

Formal Chemoselective Synthesis of
Leucascandrolide A

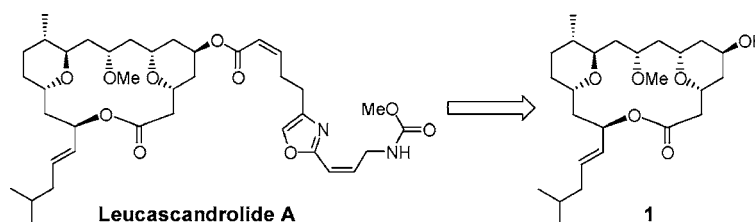
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Received March 19, 2007

ABSTRACT



A chemoselective synthesis of the macrocyclic core of leucascandrolide A has been achieved, utilizing highly enantioselective allylmetalations, an enantioselective Noyori reduction of a propargylic ketone and olefin metatheses as the key steps.

Leucascandrolide A is a structurally unique macrolide isolated in 1996 from the sponge *Leucascandra caveolata*, extracted from the northeastern coast of New Caledonia in the Coral Sea.¹ The relative stereochemistry of the substituents in macrolide **1** was determined by NMR analysis, and the absolute configuration of the stereogenic centers was assigned through correlation of the C5 stereocenter by transforming the C5 hydroxy group to a Mosher ester. The natural product has been shown to possess anticancer activity against human KB and P388 tumor cell lines displaying IC₅₀ values of 0.05 and 0.26 $\mu\text{g/mL}$, respectively. Furthermore, leucascandrolide A also exhibits potent antifungal activity against *Candida albicans*, a yeast that attacks AIDS patients. Recent reports indicate that leucascandrolide A is no longer available from its original natural source due to the fact that this compound is actually not a secondary metabolite of *Leucascandra caveolata* but that of opportunistic bacteria.² Because of its structural complexity and its interesting biological properties, leucascandrolide A has solicited considerable interest among organic chemists, and five total³ and four formal⁴ syntheses as well as the preparation of several fragments⁵ have been reported.

For our part, we would like to report here the synthesis of the macrocyclic core of leucascandrolide A. Macrolide **1** would be obtained by the macrolactonization of **A**, and the *cis*-tetrahydropyran moiety present in **1** would be obtained by an intramolecular 1,4-addition of the hydroxy group at C7 on the α,β -unsaturated ester present in **A**. Ester **A** would be synthesized by using an olefin cross-metathesis between methyl acrylate and **B**. In compound **B**, the stereogenic centers at C5, C7, and C9 would be controlled by using highly stereoselective allylmetalations of aldehydes. The

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(4) For syntheses of the macrolide core of leucascandrolide A, see: (a) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. (b) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066. (c) Williams, D. R.; Plummer, S. V.; Patnaik, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3934. (d) Williams, D. R.; Patnaik, S.; Plummer, S. V. *Org. Lett.* **2003**, *5*, 4641. (e) Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641.

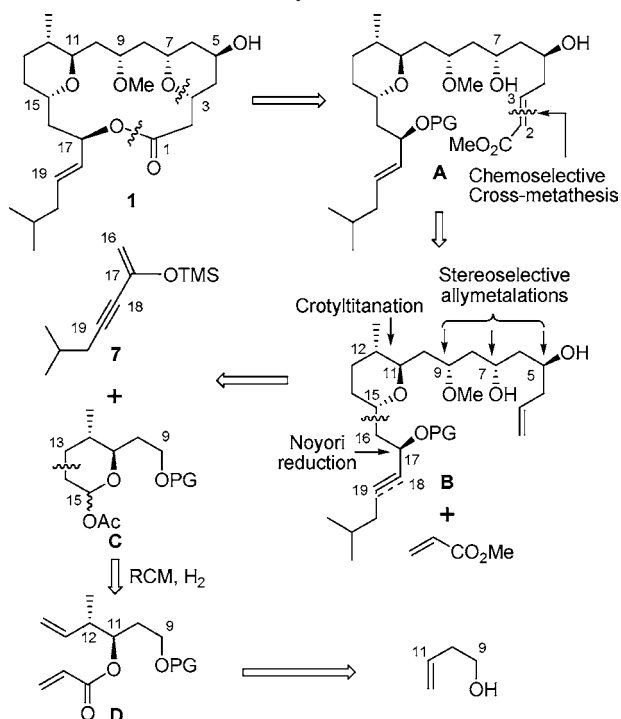
(5) For syntheses of other fragments of leucascandrolide A, see: (a) Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 579. (b) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755. (c) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2001**, *66*, 3242. (d) Dakin, L. A.; Langille, N. F.; Paneck, J. S. *J. Org. Chem.* **2002**, *67*, 6812. (e) Dakin, L. A.; Paneck, J. S. *Org. Lett.* **2003**, *5*, 3995.

