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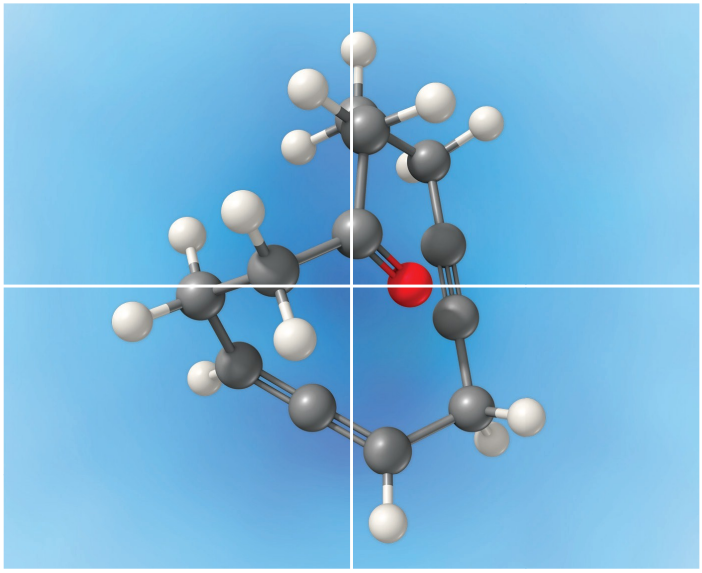

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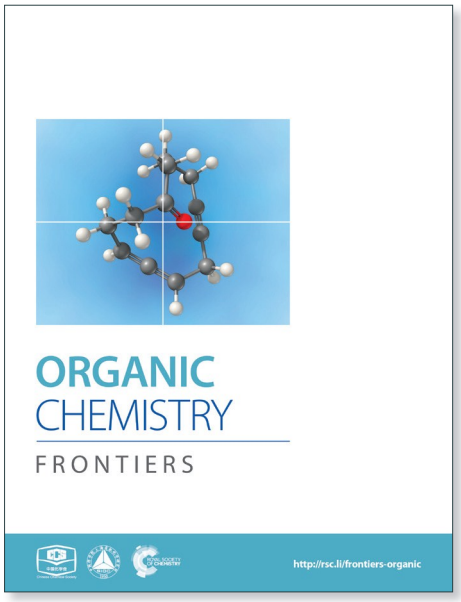

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Approach to the Synthesis of the C^1-C^{11} and C^{14}-C^{18} portion of Leucascandrolide A[a]

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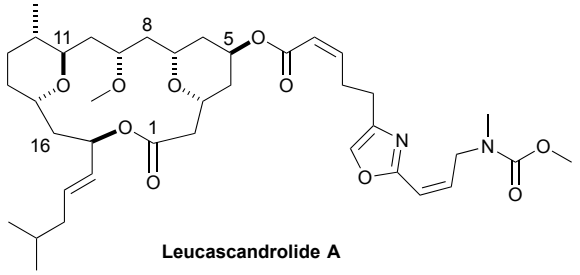
ABSTRACT

An asymmetric synthesis of the *C*1 to *C*11 and *C*14 to *C*18 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.

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 IC_{50} 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 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.



Leucascandrolide A

Figure 1 Structure 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 total[4] and 11 formal syntheses.[5] More recently, Kozmin was able to show that Leucascandrolide A inhibits oxidative phosphorylation via interaction with cytochrome bc_1 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 *C*1 to *C*11 and *C*14 to *C*18 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% OsO_4, 6% $(DHQ)_2PHAL$, K_3FeCN_6, $MeSO_2NH_2$), 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 (HCO_2H/Et_3N, 1% $Pd_2(dba)_3 \bullet CHCl_3$/5% PPh_3) it cleanly reacted to give the 5-hydroxy-1-enoate ***anti*-14a** in an excellent yield (79%).

