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

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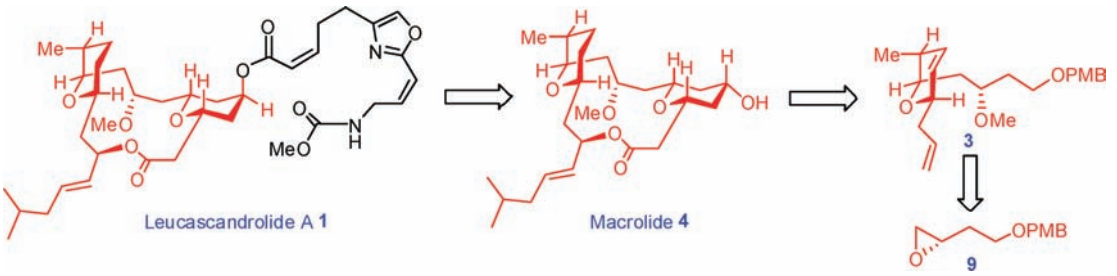
ABSTRACT



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 Calendonia 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 IC_{50} values of 0.05 and 0.25 μg/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

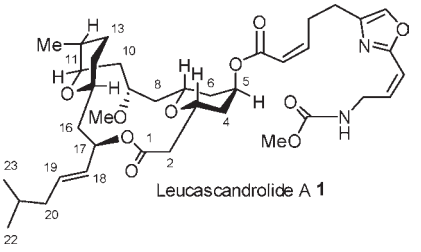


Figure 1. Structure of Leucascandrolide A (**1**).

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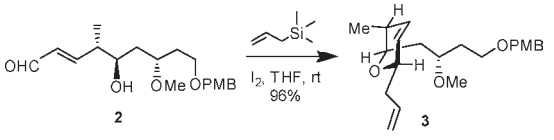
sponge, as evidenced by the large amounts of dead tissue in the initial harvest of *Leucascandra caveolata*. Currently, there is no natural source of leucascandrolide A. Based on its impressive biological activity, inaccessibility from natural sources, and structural complexity associated with ample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

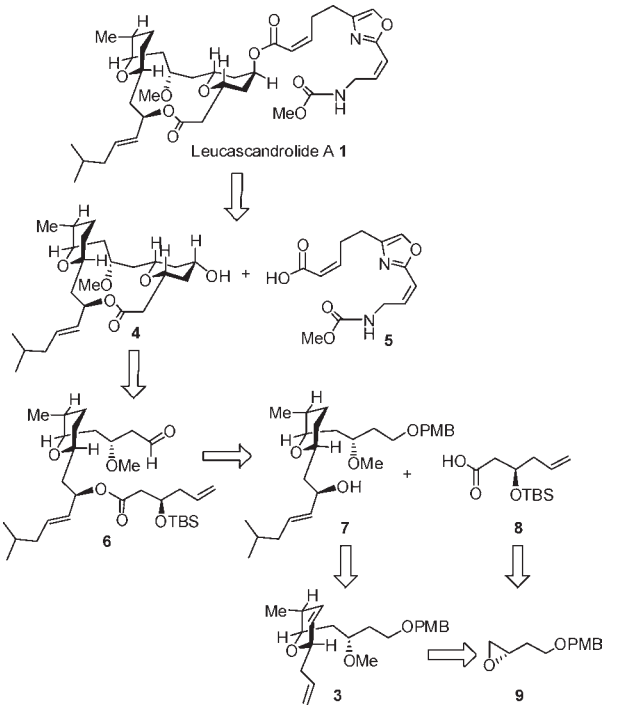
In this article, we present a unique synthetic solution for the leucascandrolide problem featuring a concise, convergent, and highly stereoselective approach to this complex natural product. Our interest for **1** arose from studies in which we demonstrated that the critical *trans*-2,6-disubstituted 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 protocol[6] 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)-catalyzed[9] addition of a vinyl Grignard reagent followed by cross-metathesis with Hoveyda−Grubbs[10] catalyst affording the α,β-unsaturated aldehyde. It was then subjected to

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(5) For syntheses of fragments and analogues of leucascandrolide A, see: (a) Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 579. (b) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755. (c) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2001**, *66*, 3242. (d) Dakin, L. A.; Langille, N. F.; Paneck, J. S. *J. Org. Chem.* **2002**, *67*, 6812. (e) Dakin, L. A.; Paneck, J. S. *Org. Lett.* **2003**, *5*, 3995. (f) Ulanovskaya, O. A.; Janjic, J.; Suzuki, M.; Sabharwal, S. S.; Schumacker, P. T.; Kron, S. J.; Kozmin, S. A. *Nat. Chem. Biol.* **2008**, *4*, 418.

