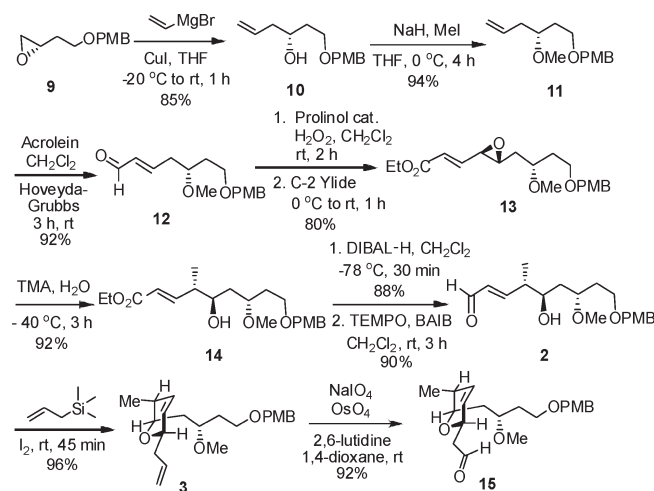
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asymmetric epoxidation under Jørgensen's conditions^{11a} with H₂O₂ in the presence of a proline-derived catalyst^{11b} to furnish an epoxy aldehyde, which on condensation with Ph₃P=CHCO₂Et afforded an epoxy ester. The epoxy ester was treated with trimethyl aluminum (TMA),¹² followed by reduction of an α,β -unsaturated aldehyde with DIBAL-H and oxidation with TEMPO/BAIB,¹³ producing δ -hydroxy α,β -unsaturated aldehyde **2** which on iodocyclization afforded **3** in 41% yield over eight steps. The ¹H and ¹³C NMR spectra revealed a single isomer which was supported by HPLC analysis data (de $\geq$ 99%). The terminal double bond was oxidatively cleaved following a modified method¹⁴ (NaIO₄ and 2,6-lutidine) to obtain aldehyde **15**.

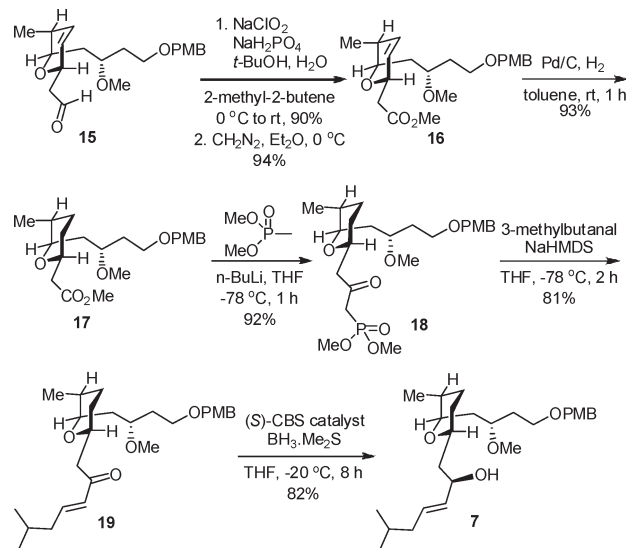
Scheme 3. Synthesis of Aldehyde **15**



Subsequent oxidation of aldehyde **15** under Pinnick conditions¹⁵ afforded a carboxylic acid which on treatment with diazomethane gave the ester **16** in 78% yield over three steps. Reduction of the double bond over Pd/C under a hydrogen atmosphere furnished tetrahydropyran derivative **17** in 93% yield. Nucleophilic addition of the lithiated derivative of dimethyl methyl phosphonate furnished the β -keto phosphonate **18** in 92% yield, which on treatment with 3-methylbutanal in the presence of NaHMDS gave α,β -unsaturated ketone **19** in 81% yield. Reduction of **19** with the Corey–Bakshi–Shibata (CBS)¹⁶ reagent [(*S*)-2-methyloxazaborolidine in the presence of borane-dimethylsulfide complex] installed the C17 stereogenic center present

in **7** with a 12:1 diastereomeric ratio (by HPLC) in 82% yield as a separable mixture (Scheme 4).

