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Approach to the Synthesis of the C¹-C¹¹ and C¹⁴-C¹⁸ portion of Leucascandrolide A

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Abstract

An asymmetric synthesis of the C¹ to C¹¹ and C¹⁴ to C¹⁸ fragments of the macrocyclic portion of the antibiotic Leucascandrolide A was achieved in 21 total steps from an achiral dienoate. The key 4-hydroxy-2,5-pyran portion of the natural product was established by oxy-Michael cyclization of a 5,7,9,11-tetraol intermediate, which in turn was established by an iterative asymmetric-hydration of dienoates. Alternative strategies for establishing the polyol stereochemistry were explored.

Graphical Abstract

An iterative asymmetric hydration of dienoates approach to Leucascandrolide A was explored.

Introduction

As part of humankind's continuous search for unique biologically active structures from the deep blue sea, Leucascandrolide A (**1**) was discovered in the Coral Sea off the northeastern coast of New Caledonia.¹ In 1996, Pietra reported the isolation of the macrocyclic lactone from the calcareous sponge *Leucascandra caveolata*. A combination of 2D-NMR and Mosher ester analysis was used to assign the absolute and relative stereochemistry of the macrocyclic natural product. In addition to its novel structure, interest in Leucascandrolide A was further peaked by discovery that it possessed potent anticancer and antifungal activity, with IC₅₀ value against the human KB (70 nM) and P388 (350 nM) cell lines and activity against *Candida albicans*.¹ As is often the problem associated with marine natural products

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^aThis manuscript is dedicated to Barry M. Trost on the occasion of this 75th birthday.

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isolated from sponges, as opposed to the bacteria that most likely produce it, Leucascandrolide A no longer appears to be available from the same sponge.² These factors have inspired synthetic organic chemist to pursue the total synthesis of Leucascandrolide A.

A mere four years after its isolation, the first total synthesis of Leucascandrolide A was completed by Leighton.³ Since the Leighton synthesis there have been 10 other total⁴ and 11 formal syntheses.⁵ More recently, Kozmin was able to show that Leucascandrolide A inhibits oxidative phosphorylation via interaction with cytochrome *b*_c₁ complex.⁶ As part of a larger program aimed at the synthesis and SAR-study of anticancer agents that act by inhibition of ion transport, we became interested in the synthesis of Leucascandrolide A.

Retrosynthetically, we envisioned that the Leucascandrolide A macrocycle (**1**) could be derived by ring closing cross metathesis and reductive cyclization of diene **2** (Scheme 1). Compound **2** in turn could be derived from an *anti*-selective crotylation of aldehyde **3**. Aldehyde **3** could be prepared by an esterification of alcohol **4** and acid **5**. Carboxylic acid **5** could be derived from protected tetraol **6** which could result from a diastereoselective allylation/cross metathesis of protected trihydroxy ester **7**.⁷ Previously we have shown that esters such as **7** can be derived by the iterative asymmetric hydration of dienoates like **8**.⁸ The β -hydroxy enone **4** was also envisioned as ultimately arising from an asymmetric hydration of a dienoate. Herein we describe our latest efforts aimed at the synthesis of the C1 to C11 and C14 to C18 containing fragment of Leucascandrolide A, aldehyde **3**.

Results and discussion

Our synthetic efforts aimed at Leucascandrolide A began with aldehyde **9** (Scheme 2), which we previously had shown could be made from the DibalH reduction of esters like **7**.⁹ Exposure of aldehyde **9** to the vinylogous Horner-Wadsworth-Emmons reagent **10** and LiOH as base gave the desired dienoate **11** (68%),¹⁰ which could be converted into the desired *syn/anti*-1,3,5-triol by our three step asymmetric hydration protocol. Thus, treating the *E,E*-dienoate **11** to the typical Sharpless asymmetric dihydroxylation conditions (5% OsO₄, 6% (DHQD)₂PHAL, K₃FeCN₆, MeSO₂NH₂), provided diol **12** in good yield (71%) and as a single diastereomer.¹¹ Exposing diol **12** to a pyridine solution of triphosgene converted it into a cyclic carbonate **13** in good yield (79%). When cyclic carbonate **13** was exposed to our Pd-reduction conditions (HCO₂H/Et₃N, 1% Pd₂(dba)₃•CHCl₃/5% PPh₃) it cleanly reacted to give the 5-hydroxy-1-enoate *anti*-**14a** in an excellent yield (79%).

Following a nearly identical procedure, we previously have shown that *anti*-**14b** with a C11 PMB-group, can be prepared from a dienoate like **8** (P³ = PMB).⁸ Similarly, the C5 diastereomer *syn*-**14b** was also prepared from the same dienoate, by simply replacing the ligand in the Sharpless dihydroxylation to (DHQD)₂PHAL.