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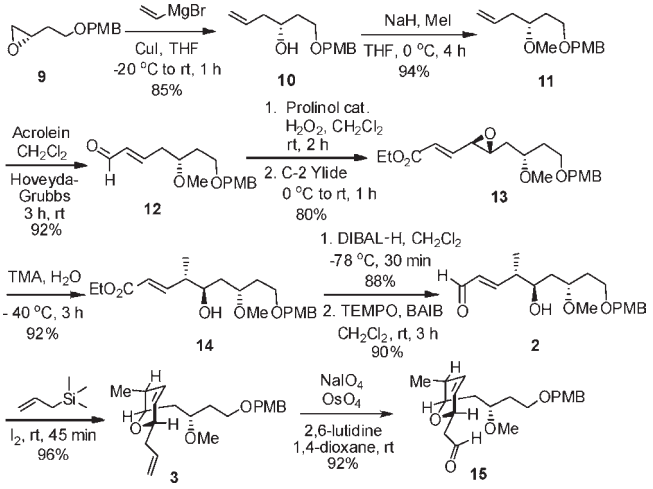
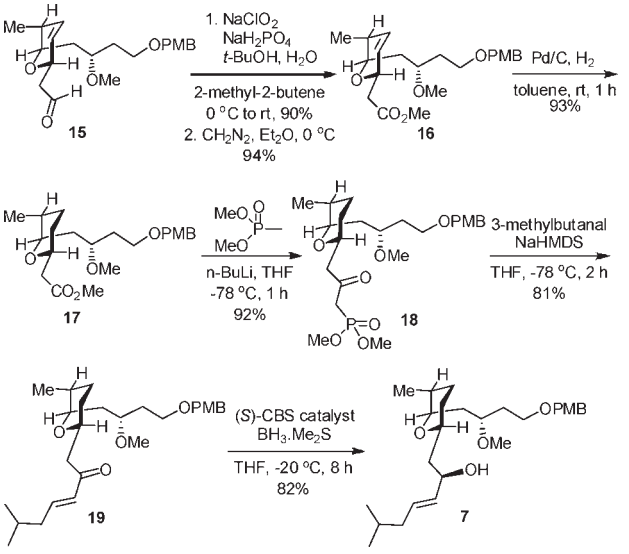
asymmetric epoxidation under Jørgensen's conditions[11a] with H_2O_2 in the presence of a proline-derived catalyst[11b] to furnish an epoxy aldehyde, which on condensation with $Ph_3P{=}CHCO_2Et$ afforded an epoxy ester. The epoxy ester was treated with trimethyl aluminum (TMA),[12] followed by reduction of an α,β-unsaturated ester 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 ^{13}C NMR spectra revealed a single isomer which was supported by HPLC analysis data (de ≥ 99%). The terminal double bond was oxidatively cleaved following a modified method[14] ($NaIO_4$ and 2,6-lutidine) to obtain aldehyde **15**.

Scheme 3. Synthesis of Aldehyde **15**



Subsequent oxidation of aldehyde **15** under Pinnick conditions[15] 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).

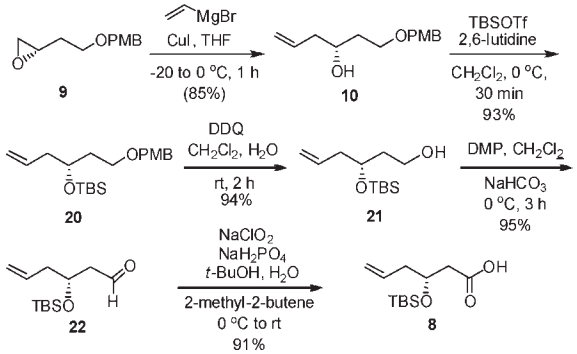
Scheme 4. Synthesis of Fragment **7**



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 CH_2Cl_2 to obtain **20** in 93% yield. Deprotection of the *p*-methoxybenzyl group with DDQ[17] in CH_2Cl_2/H_2O (9:1) yielded the primary hydroxy compound **21** in 94% yield. The resulting primary hydroxy group was oxidized with Dess−Martin periodinane[18] to afford the corresponding aldehyde **22** (Scheme 5) which on further oxidation under Pinnick conditions ($NaClO_2/NaH_2PO_4/t$-BuOH/H_2O/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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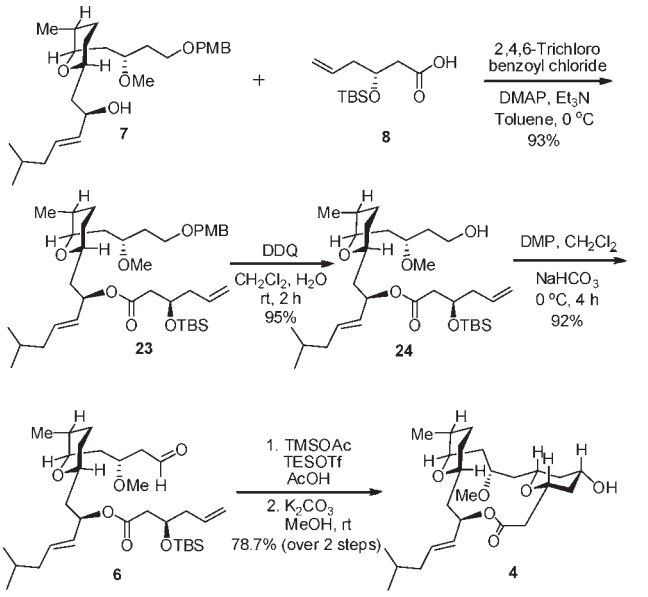
Prins-type macrocyclization on an 18-membered macrolactone. The coupling of C1−C6 fragment **8** and C7−C23 fragment **7** was initially performed employing dicyclohexyl carbodiimide (DCC)[20] and a catalytic amount of DMAP in CH_2Cl_2 to afford ester **23** in 42% yield, whereas EDCI[21] and DMAP in CH_2Cl_2 furnished the ester **23** in 57% yield. However, a better result was achieved under Yamaguchi conditions[22] 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 coworkers[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**



(^{1}H, and ^{13}C NMR, IR) and analytical data {$[\alpha]_D^{25}$ +54.7 (*c* 1.18, EtOH); lit.[3b] $[\alpha]_D^{20}$ +58 (*c* 0.1, EtOH); lit.[3h] $[\alpha]_D^{23}$ +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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