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Efficient Stereochemical Relay en Route to Leucascandrolide A

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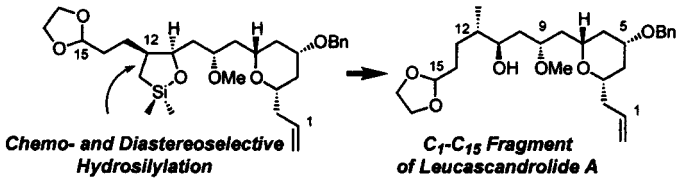
ABSTRACT



A complete relay of the initial stereochemical information is central to the efficient and highly stereocontrolled construction of the C_1–C_{15} fragment of the marine macrolide leucascandrolide A. Cyclic silane 3, assembled via Pt-catalyzed hydrosilylation, was designed to serve as a temporary template for the installation of the C_{12} stereogenic center. The strategy features a highly convergent C_{10}–C_{11} bond construction via 1,5-*anti*-selective aldol reaction and rapid assembly of the trisubstituted pyran subunit via Prins desymmetrization.

Efficient assembly of diverse stereochemical arrays containing multiple stereogenic centers plays a pivotal role in target-oriented synthesis. Advances in asymmetric synthesis involving the use of external chiral controllers (i.e., auxiliaries, reagents or catalysts) have simplified solutions of many challenging stereochemical puzzles.[1] However, creation of new chiral elements by means of internal asymmetric induction utilizing substrate-based diastereochemical relay often represents a more direct and efficient approach.[2] The ideal scenario entails formation of all asymmetric centers of the target compound starting from a single stereogenic point without any additional external chirality being used in the assembly process.[2d]

Aiming at the development of an efficient and practical strategy featuring a complete acyclic stereochemical relay, we recently initiated a program aimed at the synthesis of leucascandrolide A (**1**), a highly bioactive marine macrolide isolated by Pietra et al. from a new genus of calcareous sponges, *Leucascandra caveolata* (Scheme 1).[3,4] Due to the difficulty in isolating leucascandrolide A, combined with the presently unknown biogenetic origin,[5] an efficient chemical synthesis of this macrolide would provide an ideal approach for its efficient production for further pharmacological evaluation.[6] Herein, I present a convergent, highly stereocontrolled assembly of the C_1-C_{15} fragment (**2**) representing the central portion of leucascandrolide A and incorporating six of the requisite stereogenic centers.

Retrosynthetically, subtarget **2** was envisioned to derive from hydroxy ketone **4** via a series of diastereo- and chemoselective transformations involving reduction of the

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(2) (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3−72. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370. (c) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223. (d) Smith, A. B., III; Empfield, J. R. *Chem. Pharm. Bull.* **1999**, *47*, 1671−1678.

(3) (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51−60. (b) For isolation of leucascandrolide B, see: D'Ambrosio, M.; Tatò, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347−353.

(4) For a recent total synthesis of leucascandrolide A, see: (a) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894−12895. For another synthetic approach, see: (b) Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 597−599. (c) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 177−180.

(5) Several lines of evidence presently suggest that leucascandrolide A may originate from the microbial organism present in *L. caveolata*.

(6) In preliminary in vitro studies, leucascandrolide A displayed potent cytotoxicity against KB and P388 tumor cell lines (IC_{50} 50 ng/mL and 0.25 μg/mL respectively), as well as strong inhibition of *Candida albicans*.

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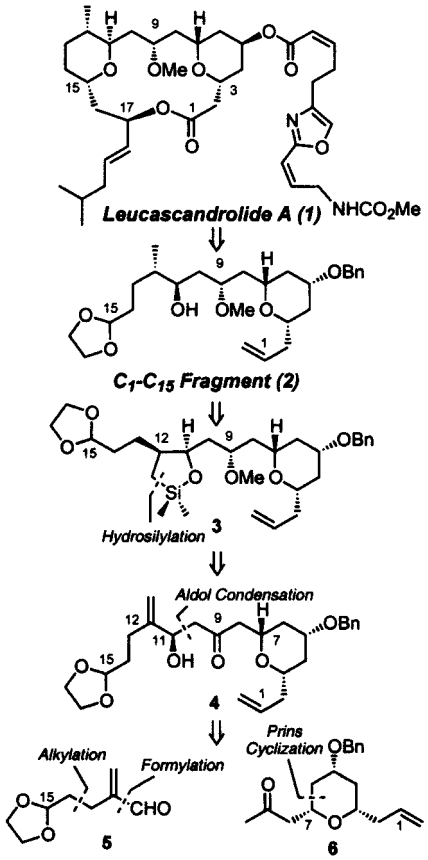
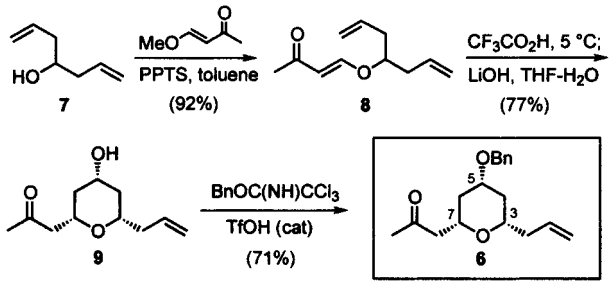
Scheme 1