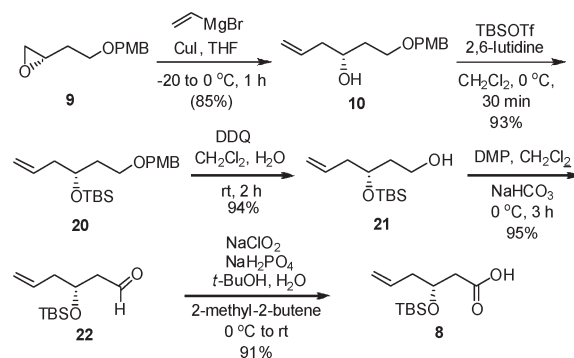
Scheme 4. Synthesis of Fragment **7**



Having the required alcohol fragment **7** in hand, our next target was to synthesize acid fragment **8**. The synthesis commenced with the copper(I)-catalyzed addition of the Grignard reagent vinyl magnesium bromide to the epoxide **9** to afford **10** in 85% yield. The resulting homoallylic alcohol was protected as its TBS-ether using TBSOTf and 2,6-lutidine in anhydrous CH₂Cl₂ to obtain **20** in 93% yield. Deprotection of the *p*-methoxybenzyl group with DDQ¹⁷ in CH₂Cl₂/H₂O (9:1) yielded the primary hydroxy compound **21** in 94% yield. The resulting primary hydroxy group was oxidized with Dess–Martin periodinane¹⁸ to afford the corresponding aldehyde **22** (Scheme 5) which on further oxidation under Pinnick conditions (NaClO₂/NaH₂PO₄/*t*-BuOH/H₂O/2-methyl-2-butene) gave acid **8** whose spectral and analytical data were in good agreement with the reported data.¹⁹

With alcohol **7** and acid fragment **8** in hand, our next task was to couple both of the fragments and verify the

Scheme 5. Synthesis of Acid Fragment **8**



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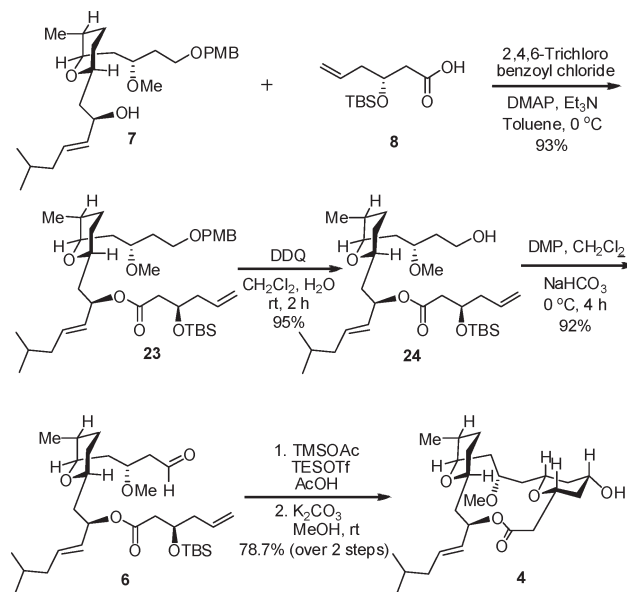
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Prins-type macrocyclization on an 18-membered macrolactone. The coupling of C1–C6 fragment **8** and C7–C23 fragment **7** was initially performed employing dicyclohexyl carbodiimide (DCC)²⁰ and a catalytic amount of DMAP in CH₂Cl₂ to afford ester **23** in 42% yield, whereas EDCI²¹ and DMAP in CH₂Cl₂ furnished the ester **23** in 57% yield. However, a better result was achieved under Yamaguchi conditions²² to obtain the ester **23** in 93% yield, which contains all 23 carbons of the target molecule (Scheme 6). Deprotection of the PMB ether in **23** upon treatment with DDQ afforded alcohol **24** in 95% yield. The primary hydroxyl group at C7 was then oxidized to an aldehyde **6** by treatment with Dess–Martin periodinane which was taken forward for the next reaction without further purification.

The next important task was to perform the Prins-macrocyclization. As expected, the construction of 18-membered macrocycle **4** by intramolecular Prins-cyclization of aldehyde **6** was a significant challenge. After extensive investigations, we eventually found that treatment of **6** with > 30 equiv of TMSOAc and TESOTf in a 0.01 M solution of AcOH resulted in the Prins adduct and hydrolysis furnished macrolide **4** in 72% yield over three steps. The outcome of **4** was derived in an analogy by a recent report for the synthesis of neopeltolide by Lee et al.²³ This macrocyclization with high diastereoselectivity (dr > 97:3) and good yield provides an additional example of the powerful and versatile nature of the Prins-macrocyclization strategy. Kozmin and co-workers^{3b,h} have already demonstrated that THE one-step protocol featuring Mitsunobu esterification could be utilized to convert alcohol **4** to leucascandrolide A (**1**). Thus, the synthesis of macrolide **4** constitutes a formal synthesis of leucascandrolide A. The spectral

Scheme 6. Synthesis of Macrolide **4**



(¹H, and ¹³C NMR, IR) and analytical data {[α]_D²⁵ +54.7 (*c* 1.18, EtOH); lit.^{3b} [α]_D²⁰ +58 (*c* 0.1, EtOH); lit.^{3h} [α]_D²³ +55 (*c* 0.05, EtOH)} were in good agreement with the reported values.

In summary, our investigations into the allylation of a δ-hydroxy α,β-unsaturated aldehyde with an allyltrimethyl silane in the presence of a catalytic amount of molecular iodine as a protocol combined with the intramolecular Prins-macrocyclization has led to a concise formal total synthesis of leucascandrolide A, which proceeded in only a 20-step longest linear sequence with a 11.5% overall yield starting from a known epoxide.

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Supporting Information Available. Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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