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(2) D'Ambrosio, M.; Tato, M.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347.

stereogenic centers at C11 and C12 would be controlled by applying an enantioselective crotylmatalation to an aldehyde, and the C17 stereogenic center would be controlled by utilizing a ruthenium-catalyzed Noyori reduction of a propargylic ketone. The addition of enol ether **7** to an oxonium species derived from **C** would control the stereogenic center at C15. To access tetrahydropyran **C**, a ring-closing metathesis of diene **D** which would be synthesized from but-3-en-1-ol was envisaged (Scheme 1).

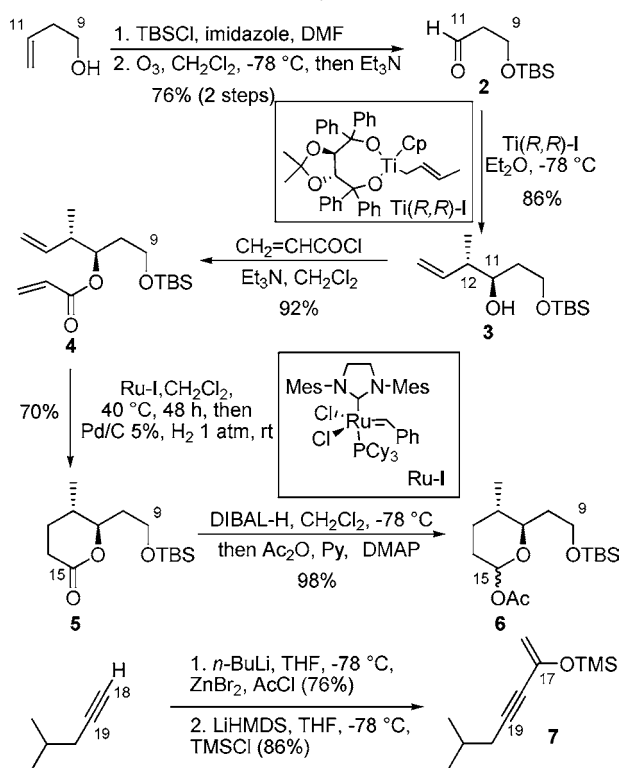
Scheme 1. Retrosynthesis of Macrolide **1**



The synthesis of fragment C9–C15 started with the transformation of but-3-en-1-ol to aldehyde **2** which was obtained in 76% yield after protection of the alcohol (TBDMSCl, imidazole) and ozonolysis (O_3 , -78°C , then Et_3N).⁶ The addition of the highly face selective titanium complex $\text{Ti}(R,R)\text{-I}^7$ to aldehyde **2** (Et_2O , -78°C) allowed us to control the stereogenic centers at C11 and C12, producing the desired homoallylic alcohol **3** in 86% yield (*dr* > 95/5 and *de* > 95/5).^{8,9} After transformation of **3** to the unsaturated ester **4** (acryloyl chloride, Et_3N , CH_2Cl_2 , 92% yield), two one-pot sequences were successfully applied to produce the desired acetoxymethyl acetal **6**. The first one-pot reaction involved a tandem RCM/hydrogenation¹⁰ (Ru-I , 3 mol %, then H_2 , Pd/C) forming lactone **5** in 70% yield. The

second one-pot reaction was the transformation of **5** to **6** in 98% yield by reduction of lactone **5** with DIBAL-H (-78°C , CH_2Cl_2) followed by acylation of the alkoxy aluminum intermediate (Ac_2O , Py, DMAP).¹¹ On the other hand, silyl enol ether **7** was prepared in two steps from the commercially available 4-methyl pent-1-yne. The starting alkyne was acylated via an organozinc intermediate (*n*-BuLi, THF, -78°C , then ZnBr_2 and AcCl) providing the propargylic ketone (76% yield). This ketone was treated with LiHMDS to furnish the corresponding lithium enolate, which was trapped with TMSCl to give the silyl enol ether **7** (86% yield)^{3b} (Scheme 2).