C_9-carbonyl and hydrosilylation of the C_{12}-methylene. The resulting silacycle **3** was designed to reveal advanced fragment **2** upon cleavage of the C−Si and O−Si linkages. Highly convergent disconnection of ketone **4** at C_{10}−C_{11} furnished the corresponding aldol coupling partners **5** and **6.** According to the precedent recently provided by Paterson[7] and Evans,[8] boron-enolate mediated aldolization was expected to deliver the desired *anti*-stereochemical relationship between the newly created C_{11}-hydroxyl and C_7-alkoxy group. Aldehyde **5** would be rapidly assembled via an alkylation−formylation sequence (vide infra). Construction of ketone **6**, incorporating an all-*cis* trisubstituted tetrahydropyran subunit, would entail a highly diastereoselective Prins cyclization.[9]

Assembly of ketone **6** began with vinylogous transesterification[10] of 4-methoxy-3-butenone with heptadienol **7**[11]

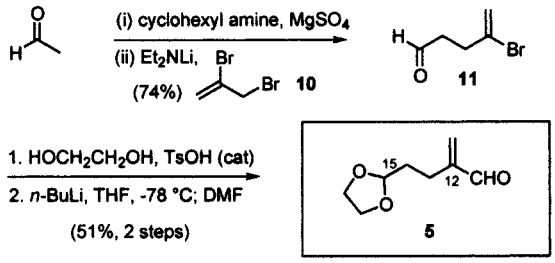
Scheme 2



(PPTS, toluene, 110 °C), furnishing the Prins cyclization precursor **8** in 92% yield (Scheme 2). Treatment of vinylogous ester **8** with TFA[12] at 5 °C followed by basic hydrolysis of the trifluoroacetate resulted in formation of the all-*cis* tetrahydropyran **9** in 77% yield.[13] Equatorial disposition of substituents was rigorously established at this stage by a combination of DQF COSY and NOESY experiments. The highly stereocontrolled construction of three stereogenic centers in a single step is illustrative of the power of Prins desymmetrization tactics for the assembly of polysubstituted tetrahydropyrans. Acid-catalyzed benzylation of alcohol **9** ($BnOC(NH)CCl_3$, TfOH (cat.), CH_2Cl_2−cyclohexane)[14] then afforded ketone **6**, completing construction of the first aldol coupling partner in three steps and 50% overall yield.

Preparation of aldehyde **5**, the second aldol component, was similarly accomplished in three steps (Scheme 3).

Scheme 3



Conversion of acetaldehyde to the corresponding cyclohexyl imine, followed by lithiation[15] and alkylation with 2,3-dibromopropene (**10**), afforded aldehyde **11** in 74% yield.[16] Acetalization (ethylene glycol, TsOH) and formylation via metal−halogen exchange, followed by addition of dimethylformamide, furnished aldehyde **5** in 38% overall yield for the three steps.

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(8) (a) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788−789. (b) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671−8726. (c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046.

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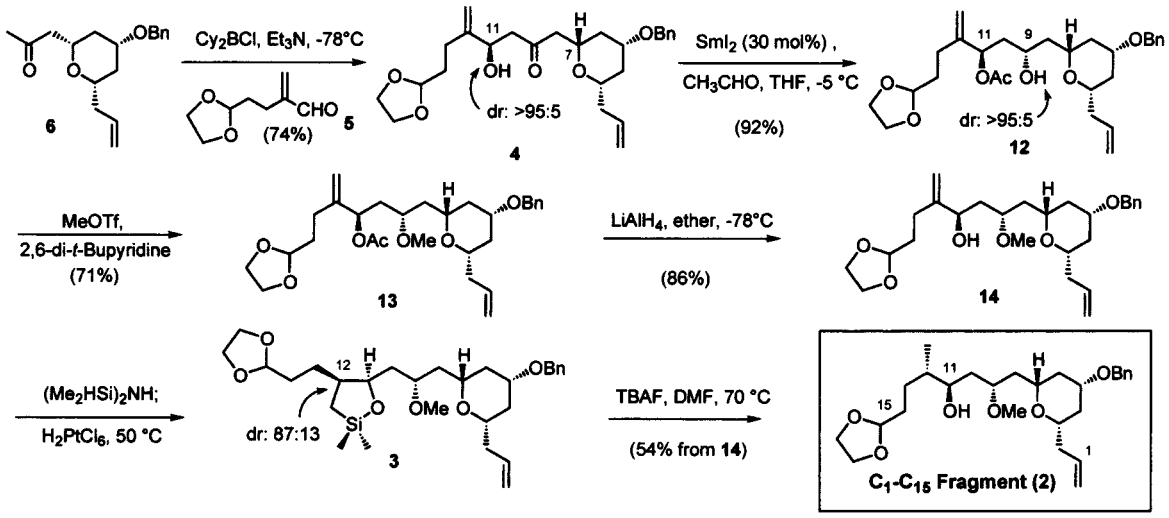
Scheme 4

