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Synthesis of the C1–C13 Fragment of Leucascandrolide A

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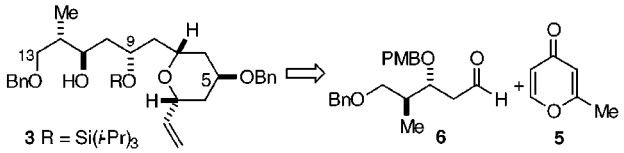
ABSTRACT



The synthesis of the C1–C13 fragment 3 of leucascandrolide A has been completed utilizing a stereoselective and regioselective reductive cleavage of a highly functionalized spiroketal to incorporate the *cis*-2,6-disubstituted tetrahydropyan. The spiroketal was constructed by addition of a lithiated pyrone 5 to aldehyde 6.

Leucascandrolide A (**1**) was isolated from the calcareous sponge *Leucascandra caveolata* collected from the Coral Sea off the coast of New Caladonia. The gross structure and relative stereochemistry were assigned on the basis of extensive two-dimensional NMR experiments, and the absolute configuration was assigned by Mosher's method using the Mosher ester of the C5 hydroxyl. Leucascandrolide A displayed significant cytotoxicity in vitro (IC_{50} = 0.05 and 0.25 μg/mL with KB and P388 cells, respectively) as well as very strong inhibition of *Candida albicans*, a pathogenic yeast that attacks AIDS patients.[1]

The unusual macrolide structure, combined with its novel biological activity, prompted us to investigate the total synthesis of leucascandrolide A. The strategy for the total synthesis of leucascandrolide A is illustrated in Figure 1. Leucascandrolide A (**1**) would be derived from a macrolactonization of the seco acid **2** with a subsequent attachment of the ester at the C5 hydroxyl. The seco acid **2** would be derived from tetrahydropyran **3** by formation of the C13−C14 bond through an alkylation of a C13 iodide derived from **3** with an appropriate C14−C22 nucleophilic fragment or a similar strategy. Tetrahydropyran **3** would be revealed through a chelation-controlled, stereoselective reductive cleavage of spiroketal **4** according to our recently developed protocol.[2] Spiroketal **4** can be prepared from addition of metalated pyrone **5** to aldehyde **6** and subsequent spirocyclization.[3] We report here the implementation of this

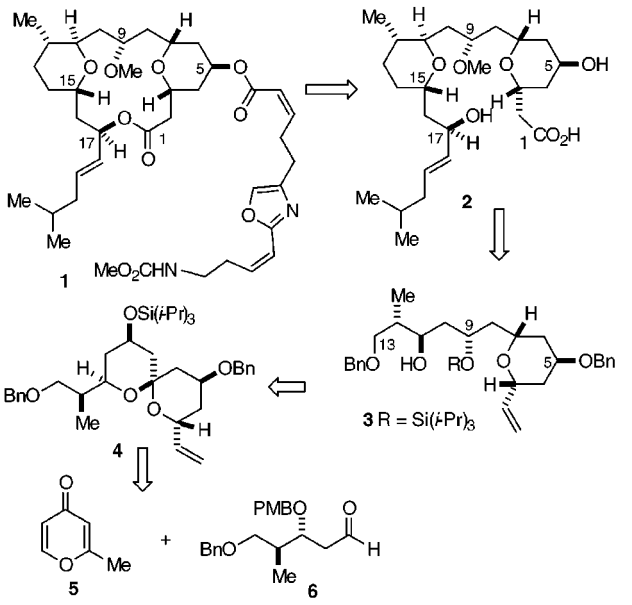


Figure 1. Retrosynthesis of Leucascandrolide A.

(1) Ambrosio, M. D.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51−59.