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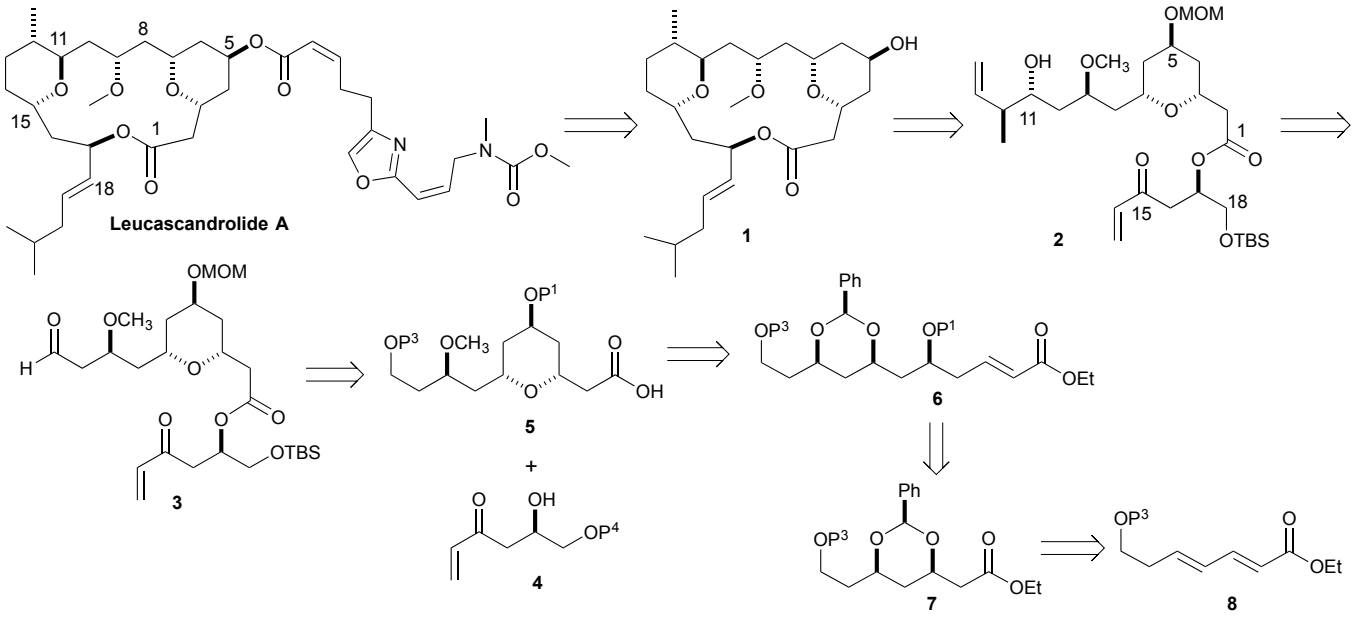
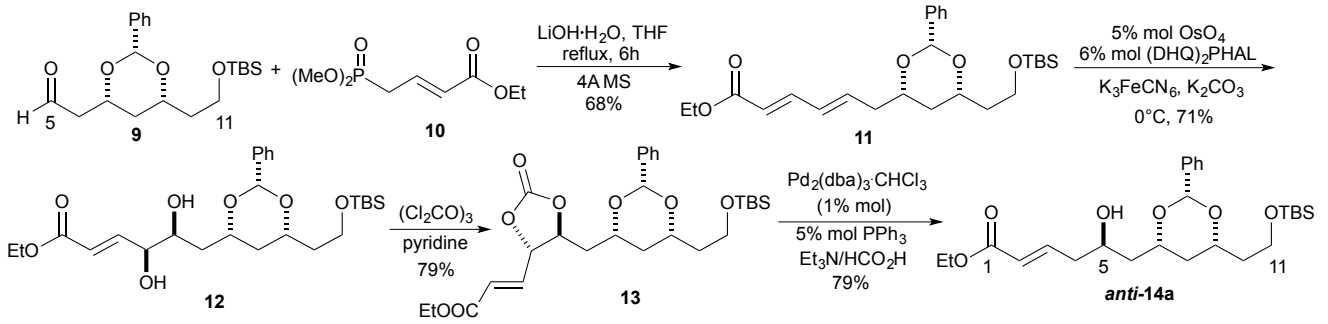


Scheme 1 Retrosynthesis of Leucascandrolide A



Scheme 2 Os/Pd approach to protected triol

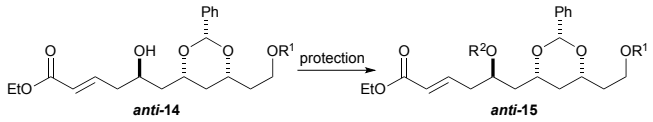
Following a nearly identical procedure, we previously have shown that ***anti*-14b**, with a *C*11 PMB-group, can be prepared from a dienoate like **8** (P^3 = PMB).[8] Similarly, the *C*5 diastereomer ***syn*-14b**, was also prepared from the same dienoate, by simply replacing the ligand in the Sharpless dihydroxylation to $(DHQD)_2PHAL$.