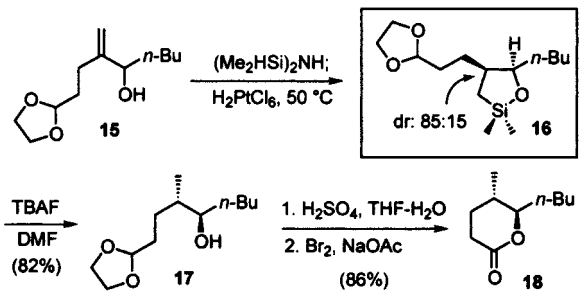


Generation of the dicyclohexylboron enolate from ketone **6** followed by addition of aldehyde **5** (−78 °C, ether)[7] efficiently accomplished the union of these aldol reaction partners, furnishing hydroxy ketone **4** as a single diastereomer (Scheme 4). Apart from the high convergency, this operation delivered the requisite stereochemistry of the newly created C_{11} alcohol as a result of efficient 1,5-*anti* stereochemical induction by the C_7-alkoxy group.[7,8]

Diastereoselective ketone reduction [SmI_2 (30 mol %), CH_3CHO, THF][17] cleanly established the C_9-stereogenic center (92% yield, dr >95:5). Methylation (MeOTf, 2,6-di-*tert*-butylpyridine),[18] followed by removal of the acetate with $LiAlH_4$, gave allylic alcohol **14** in 86% yield.

The validation of the projected late-stage hydrosilylation was initially achieved in a model study summarized in Scheme 5. Conversion of alcohol **15**[19] into the corresponding

Scheme 5



silyl ether using tetramethyldisilazane, followed by treatment with H_2PtCl_6 (0.3 mol %) in benzene at 50 °C, resulted in facile formation of silacycle **16** (dr 85:15). Importantly, no products resulting from competing olefin isomerization were detected. Stereochemical assignment of **16**, initially based on the precedent by Tamao,[20] was achieved by conversion to the known lactone **18**[21] involving protodesilylation (TBAF, DMF)[22] and acid-catalyzed acetal hydrolysis, followed by oxidation of the resulting lactol to the lactone (Br_2, NaOAc, $AcOH-H_2O$).[23]

Having established a reliable hydrosilylation protocol, attention was focused on conversion of alcohol **14** to subtarget **2** (Scheme 4). Silylation [$(Me_2HSi)_2NH$, $CHCl_3$, 15 min), followed by addition of H_2PtCl_6 (0.5 mol %), resulted in diastereoselective formation of silacycle **3** (dr 87:13) without detectable hydrosilylation of the terminal olefin. Protodesilylation was then achieved using TBAF (DMF, 70 °C, 15 min)[22] to give the fully elaborated C_1-C_{15} fragment (**2**) of leucascandrolide A.

The stereochemical outcome of the intramolecular hydrosilylation of alcohols **14** and **15** resulting in predominant formation of *anti*-diastereomeric products **2** and **17**, respectively, is in agreement with *erythro* selectivity previously observed by Tamao.[20] If hydroplatination is assumed to be a stereochemistry-determining step,[20c] examination of the diastereomeric transition structures **C** and **D** (Scheme 6) provides a rationale for the observed selectivity. Indeed, transition state **D** is expected to be higher in energy due to the unfavorable nonbonding interaction between R^1 and R^2 resulting in significant $A_{1,2}$-strain. Therefore, formation of