Scheme 2. Construction of Synthetic Intermediates **6** and **7**



Fragment C16–C22 **7** was then coupled with the C9–C15 fragment **6** by using a Mukaiyama-type reaction. An oxonium intermediate which was generated from **6** by treatment with ZnCl_2 at -78°C was quenched with enol ether **7** to afford tetrahydropyran **8** (*trans/cis* = 13/1, 89% yield).¹² After reduction of ketone **8** by using Noyori catalyst $\text{Ru}(R,R)\text{-II}$ under phase transfer conditions (HCO_2Na , *n*-Bu₄NCl, $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$),^{13,14} the desired propargylic alcohol **9** was isolated in 76% yield accompanied by ketone **9'** (18%).¹⁵ The propargyl alcohol **9** was reduced with RedAl

(6) Hon, Y. S.; Lin, S. W.; Lu, L.; Chen, Y. J. *Tetrahedron* **1995**, *51*, 5019.

(7) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rhoté-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.

(8) *dr* based on the ^1H NMR spectra of the crude reaction mixture.

(9) Titanium complex $\text{Ti}(R,R)\text{-I}$ or $\text{Ti}(R,R)\text{-II}$ allows the delivery of the nucleophile on the *Si* face of an aldehyde.

(10) Bargiggia, F. C.; Bouzbouz, S.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 6715.

(11) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191.

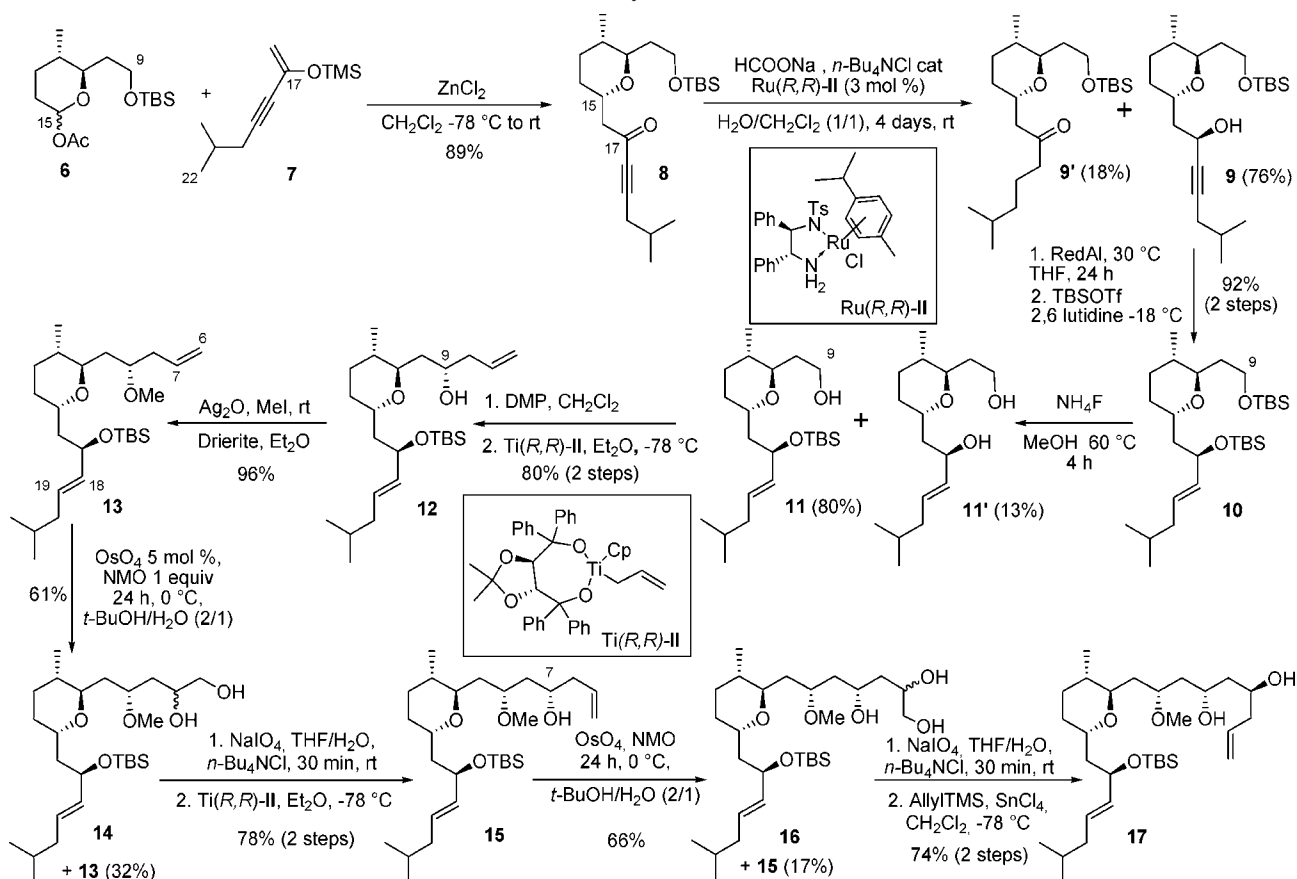
(12) *Trans/cis* ratio determined by GC/MS and GC analysis.