To our surprise, we found it difficult to protect the *C*5 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 *C*5 diastereomer ***syn*-14e** reacted under a similar procedure to give ***syn*-15e** in a similar yield (52%).

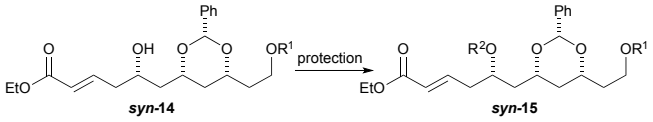
We surmised that the difficulty associated with the protection of the *C*5 hydroxyl group could be due to the acidity of the *C*4 position and the propensity of the substrate to undergo elimination to form dienoates **11**. Thus we decided to explore an alternative procedure (Scheme 3) for the synthesis 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).

Table 1 Screening of protection groups on δ-hydroxyl enoate



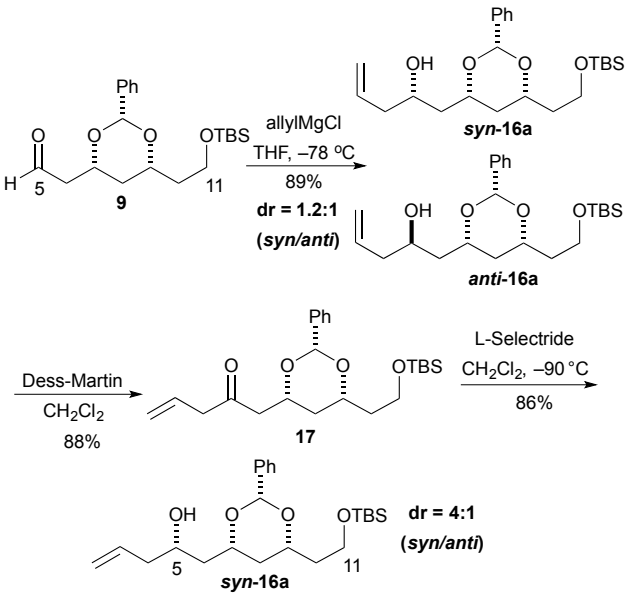
Entry	SM	R^1	R^2	Yield (***anti*-15**)
1[a]	***anti*-14a**	TBS	TBDPS	NR[e] (***anti*-15a**)
2[b]	***anti*-14a**	TBS	Bn	low (***anti*-15b**)
3[c]	***anti*-14b**	PMB	Bn	low (***anti*-15c**)
4[d]	***anti*-14b**	PMB	MOM	47% (***anti*-15d**)



Entry	SM	R^1	R^2	Yield (***syn*-15**)
5[d]	***syn*-14b**	PMB	MOM	52% (***syn*-15e**)

Reaction conditions: a) TBDPSCl (2 equiv), imidazole (2.5 equiv), DMF, 18h; b) benzyl trichloroacetimidate (1.2 equiv), TMSOTf, CH_2Cl_2; c) BnBr (2 equiv), NaH, TBAI, THF, 24h; d) MOMCl (4 equiv), DMAP (3% equiv), *i*-Pr_2NEt, CH_2Cl_2, 0 °C; e) NR = no reaction.