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(18) Walba, D. M.; Thurmes, W. H.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046−1056.
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(20) (a) Tamao, K.; Nakajima, T.; Sumiiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090−6093. (b) Tamao, K.; Yamauchi, T.; Ito, Y. *Chem Lett.* **1987**, 171−174. (c) Tamao, K.; Nakagawa, Y.; Ito, Y. *Organometallics* **1993**, *12*, 2297−2308. Also, see: (d) Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 2121−2128. (e) Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 2128−2135.
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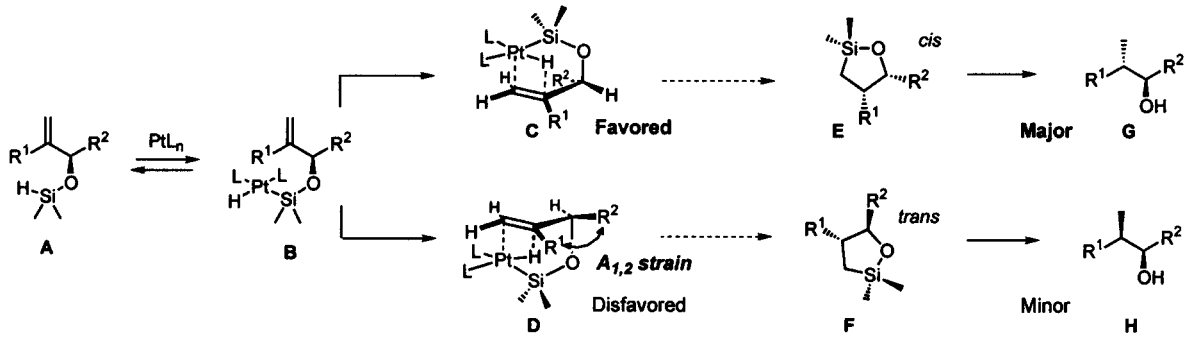
Scheme 6



the *cis*-disubstituted cyclic silane **E**, as the major product, proceeds through transition state **C** involving diastereoselective delivery of hydride from the *re*-face. Final cleavage of the O−Si and C−Si bonds reveals the observed *anti*-alcohol **G**.

In summary, the assembly of C_1-C_{15} fragment **2** of leucascandrolide A (**1**) has been achieved in nine steps and 11% overall yield. The six requisite stereogenic centers were assembled via a stereochemical relay featuring a series of highly diastereoselective processes including Prins desymmetrization, aldol condensation, and Pt-catalyzed hydrosilylation. Completion of the synthesis of leucascandrolide A, along with further applications of cyclic silanes for the development of new stereoselective transformations, are currently under active investigation and will be reported in due course.

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Supporting Information Available: Complete experimental procedures and spectral characterization of all new compounds. This material is available free of charge at http://pubs.acs.org.

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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]

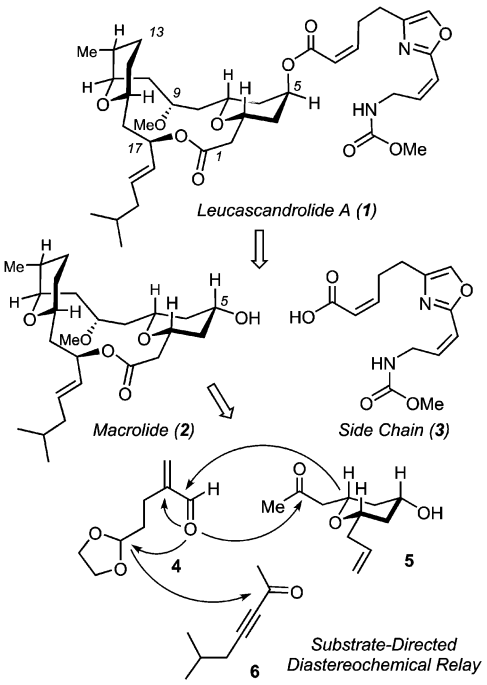
In this communication, we present a unique synthetic solution of the leucascandrolide problem, featuring a concise, convergent, and stereocontrolled approach to this complex natural product. *Our synthesis led to the discovery of a spontaneous intramolecular macroacetalization, providing an unprecedented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

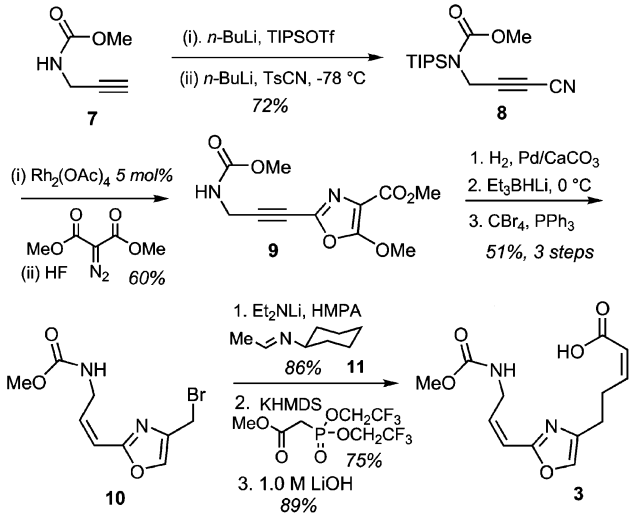
Construction of the side chain **3** commenced with the conversion of alkyne **7** to nitrile **8** via a one-pot silylation-cyanation protocol employing TsCN (Scheme 2).[6] Assembly of the oxazole subunit was designed to probe the participation of alkynyl nitriles in the metal-catalyzed condensations 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



* To whom correspondence should be addressed. E-mail: skozmin@uchicago.edu.