(13) Matsumura, K.; Hashigushi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

(14) When the formic acid/ Et_3N system was used for the reduction, cleavage of the TBS ether in compound **8** was observed, and when *i*-PrOH was used as the hydride source with the 16-electron Noyori catalyst, high catalytic loading was required to achieve the reduction of **8**.

(15) A single diastereoisomer was observed by GC and NMR.

Scheme 3. Synthesis of Diol 17



to the (*E*)-allylic alcohol, but a partial deprotection of the primary alcohol at C9 was observed. Due to the formation of this by-product, the crude material was directly treated with TBSOTf (92% yield over two steps) to give compound **10**. The primary alcohol was chemoselectively deprotected (NH_4F , MeOH)¹⁶ to afford alcohol **11** (80% yield) along with diol **11'** (13%). Despite the formation of by-product **11'**, this compound could be easily recycled to **10** and transformed to **11**. Once primary alcohol **11** was obtained, it was oxidized to an aldehyde (Dess–Martin periodinane) which was directly treated with the highly face-selective titanium complex $\text{Ti}(\text{R,R})\text{-II}$,⁷ to produce homoallylic alcohol **12** (80% yield from **11**, dr > 95:5).^{8,9} The hydroxy group at C9, in compound **12**, was then transformed to a methyl ether, leading to compound **13** (Ag_2O , MeI, 96% yield). To introduce the stereogenic centers at C7 by allylation, compound **13** had to be converted to an aldehyde by oxidative cleavage of the terminal double bond. However, it was necessary to perform the oxidative cleavage of the terminal double bond selectively over the internal C18–C19 double bond. As the internal double bond was protected by the use of the bulky TBS protecting group at C17, the dihydroxylation of **13** [OsO_4 cat, NMO (1.1 equiv)] led chemoselectively to diol **14** (61% yield, 32% unreacted starting material),¹⁷ which was then treated with NaIO_4 to

furnish the desired aldehyde. This aldehyde was directly subjected to a stereoselective allylation using $\text{Ti}(\text{R,R})\text{-II}$ to produce homoallylic alcohol **15** (78% from diol **14**). At this stage, the stereodirected introduction of the C5 stereogenic center was envisaged by using a stereoselective allylstannylation.¹⁸ To realize this transformation, alcohol **15** was transformed to an aldehyde using the same chemoselective two-step oxidative cleavage as before. At first, triol **16** was obtained by dihydroxylation (OsO_4 cat, NMO, 66% yield, 17% recovered starting material),¹⁷ and its subsequent oxidative cleavage with NaIO_4 generated the corresponding aldehyde. The obtained hydroxy-aldehyde was then directly treated with a premixed solution of allyltrimethylsilane and SnCl_4 at $-78\text{ }^\circ\text{C}$,¹⁶ producing *syn*-1,3-diol **17** (74% yield, two steps from **16**) (Scheme 3).