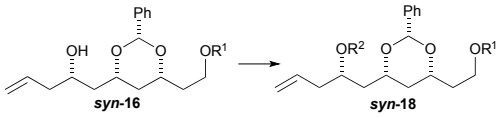
Thus, the mixture of alcohols ***syn/anti*-16a** was treated with the Dess-Martin reagent to give β,γ-unsaturated enone **17** in good yield (88%). Then reduction of enone **17** with L-selectride occurred to give the ***syn*-16a** as the major isomer. When the reaction was performed at –90 °C the maximal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



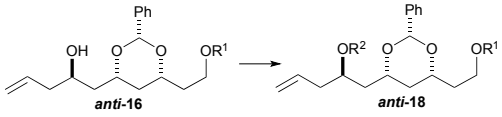
Scheme 3 Alternative synthesis of protected triol

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).

Table 2 Screening of protection groups on homoallyic alcohol



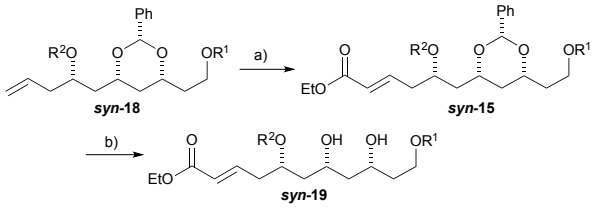
Entry	SM	R^1	R^2	Yield (***syn*-18**)
1[a]	***syn*-16a**	TBS	TBDPS	83% (***syn*-18a**)
2[b]	***syn*-16a**	TBS	Bn	48% (***syn*-18b**)
3[c]	***syn*-16b**	PMB	Bn	49% (***syn*-18c**)
4[d]	***syn*-16b**	PMB	MOM	87% (***syn*-18d**)



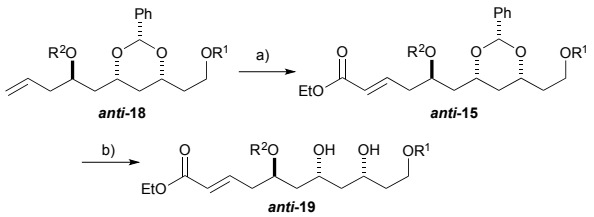
Entry	SM	R^1	R^2	Yield (***anti*-18**)
5[a]	***anti*-16a**	TBS	TBDPS	78% (***anti*-18a**)
6[b]	***anti*-16b**	PMB	Bn	52% (***anti*-18c**)
7[d]	***anti*-16b**	PMB	MOM	85% (***anti*-18d**)

Reaction conditions: a) TBDPSCl (2 equiv), imidazole (2.5 equiv), DMF, 18h; b) benzyl trichloroacetimidate (1.2 equiv), TMSOTf, CH_2Cl_2; c) BnBr (2 equiv), NaH, TBAI, THF, 24h; d) MOMCl (4 equiv), DMAP (3% equiv), *i*-Pr_2NEt, CH_2Cl_2, 0 °C.

Table 3 Alternative route to diol **19**



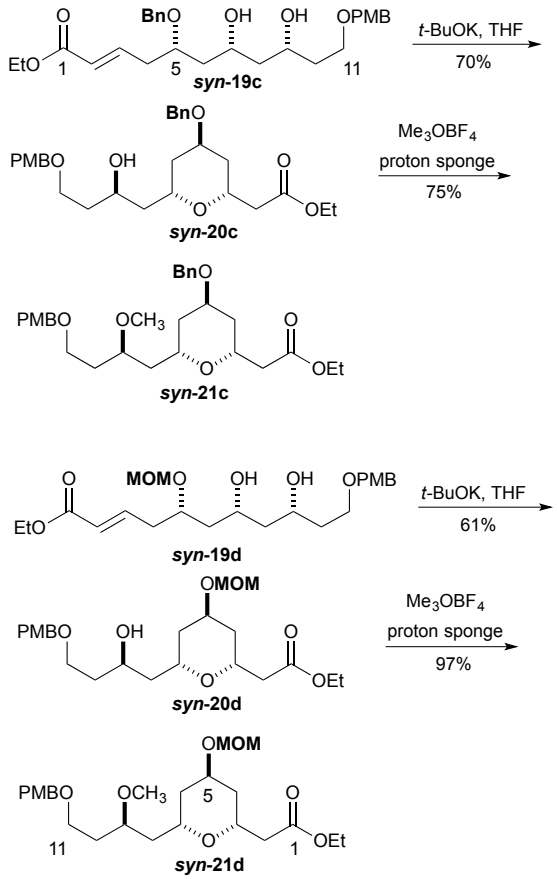
Entry	SM	R^1	R^2	Yield (***syn*-15**)	Yield (***syn*-19**)
1	***syn*-16b**	TBS	Bn	96% (***syn*-15b**)	NA[c] (***syn*-19b**)
2	***syn*-16c**	PMB	Bn	91% (***syn*-15c**)	72% (***syn*-19c**)
3	***syn*-16d**	PMB	MOM	90% (***syn*-15d**)	80% (***syn*-19d**)