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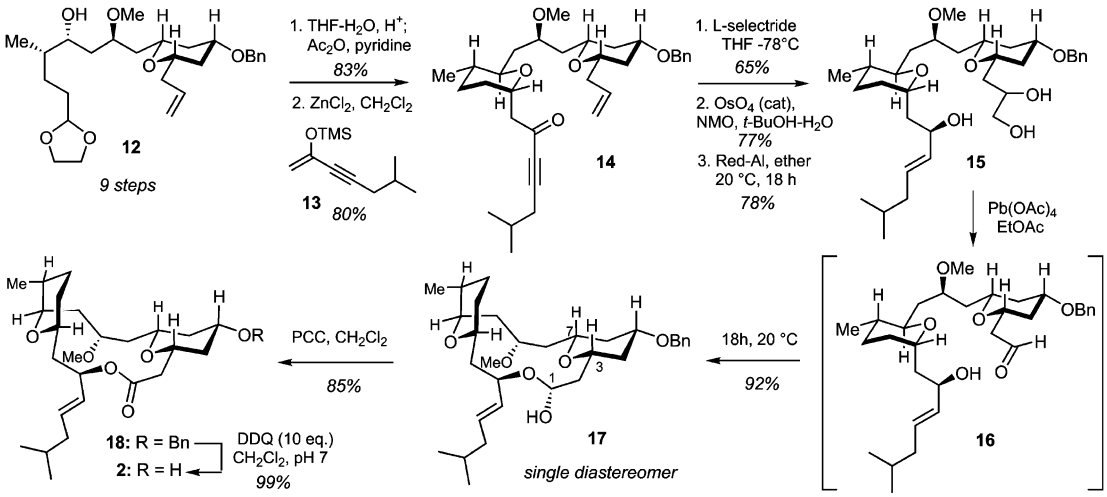
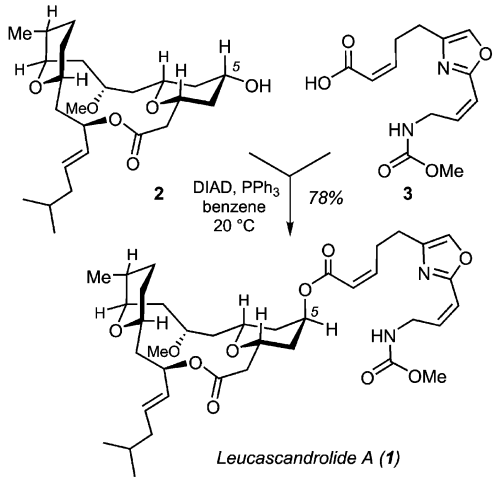
Scheme 3



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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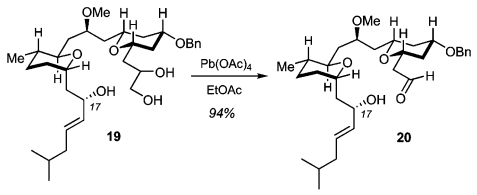
(9) For details, see the Supporting Information.
(10) While moderate diastereoselection was observed (67:33), the desired alcohol was obtained in 65% isolated yield after routine chromatographic separation. In addition, the undesired epimer can be readily converted to the requisite diastereomer via a 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

