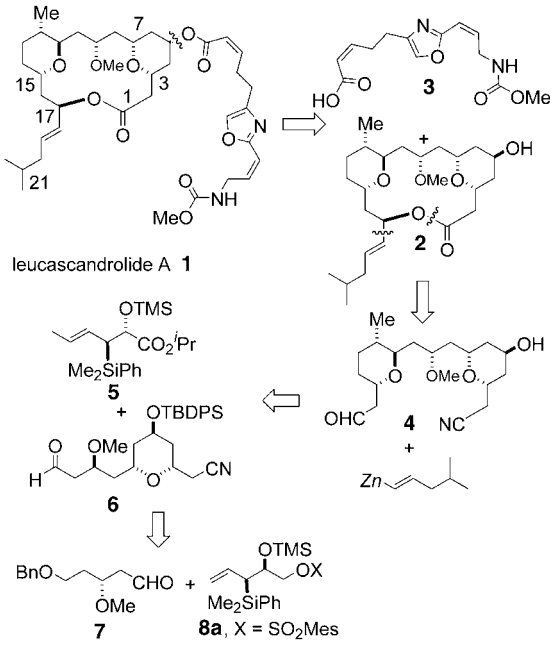
Natural Product Synthesis

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

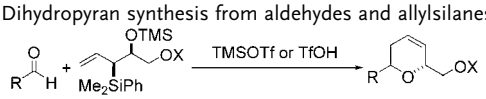


Scheme 1. Retrosynthesis of **1**; SO_2Mes = 2-mesitylenesulfonate.

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 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

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).

[*] Q. Su, Prof. Dr. J. S. Panek
Department of Chemistry and
Center for Chemical Methodology and Library Development
Boston University
590 Commonwealth Ave., Boston, MA 02215 (USA)
Fax: (+1) 617-353-6466
E-mail: panek@chem.bu.edu

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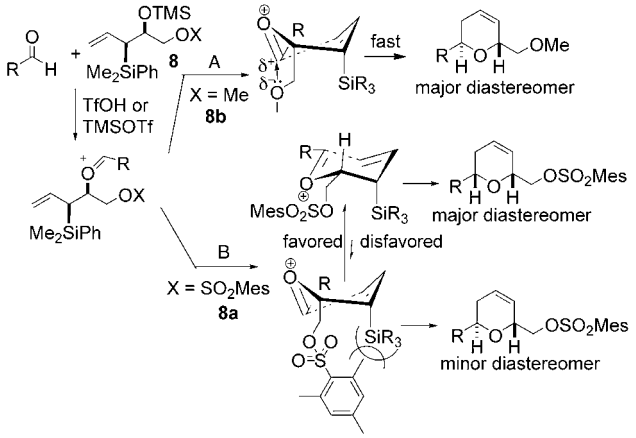


Scheme 2. Possible transition states for the [4+2] annulation of aldehydes with **8**.

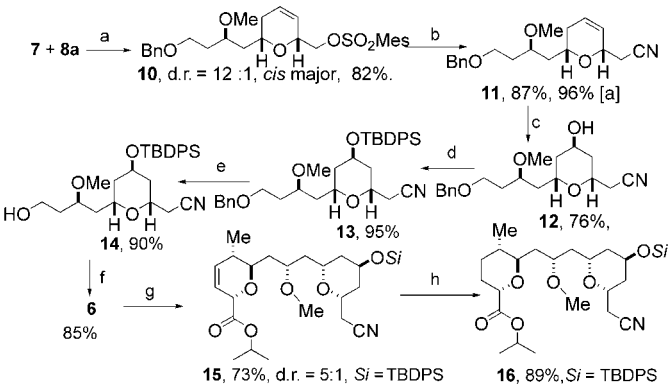
properties of the X substituent in the starting allylsilane **8**, for example by using a) an electron-withdrawing group X to minimize anchimeric assistance onto the oxocarbenium ion, and b) a sterically demanding functional group X to maximize destabilizing 1,2-diaxial interactions between X and the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

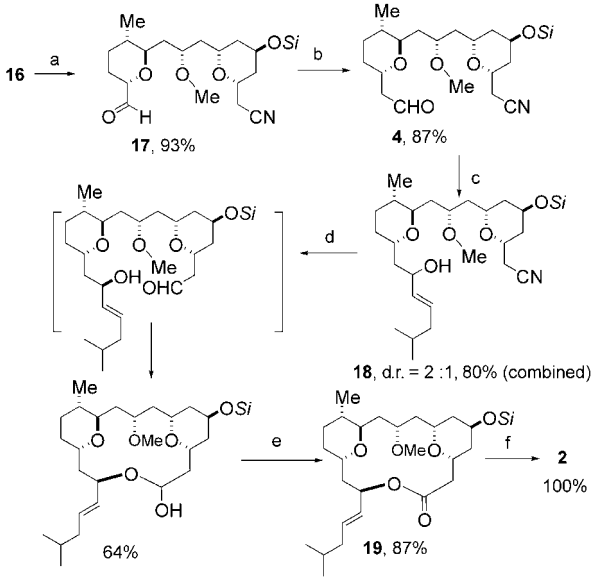
Oxymercuration of the double bond of **11** installed the C5-hydroxy group, as the single regio- and diastereomer **12**,[13] which was protected as the TBDPS ether **13**. Subsequent debenzylation with BCl_3 furnished the primary alcohol **14**, which was oxidized to aldehyde **6** using PCC.[14] Next, 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.

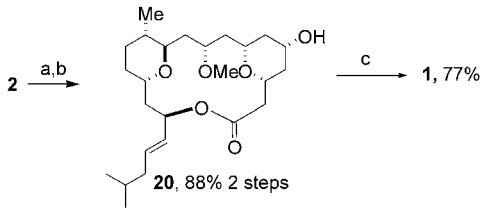
aldehyde **17** in high yield (Scheme 4). Homologation of the aldehyde group by a phosphorus-based olefination with methoxymethylenetriphenylphosphine and subsequent mercury acetate mediated hydrolysis of the resulting enol ether furnished aldehyde **4** in 87% over two steps.[15] Finally, addition of 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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