To our surprise, we found it difficult to protect the C5 alcohol of *anti*-**14a** with either a TBDPS-group or a benzyl-group (Table 1). The benzyl protection was similarly problematic, whether acidic or basic conditions were used. In contrast, we were able to react alcohol *anti*-**14b** with MOMCl to give MOM-ether *anti*-**15e** in a satisfactory yield (47%). To our

delight, the *C5* diastereomer **syn-14e** reacted under a similar procedure to give **syn-15e** in a similar yield (52%).

We surmised that the difficulty associated with the protection of the *C5* hydroxyl group could be due to the acidity of the *C4* position and the propensity of the substrate to undergo elimination to form dienates **11**. Thus we decided to explore an alternative procedure (Scheme 3) for the synthesis of enoates, like **syn-15**. Specifically, we decided to pursue a route where the protection step occurred before the ester group was introduced. This revised route was envisioned to occur through an allylation, protection and cross-metathesis sequence.

The revised route began with the unselective allylation of aldehyde **9** with an allylic Grignard reagent (AllylMgCl). The Grignard addition occurred to give a mixture of diastereomeric homo-allylic alcohols **syn-16a** and **anti-16a** (1.2:1), which could be separated by silica gel chromatography. Fortunately, the diastereoselectivity for the formation of **syn-16a** could be improved by an oxidation/reduction sequence (Scheme 3).

Thus, the mixture of alcohols **syn/anti-16a** was treated with the Dess-Martin reagent to give β,γ -unsaturated enone **17** in good yield (88%). Then reduction of enone **17** with L-selectride occurred to give the **syn-16a** as the major isomer. When the reaction was performed at $-90\text{ }^{\circ}\text{C}$ the maximal *syn/anti* ratio was achieved ($>4:1$).

To our delight we were able to protect both homo-allylic alcohols **syn-16a** and **anti-16a** with both the TBDPS and Bn- ether groups, as well as the MOM-group (Table 2). While the yields for the benzyl protection of either the *syn*- or *anti*-homoallylic alcohols were suboptimal, both TBDPS- and MOM-groups could be installed in excellent yields (78–87%), providing ample quantities **syn-18a** and **syn-18b** and **anti-18a** and **anti-18b** to pursue the cross metathesis protocol (Table 3).

With an improved procedure for installing protecting groups at the *C5* position in **syn-/anti-18** we next investigated the cross metathesis of **syn-18** and **anti-18** to form **syn-15** and **anti-15** and the subsequent deprotection to form diols **syn-19** and **anti-19** (Table 3). Treatment of **syn-18b-d** with ethyl acrylate and Grubbs II catalyst (1.5%) cleanly provided the desired enoates **syn-15b-d** in excellent yields (90–96%). Unfortunately, the primary TBS-groups were not compatible with the benzylidene deprotection conditions, whereas the PMB-group survived. The deprotection of the benzylidene group was accomplished by heating the enoates **syn-15b/d** in 80% aqueous acetic acid ($60\text{ }^{\circ}\text{C}$) to provide the *syn*-diols **syn-19b/d** (72% and 80%). Following a similar procedure, the *anti*-diastereomer **anti-16g** was also converted into **anti-19g**.

We next pursued the formation of the 2,6-*cis*-pyran ring. This was most easily accomplished under basic conditions. The addition of 1 equiv of potassium *t*-butoxide to a $-40\text{ }^{\circ}\text{C}$ solution of **syn-19c** in THF, followed by warming to room temperature led to the formation of tetrahydropyran **syn-20c** (70%). Under similar condition **syn-19d** was converted into tetrahydropyran **syn-20d** (61%). These conditions produced tetrahydropyran **syn-21c** in 70% yield as a 6:1 ratio of *cis* and *trans* diastereomers, and tetrahydropyran **syn-21d** product in a

61% yield with a 7:1 ratio of *cis* to *trans* diastereomers. Formation of the methyl ether was accomplished using Me₃OBF₄ on **syn-20c** and **syn-20d** to produce the products **syn-21c** and **syn-21d** in excellent yields (75 and 97%, respectively). Turning to the synthesis of the C1 to C11 and the C14 to C18 portion of Leuscandrolide A, we undertook the synthesis of alcohol **24** from 6-hydroxy enoate **22**. Previously we have shown that **22** can be prepared by an asymmetric hydration of the corresponding dienoate.⁸ The double bond of enoate **22** was oxidatively cleaved by a dihydroxylation (OsO₄/NMO)/diol cleavage (NaIO₄) sequence to form aldehyde **23**. Addition of vinylmagnesium bromide to the aldehyde **23** and manganese dioxide oxidation of the allylic alcohol completed the synthesis of enone **24**.

