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COMMUNICATIONS

Published on Web 10/24/2002

Synthesis of Leucascandrolide A via a Spontaneous Macrolactolization

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Received September 5, 2002

In 1996, Pietra identified a new genus of calcareous sponges, *Leucascandra caveolata*, which resulted in the discovery of a natural product designated as leucascandrolide A (**1**, Scheme 1).[1] In preliminary studies, this metabolite displayed potent cytotoxicity against KB and P388 tumor cell lines, and strong inhibition of the animal-pathogenic yeast *Candida albicans*. Structurally, leucascandrolide A was shown to embody several unique features, including a dioxotricyclic core, featuring a 14-membered lactone, and a highly unsaturated, oxazole-containing side chain. Complex molecular architecture of leucascandrolide A, highly unusual for metabolites produced by calcareous sponges, led Pietra to hypothesize that this natural product originated from an unknown microbial organism present in *L. caveolata*.[2] The structural complexity of leucascandrolide A, potent cytotoxic and antifungal properties, combined with the uncertainty of the biogenetic origin, stimulated considerable synthetic interest in this target,[3,4] with the first total synthesis recently achieved by Leighton.[3a]

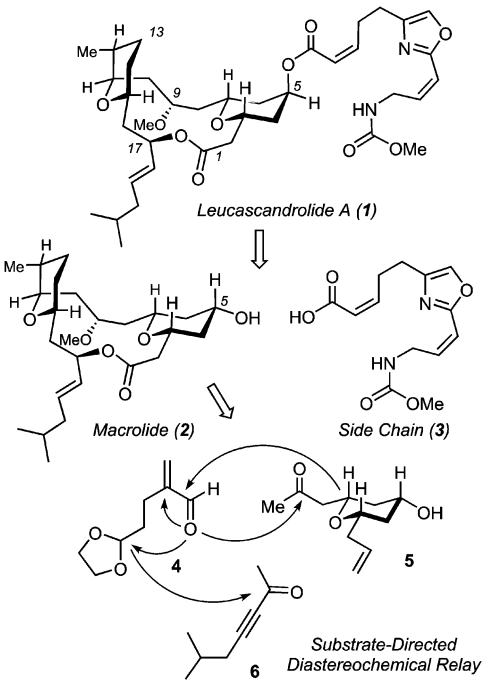
In this communication, we present a unique synthetic solution of the leucascandrolide problem, featuring a concise, convergent, and stereocontrolled approach to this complex natural product. *Our synthesis led to the discovery of a spontaneous intramolecular macroacetalization, providing an unprecedented and efficient route to this macrolide.*[5]

Our strategy was designed to exploit the substrate-directed diastereoselection in establishing all of the stereogenic elements of leucascandrolide A (Scheme 1).[4] Following the initial disconnection at the C_5 ester linkage, macrolide **2** would originate from three simplified segments **4**, **5**, and **6**. The chirality of macrolide **2** would solely derive from pyran **5** via a series of diastereoselective transformations. Following this logic, one of us previously described an efficient synthesis of the fully functionalized C_1-C_{15} fragment (**12**, Scheme 3) of leucascandrolide A, featuring Prins desymmetrization, convergent 1,5-*anti*-selective aldol condensation, and highly chemo- and diastereoselective Pt-catalyzed hydrosilylation.[4] The remaining challenges entailed the efficient conversion of this segment to the macrolide **2**, assembly of the oxazole-bearing side chain **3**, and effective union of the two fragments en route to the final target **1**.

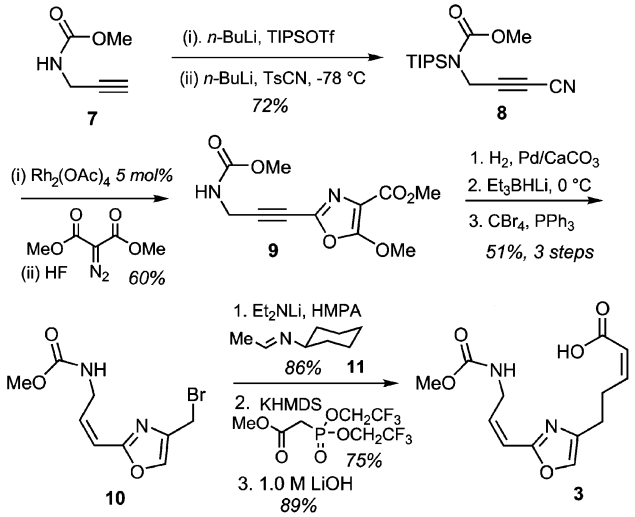
Construction of the side chain **3** commenced with the conversion of alkyne **7** to nitrile **8** via a one-pot silylation-cyanation protocol employing TsCN (Scheme 2).[6] Assembly of the oxazole subunit was designed to probe the participation of alkynyl nitriles in the metal-catalyzed condensations with diazo carbonyl compounds.[7] In the event, subjection of nitrile **8** to diazomalonate in the presence of $Rh_2(OAc)_4$ (5 mol %) according to the Helquist protocol,[7b] followed by protodesilylation, afforded oxazole **9**. Hydrogenation, Super-Hydride reduction, followed by bromination of the resulting alcohol, furnished bromide **10**. Alkylation of the lithium enolate of imine **11** with bromide **10** efficiently afforded the two-carbon extended aldehyde. *Z*-Selective olefination,[8] followed by saponification, completed the assembly of the side chain subunit **3** (eight steps, $Z{:}E = 11{:}1$).