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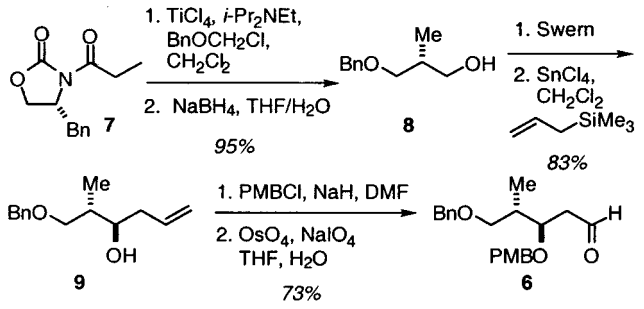
strategy for the preparation of the C1−C13 fragment **3** which contains six of the eight stereogenic centers of leucascandrolide A.

The synthesis of fragment **3** began with the preparation of aldehyde **6** as illustrated in Scheme 1. The known alcohol

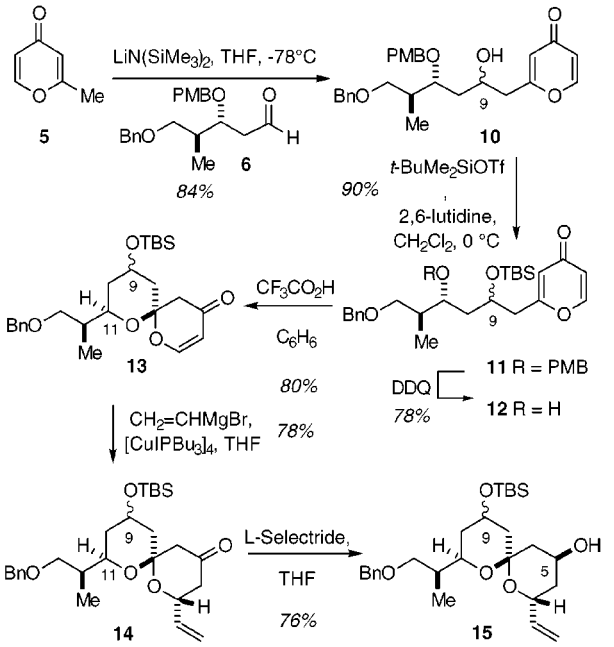
Scheme 1



8[4] was prepared by alkylation of the titanium enolate of propionyl oxazolidinone **7** with chloromethylbenzyl ether[5] followed by reductive removal of the auxiliary[6] (95% overall). The primary alcohol was oxidized under Swern[7] conditions, and the resultant aldehyde was exposed to the well-documented chelation-controlled, Lewis acid mediated addition of allylsilanes to aldehydes[8] to provide the *anti* alcohol **9** as the major diastereomer (83% overall; 89:11 dr).[9] After chromatographic separation, the major diastereomer was protected as its *p*-methoxybenzyl ether and the terminal olefin was cleaved to the desired aldehyde **6** under Lemeiux−Johnson conditions.

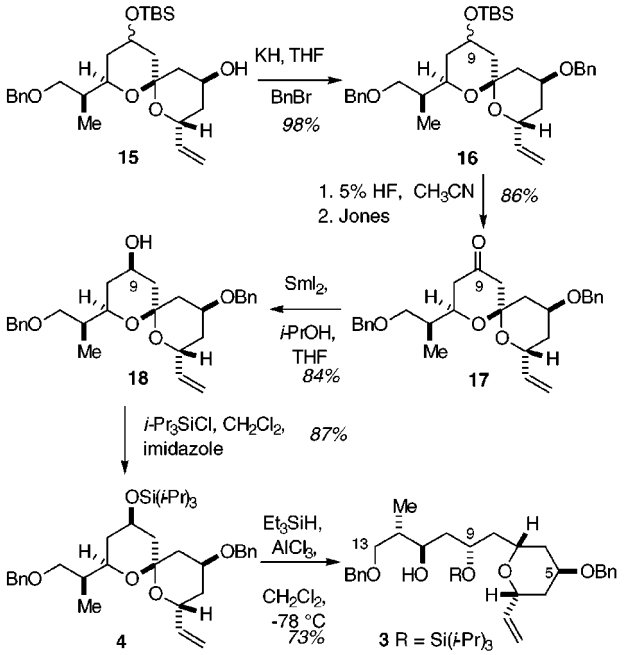
Conversion of aldehyde **6** to the required spiroenone **13** was accomplished according to our established protocol[10] (see Scheme 2). Metalation of pyrone **5**[11] at −78 °C followed by addition of aldehyde **6** resulted in formation of hydroxypyrone **10** in 84% yield as a 1:1 mixture of diastereomers. The mixture was carried forward in anticipation of using the spiroketal as a template in a stereoselective reduction to control the C9 stereocenter. The secondary alcohol was treated with *t*-BuMe$_2$SiOTf to give silyl ether **11** in high