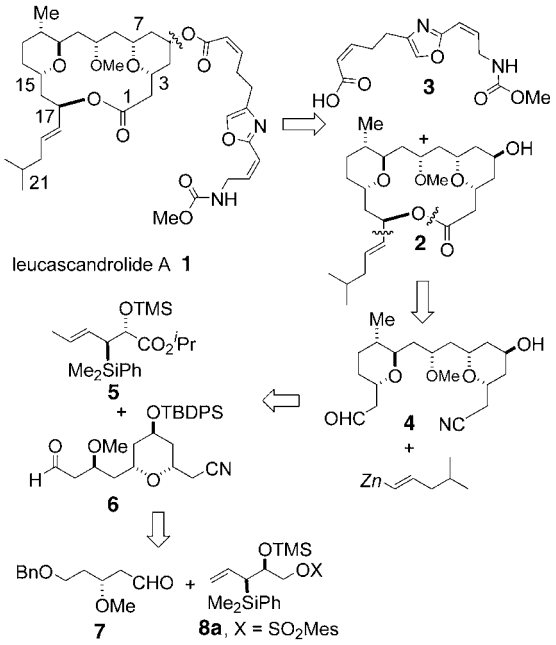
Natural Product Synthesis

Total Synthesis of (+)-Leucascandrolide A**

*Qibin Su and James S. Panek**

Leucascandrolide A (**1**) is a bioactive metabolite isolated by Pietra and coworkers from the calcareous sponge *Leucascandra caveolata*, found off the east coast of New Caledonia in the Coral sea.[1] Two-dimensional NMR experiments were used to determine the relative configuration of **1**, while its absolute configuration was assigned by employing a Mosher analysis at the C5-hydroxy group. This natural product possesses an 18-membered macrolide ring that includes two trisubstituted tetrahydropyran rings, and an unsaturated oxazole-containing side chain. Leucascandrolide A (**1**) displays significant in vitro cytotoxicity against human KB and P388 tumor cell lines with low IC_{50} values (0.05 and 0.26 $\mu g\,mL^{-1}$, respectively) as well as strong inhibition of *Candida albicans*, a pathogenic yeast. Recent reports[2] indicate that **1** is no longer available from its original natural source. It has been postulated that **1** is not a metabolite of *Leucascandra caveolata*, but rather of an opportunistic bacteria that colonized the sponge, as evidenced by the large amounts of dead tissue in the initial harvest of the marine organism. As a consequence, all known sources of the natural product have been depleted.[2] This fact, the potent bioactivity, and the unique structure of **1** have led to much attention among the synthetic community. Following the first total synthesis by Leighton et al.,[3] there have been additional reports detailing total,[4] formal,[5] and fragment syntheses.[6]

Herein, we describe an enantioselective total synthesis of (+)-leucascandrolide A (**1**). This synthesis is highlighted by the rapid and efficient construction of the bispyran **4** which contains a *cis*- and a *trans*-2,6-disubstituted tetrahydropyran ring. These rings were assembled in two [4+2] annulation reactions between aldehydes **7** and **6** and our newly introduced chiral allylsilane **8a** and crotylsilane **5**,[7] respectively. Our retrosynthetic analysis is illustrated in Scheme 1. Disconnection at the C5–ester bond reveals a macrolactone containing two pyran rings (**2**) and an oxazole-containing side chain **3**. Upon further analysis of the macrolide, we envisaged

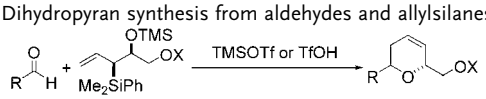


Scheme 1. Retrosynthesis of **1**; SO_2Mes = 2-mesitylenesulfonate.

that the allylic alcohol could be obtained from the addition of an alkenyl zinc species to aldehyde **4**.

Recently, we have described a highly diastereomerically and enantiomerically controlled [4+2] annulation between aldehydes and *syn* allylsilane **8b**, which produces *trans*-2,6-disubstituted dihydropyrans (Table 1).[8] Our attempt to

Table 1: Dihydropyran synthesis from aldehydes and allylsilanes **8**.



Entry	R	Silane	Product, yield [%][a]	d.r. (*trans*:*cis*)[b]
1	*i*Pr	**8a**, X = SO_2Mes	**9a**, 90	1:25
2	$PhCH_2$	**8a**, X = SO_2Mes	**9b**, 91	1:8
3	C_4H_9	**8a**, X = SO_2Mes	**9c**, 85	1:16
4[8]	*i*Pr	**8b**, X = Me	**9d**, 91	>30:1
5[8]	$PhCH_2$	**8b**, X = Me	**9e**, 91	>30:1
6[8]	*c*-Hex	**8b**, X = Me	**9f**, 95	10:1

[a] Yields are based on pure materials isolated after chromatography on SiO_2. [b] The configuration of the pyran products was assigned by NOE measurements. The product ratio was determined by ^1H NMR spectroscopy (400 MHz).

rationalize such a stereochemical outcome of the annulation process is depicted in Scheme 2. When allylsilane **8b** reacts with the aldehyde, we suggested that stabilization of the oxocarbenium cation by the neighboring electron-rich methyl ether favored a twist-boat intermediate thus accelerating the formation of the *trans*-2,6-dihydropyran product (route A in Scheme 2). If this were the case, the complementary *cis*-2,6-dihydropyran adducts could also be obtained from a *syn* allylsilane if the ring formation process occurred predominantly through a chair-like transition state. We predicted this could be achieved by tuning the steric and stereoelectronic

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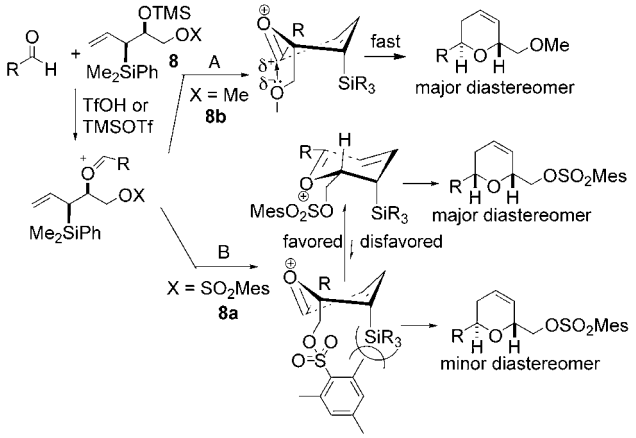


Scheme 2. Possible transition states for the [4+2] annulation of aldehydes with **8**.