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

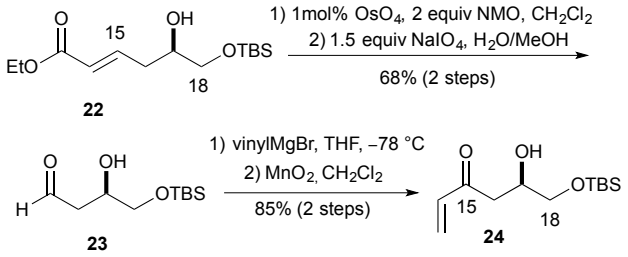
Reaction conditions: a) ethyl acrylate (2.5 equiv), Grubbs II catalyst (1.5% equiv), CH_2Cl_2, reflux, 4h; b) 80% acetic acid/H_2O, 60 °C, 4h; c) not attempted.

With an improved procedure for installing protecting groups at the *C*5 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 °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**.



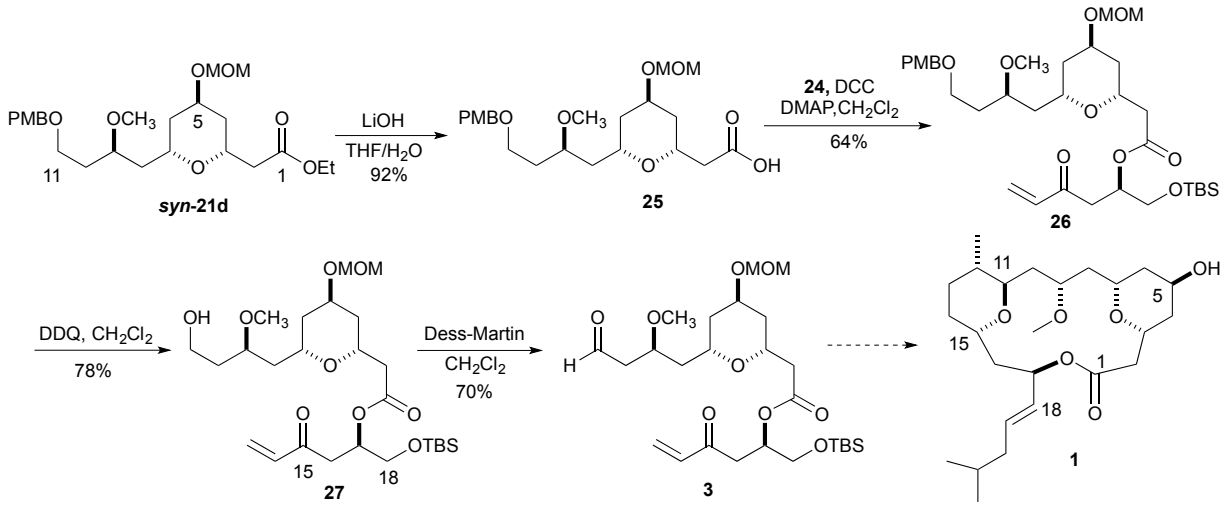
Scheme 4 Synthesis of tetrahydropyran

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 °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 Me_3OBF_4 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 *C*1 to *C*11 and the C14 to *C*18 portion of Leuscandrolide A, we undertook the synthesis of alcohol **24** from δ-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 (OsO_4/NMO)/diol cleavage ($NaIO_4$) 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**.



Scheme 5 Synthesis of enone

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 H_2O. The conversion of the PMB-ether to the aldehyde began with a DDQ deprotection. Treatment of a dichloromethane solution of **26** with H_2O 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.



Scheme 6 Completion of Leucascandrolide A fragment

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.

Acknowledgements

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