Scheme 2



yield. Removal of the *p*-methoxybenzyl ether with DDQ[12] (pH 7 buffer, CH_2Cl_2) produced alcohol **12**, which upon exposure to trifluoroacetic acid in benzene resulted in the formation of a 1:1 thermodynamic mixture of spiroenone **13** and pyrone **12**. Starting pyrone **12** and spiroenone **13** were easily separable by flash chromatography, and resubjection of pyrone **12** to the reaction conditions ultimately provided spiroenone **13** in 80% yield after three recycles. Copper-catalyzed addition of vinylmagnesium bromide to enone **13**

Scheme 3



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(9) All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, and optical rotation. Yields are for isolated, chromatographically purified products.

(10) Zawacki, F. J.; Crimmins, M. T. *Tetrahedron Lett.* **1996**, *37*, 6499−6502.

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to establish the C3 stereocenter resulted in 78% yield of spiroketal **14** with excellent stereocontrol (95:5 dr). The selective equatorial addition appears to be controlled by steric shielding of the substituent at C11 of the spiroketal (leucascandrolide A numbering).[13] Reduction of the C5 ketone with L-Selectride[14] provided axial alcohol **15** in high yield as a single detectable isomer at C5. Protection of alcohol **15** (KH, THF, BnBr) gave benzyl ether **16** in excellent yield (Scheme 3), and the C9 stereocenter was established in an oxidation−reduction sequence using the spiroketal as a template for stereocontrol. Removal of the TBS ether with *n*-Bu_4NF followed by Jones oxidation of the C9 alcohol gave ketone **17**. The ketone was reduced with sammarium iodide in the presence of 2-propanol as described by Evans,[14] producing exclusively the equatorial alcohol **18**. Alcohol **18** was subsequently protected as a triisopropylsilyl ether to give spiroketal **4**, leaving only the incorporation of the C7 stereogenic center to be completed. To this end, chelation-controlled reductive cleavage of the spiroketal was investigated. Exposure of spiroketal **4** to $AlCl_3$−Et_3SiH[14] at −78 °C afforded *cis*-2,6-disubstituted tetrahydropyran **3** as a single, detectable isomer. Bidentate coordination of the C13 benzyl and the C11 spiroketal oxygen to the metal center allows selective activation of the C11 oxygen−anomeric carbon bond. Subsequent reduction of the resulting oxacarbenium ion results in axial approach of the hydride to give tetrahydropyran **3**.

The synthesis of the C1−C13 fragment of leucascandrolide A has been accomplished using a metalated pyrone addition to a β-alkoxy aldehyde to construct the key spiroketal intermediate. The spiroketal serves as a rigid template, allowing the stereocontrol of the C5 and C9 hydroxyl groups through stereoselective ketone reductions. Finally, the chelation-controlled, stereoselective and regioselective reductive cleavage of the spiroketal anomeric center incorporates the required *cis*-2,6-disubstituted tetrahydropyran. Completion of the synthesis of leucascandrolide A from the C1−C13 fragment **3** is currently in progress.

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