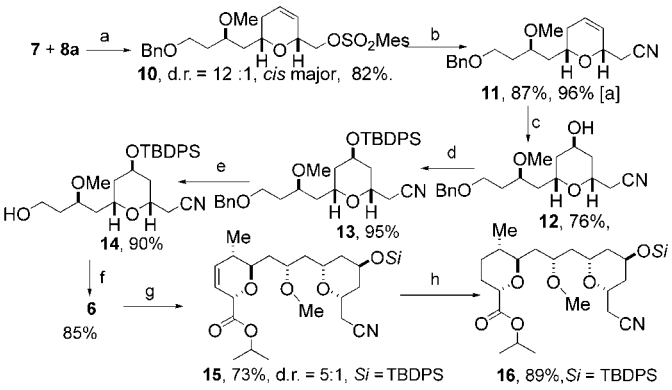
properties of the X substituent in the starting allylsilane **8**, for example by using a) an electron-withdrawing group X to minimize anchimeric assistance onto the oxocarbenium ion, and b) a sterically demanding functional group X to maximize destabilizing 1,2-diaxial interactions between X and the allylsilane moiety in the twist-boat conformer (route B in Scheme 2).

Accordingly, we evaluated the reactivity and selectivity of allylsilane **8a** bearing a mesitylsulfonate group in our [4+2] annulation (Table 1). The desired *cis*-2,6-dihydropyran products were obtained in very good yields and with high levels of diastereoselectivity (entries 1–3);[9] the annulation using allylsilane **8b** to produce *trans*-2,6-dihydropyrans (entries 4–6)[8] shows the generality of the methodology for synthesizing this class of heterocycles. Moreover, the reversal in the sense of diastereoinduction, resulting from the subtle structural differences between the two allylsilanes, is in accordance with our proposed transition states (Scheme 2) and gives further insight into a plausible mechanism of this interesting [4+2] annulation.

We were then ready to exploit the accessibility of *cis*-2,6-dihydropyrans in the synthesis of leucascandrolide A (**1**). Gratifyingly, annulation between allylsilane **8a**[10] and aldehyde **7**[11] proceeded smoothly in the presence of TfOH to afford the desired dihydropyran **10** in good yield and with good diastereoselectivity (Scheme 3).[12] The presence of the sulfonate in this product allowed an efficient one-carbon homologation through S_N2 displacement using NaCN to yield nitrile **11**.

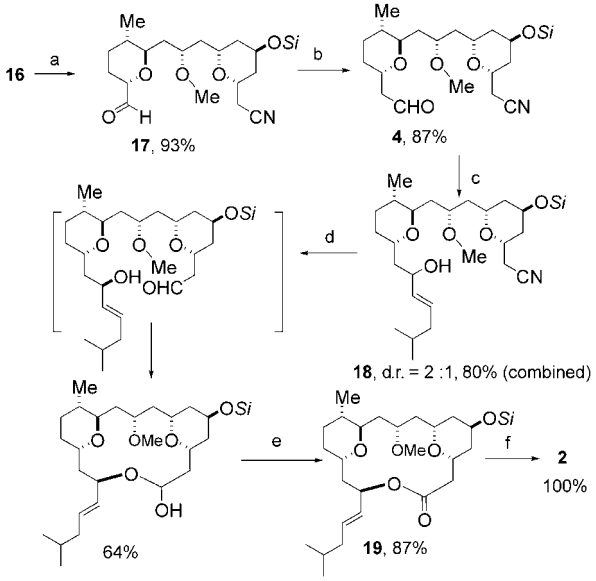
Oxymercuration of the double bond of **11** installed the C5-hydroxy group, as the single regio- and diastereomer **12**,[13] which was protected as the TBDPS ether **13**. Subsequent debenzylation with BCl_3 furnished the primary alcohol **14**, which was oxidized to aldehyde **6** using PCC.[14] Next, the crucial [4+2] annulation between **6** and crotylsilane **5** was carried out with useful diastereoselectivity and in good yield to produce dihydropyran **15**,[7a] which was hydrogenated to bispyran **16**.