To demonstrate the viability of the synthesis going forward, we chose to pursue the fragment coupling sequence with ester **syn-21d**. With the synthesis of enone **24** complete, the ester **26** was synthesized via a DCC coupling of the carboxylic acid of ester **25** and alcohol **24**. The hydrolysis of ester **syn-21d** was accomplished by treatment with LiOH in THF and H₂O. The conversion of the PMB-ether to the aldehyde began with a DDQ deprotection. Treatment of a dichloromethane solution of **26** with H₂O and DDQ produced the primary alcohol **27** in 78% yield. Oxidation of the primary alcohol **27** to the aldehyde **3** was accomplished with Dess-Martin reagent.

Conclusions

In conclusion we have shown the viability of the asymmetric hydration of dienoate for the synthesis of key chiral building blocks for the synthesis of a potential Leuscandrolide A precursor **2**. The further elaboration of this advanced intermediate is ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Structure of Leucascandrolide A

Scheme 1.
Retrosynthesis of Leucascandrolide A

Scheme 2.
Os/Pd approach to protected triol

Scheme 3.
Alternative synthesis of protected triol

Scheme 4.
Synthesis of tetrahydropyran

Scheme 6.
Completion of Leucascandrolide A fragment

Table 1

Screening of protection groups on δ -hydroxyl enoate

Entry	SM	R ¹	R ²	Yield (<i>anti</i> -15)
1 ^a	<i>anti</i> -14a	TBS	TBDPS	NR ^e (<i>anti</i> -15a)
2 ^b	<i>anti</i> -14a	TBS	Bn	low (<i>anti</i> -15b)
3 ^c	<i>anti</i> -14b	PMB	Bn	low (<i>anti</i> -15c)
4 ^d	<i>anti</i> -14b	PMB	MOM	47% (<i>anti</i> -15d)

Entry	SM	R ¹	R ²	Yield (<i>syn</i> -15)
5 ^d	<i>syn</i> -14b	PMB	MOM	52% (<i>syn</i> -15e)

Reaction conditions:

- a) TBDPSCl (2 equiv), imidazole (2.5 equiv), DMF, 18h;
- b) benzyl trichloroacetimidate (1.2 equiv), TMSOTf, CH₂Cl₂;
- c) BnBr (2 equiv), NaH, TBAI, THF, 24h;
- d) MOMCl (4 equiv), DMAP (3% equiv), *i*-Pr₂NEt, CH₂Cl₂, 0 °C;
- e) NR = no reaction.

Table 2

Screening of protection groups on homoallylic alcohol

Entry	SM	R ¹	R ²	Yield (<i>syn</i> -18)
1 ^a	<i>syn</i> -16a	TBS	TBDPS	83% (<i>syn</i> -18a)
2 ^b	<i>syn</i> -16a	TBS	Bn	48% (<i>syn</i> -18b)
3 ^c	<i>syn</i> -16b	PMB	Bn	49% (<i>syn</i> -18c)
4 ^d	<i>syn</i> -16b	PMB	MOM	87% (<i>syn</i> -18d)

Entry	SM	R ¹	R ²	Yield (<i>anti</i> -18)
5 ^a	<i>anti</i> -16a	TBS	TBDPS	78% (<i>anti</i> -18a)
6 ^b	<i>anti</i> -16b	PMB	Bn	52% (<i>anti</i> -18c)
7 ^d	<i>anti</i> -16b	PMB	MOM	85% (<i>anti</i> -18d)

Reaction conditions:

- a) TBDPSCl (2 equiv), imidazole (2.5 equiv), DMF, 18h;
 b) benzyl trichloroacetimidate (1.2 equiv), TMSOTf, CH₂Cl₂;
 c) BnBr (2 equiv), NaH, TBAI, THF, 24h;
 d) MOMCl (4 equiv), DMAP (3% equiv), *i*-Pr₂NEt, CH₂Cl₂, 0 °C.

Table 3

Alternative route to diol **19**

Entry	SM	R ¹	R ²	Yield (syn-15)	Yield (syn-19)
1	<i>syn</i> - 16b	TBS	Bn	96% (<i>syn</i> - 15b)	NA ^c (<i>syn</i> - 19b)
2	<i>syn</i> - 16c	PMB	Bn	91% (<i>syn</i> - 15c)	72% (<i>syn</i> - 19c)
3	<i>syn</i> - 16d	PMB	MOM	90% (<i>syn</i> - 15d)	80% (<i>syn</i> - 19d)

Entry	SM	R ¹	R ²	Yield (<i>anti</i> -15)	Yield (<i>anti</i> -19)
4	<i>anti</i> - 16e	TBS	TBDPS	88% (<i>anti</i> - 15e)	low (<i>anti</i> - 19e)
5	<i>anti</i> - 16g	PMB	MOM	92% (<i>anti</i> - 15g)	71% (<i>anti</i> - 19g)

Reaction conditions:

a) ethyl acrylate (2.5 equiv), Grubbs II catalyst (1.5% equiv), CH₂Cl₂, reflux, 4h;

b) 80% acetic acid/H₂O, 60 °C, 4h;

c) not attempted.