Synthesis of the macrolide continued from the previously described alcohol **12**[4] (Scheme 3) efficiently assembled from aldehyde **4** and ketone **5**. Following the dioxolane removal, and acetylation of the resulting lactol, C-glycosidation with enol silane

Scheme 1



Scheme 2



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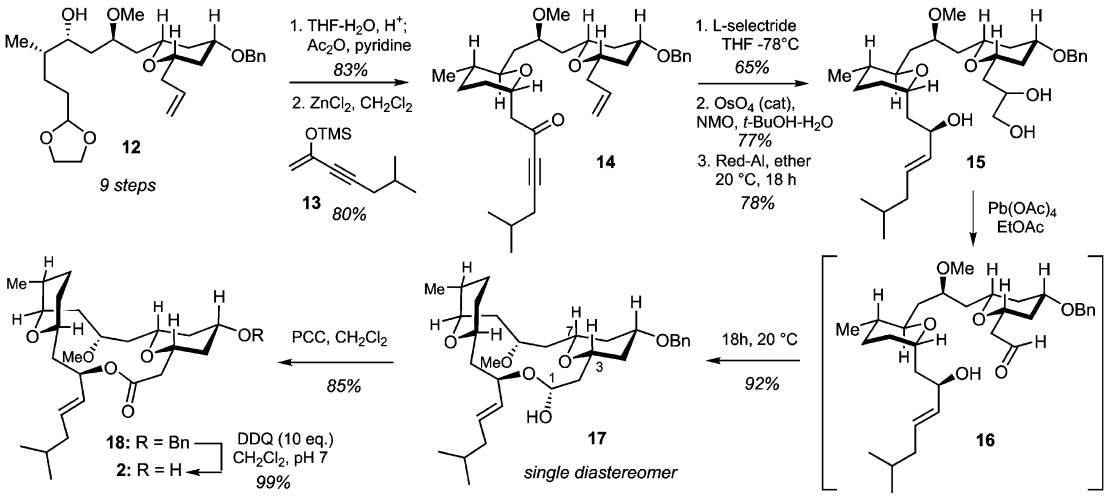
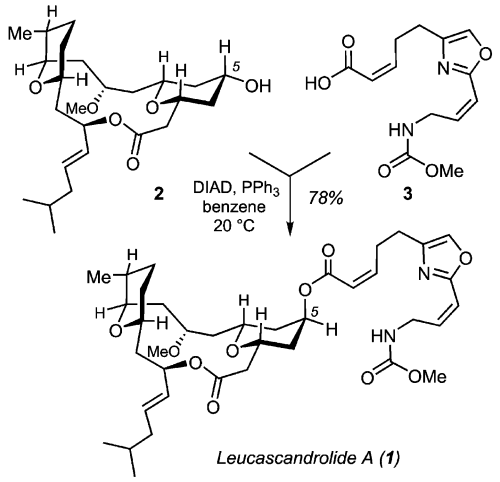
Scheme 3



13[9] furnished ynone **14** as a single diastereomer. L-Selectride reduction,[10] followed by chemoselective dihydroxylation of the terminal alkene and Red-Al reduction of the alkyne, gave triol **15**. Unexpectedly, treatment of triol **15** with $Pb(OAc)_4$ afforded lactol **17** in 92% yield as a single diastereomer,[11] arising spontaneously via intramolecular macroacetalization of the intermediate hydroxy aldehyde **16**.[12] Subjection of lactol **17** to pyridinium chlorochromate in CH_2Cl_2 gave lactone **18**, providing further evidence of the unusual thermodynamic stability of this 14-membered macrocycle. Oxidative removal of the benzyl ether with DDQ[13] completed the construction of macrolide **2** (17 steps).

Designed to invert the relative stereochemistry at the C_5, the end game entailed Mitsunobu esterification of alcohol **2** with carboxylic acid **3** (Scheme 4). To our delight, despite the highly congested steric environment, treatment of the two coupling fragments with PPh_3 and DIAD afforded the final target (±)-**1** directly in 78% yield. 500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR spectra of synthetic leucascandrolide A were in excellent agreement with those reported in the literature.[1,3a]

Scheme 4



In closing, we have developed an efficient synthesis of leucascandrolide A, which provided access to the natural product with the longest linear sequence of 18 steps from commercially available precursors. The spontaneous intramolecular acetalization demonstrated the possibility of accessing large-ring systems in a highly controlled and efficient manner.

Acknowledgment. Financial support of this work was provided by the National Institute of Health (National Cancer Institute, R01 CA93457). We thank Professor Leighton for a copy of the 500 MHz ^{1}H NMR spectrum of leucascandrolide A.

Supporting Information Available: Full characterization of new compounds and selected experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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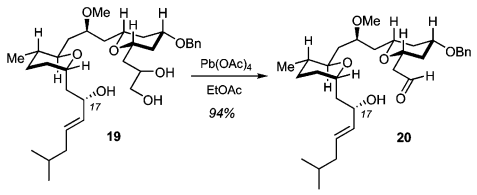
(9) For details, see the Supporting Information.
(10) While moderate diastereoselection was observed (67:33), the desired alcohol was obtained in 65% isolated yield after routine chromatographic separation. In addition, the undesired epimer can be readily converted to the requisite diastereomer via a one-pot Mitsunobu esterification-hydrolysis protocol (p-$NO_2C_6H_4CO_2H$, DMAD, PPh_3; K_2CO_3, 89% yield).[8]
(11) Relative stereochemistry at the C_1 was assigned by a combination of DQF COSY and NOESY, revealing an intramolecular hydrogen bonding motif between C_1−OH and C_3−O−C_7.
(12) In contrast, subjection of the C_{17} epimeric triol **19** to the oxidative cleavage conditions resulted only in formation of the corresponding hydroxy aldehyde **20**.



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JA028428G