Reduction of the isopropyl ester of **16** in presence of the nitrile group was conducted with complete chemoselectivity using DIBAL-H (2.1 equiv.) in Et_2O at −78 °C thus providing



Scheme 3. Reagents and conditions: a) TfOH, CH_2Cl_2, −78 °C; b) NaCN, DMF, 60 °C; c) mercury(II) trifluoroacetate, THF/H_2O, then $NaBH_4$ in NaOH (aq.); d) TBDPSCl, imidazole, DMF; e) BCl_3, CH_2Cl_2, −78 °C; f) PCC, CH_2Cl_2; g) **5**, TMSOTf, CH_2Cl_2, −50 °C; h) H_2, Pd/C. TfOH = trifluoromethanesulfonic acid, DMF = dimethylformamide, TBDPS = *tert*-butyldiphenylsilyl, PCC = pyridinium chlorochromate, TMSOTf = trimethylsilyl trifluoromethanesulfonate. [a] Yield based on recovered starting material.

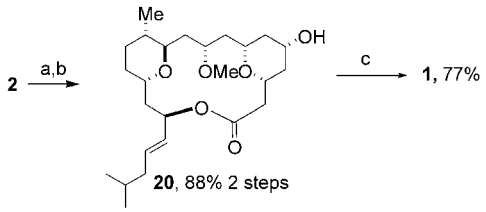
aldehyde **17** in high yield (Scheme 4). Homologation of the aldehyde group by a phosphorus-based olefination with methoxymethylenetriphenylphosphine and subsequent mercury acetate mediated hydrolysis of the resulting enol ether furnished aldehyde **4** in 87% over two steps.[15] Finally, addition of an alkenyl zinc species to **4** afforded allylic alcohol **18** in good yield, albeit with disappointing diastereoselectivity.[16] The diastereomers **18** were separated and the (17-*R*) alcohol obtained in 53% yield.



Scheme 4. Reagents and conditions. a) DIBAL-H, Et_2O, −78 °C; b) $Ph_3P{=}CHOMe$, THF, −78 °C to room temperature, then $Hg(OAc)_2$, THF/H_2O; c) in situ synthesis of the zinc reagent: 4-methyl-1-pentyne, CH_2Cl_2, [$Cp_2Zr(H)Cl$], room temperature; then $ZnMe_2$, −60 to 0 °C; then reaction with **4**, 0 °C; d) DIBAL-H, CH_2Cl_2, −78 °C, then HCl (aq., 1 N); e) PCC, CH_2Cl_2; f) TBAF, THF. DIBAL-H = diisobutylaluminum hydride, TBAF = tetrabutylammonium fluoride, *Si* = TBDPS.

Inspired by a spontaneous macroacetalization reported by Kozmin et al.,[4a] we decided for a similar transformation of nitrile **18**. Therefore, careful addition of DIBAL-H to a solution of **18** in CH_2Cl_2 at −78 °C followed by acidic hydrolysis of the resulting imine furnished a transient hydroxyaldehyde which spontaneously cyclized into the desired macrolactol. Oxidation to the macrolactone **19** using PCC followed by a TBAF-promoted deprotection of the C5-TBDPS ether provided macrolide **2** in excellent yield, establishing, at this stage, a formal total synthesis of leucascandrolide A (**1**).

It has been reported that it was difficult to achieve a direct acylation of the axially orientated C5-hydroxy group of **2**.[4c] We therefore turned our attention to the Mitsunobu reaction[17] to install the side chain at this center. Inversion of the configuration at C5 was achieved by a two-step oxidation–reduction sequence in excellent yield and with excellent selectivity (Scheme 5). Acid **3**[6c] and macrolide **20** were then united smoothly under Mitsunobu conditions to conclude the total synthesis of leucascandrolide A (**1**); the physical and spectroscopic properties of our compound were identical to those reported for **1**.[1,3]



Scheme 5. Reagents and conditions. a) Dess–Martin periodinane, pyridine, CH_2Cl_2; b) $NaBH_4$, MeOH, 0 °C; c) **3**, PPh_3, DIAD, THF/benzene. DIAD = diisopropyl azodicarboxylate.

In summary, we accomplished a convergent and enantioselective total synthesis of (+)-leucascandrolide A (**1**) in 17 steps from available aldehyde **7** and allylsilane **8a**. The present synthesis features an efficient route to **4** using two consecutive [4+2] annulation reactions between aldehydes and our chiral allyl- and crotylsilanes for the rapid and efficient integration of the bispyran moiety into **1**. Thus, chiral organosilane reagents were shown to be of salient utility for synthesizing complex pyran-containing natural products. Moreover, studies toward the completion of structural analogues of **1** using this silane methodology are currently in progress in our laboratory.

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[9] Other electron-withdrawing groups such as acetate, pivaloate, trifluoroacetate, benzoate, and methyl carbonate as X gave predominantly the *cis* isomers, however with lower diastereoselectivities and in lower yields.
[10] For a high-yielding preparation of silane **8a**, see Supporting Information.
[11] Aldehyde **7** was prepared in high yield from the known alcohol; see Supporting Information.
[12] Using a less bulky sulfonate group (*p*-toluenesulfonate) as X in **8** produced the corresponding *cis* pyran with lower diastereoselectivity (d.r. = 9:1).
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