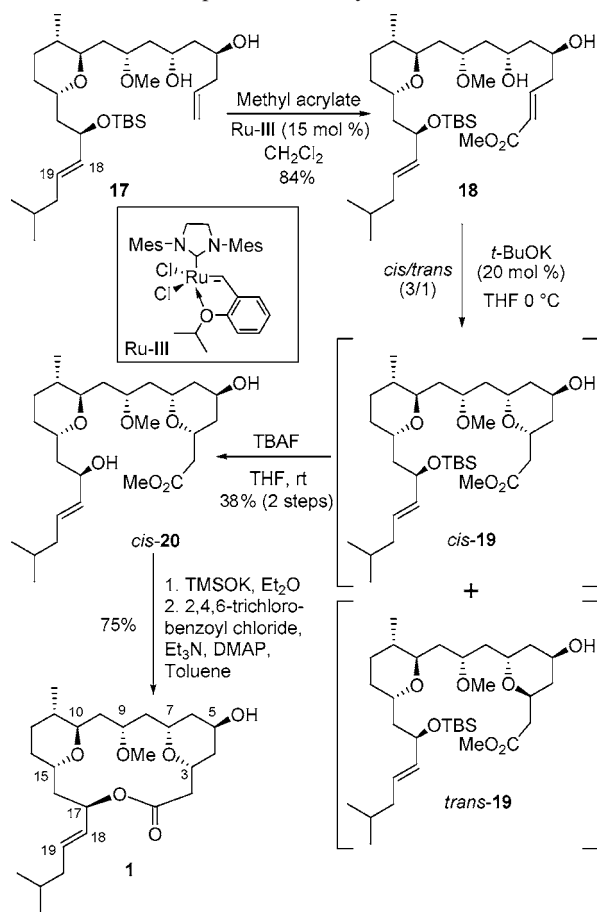
At this point of the synthesis, seven of the eight stereogenic centers of leucascandrolide A were installed. To complete the synthesis of macrolactone **1** and to introduce the last C3 stereogenic center, an intramolecular 1,4-addition of the hydroxy group at C7 to an α,β -unsaturated ester was envisaged. Compound **17** was treated with methyl acrylate

(17) After 24 h, no evolution of the conversion was observed and the conditions were not forced to preserve the chemoselectivity of the dihydroxylation.

(18) (a) Allais, F.; Cossy, J. *Org. Lett.* **2006**, *8*, 3655. (b) Allais, F.; Louvel, M.-C.; Cossy, J. *Synlett* **2007**, 451. (c) Allais, F.; Roche, C.; Bouzbouz, S.; Cossy, J., unpublished results.

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Scheme 4. Completion of the Synthesis of Macrolide **1**



in the presence of Hoveyda–Grubbs catalyst Ru-III¹⁹ (15 mol %) to provide chemoselectively the unsaturated ester **18** (84% yield).²⁰ The elaboration of *cis*-tetrahydropyran **19** was realized under basic conditions by using a catalytic amount of *t*-BuOK²¹ (20 mol %) which afforded two diastereoisomers in a modest ratio (*cis*-**19**/*trans*-**19** = 3/1). These two epimers were difficult to separate at this stage,

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but fortunately, they were separated in the next step by column chromatography on silica gel. After treatment with TBAF in THF, diol *cis*-**20** was isolated as a single diastereoisomer (38% over the two steps).²²

Finally, macrolactone **1** was obtained by applying two reported procedures.^{3,4} At first, a mild saponification of the methyl ester with TMSOK²³ in Et₂O afforded the hydroxy acid, the cyclization of which provided selectively the macrocyclic core of leucascandrolide A **1** under the Yonemitsu-modified Yamaguchi protocol²⁴ (75% yield from *cis*-**20**). Macrolide **1** was identical in all respects with the spectral data and the specific rotation reported previously (Scheme 4).^{3,4}

Macrolide **1** was synthesized in 25 steps and 1.2% overall yield from but-3-en-1-ol. Synthetic highlights include highly stereoselective allylmetalations to control the stereogenic centers at C5, C7, C9, C11, and C12, an enantioselective Noyori reduction of a propargylic ketone to control the stereogenic center at C5, a cross-metathesis followed by an intramolecular 1,4-addition to build up the *cis*-tetrahydropyran, and a ring-closing metathesis Mukaiyama reaction to build up the *trans*-tetrahydropyran. Furthermore, by using chemoselective reactions such as selective cleavage of TBS ethers, dihydroxylation and cross-metatheses, this synthesis appears to be one of the shortest syntheses of the macrolide core of leucascandrolide A, considering the total number of steps.

Acknowledgment. L.F. thanks the MRES for a grant.

Supporting Information Available: Experimental procedure and ¹H and ¹³C NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(22) The major isomer *cis*-**20** showed the same spectral data as those described by Crimmins: see ref 4e.

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