## A Stereoselective Formal Synthesis of Leucascandrolide A

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A stereoselective formal synthesis of leucascandrolide A was accomplished through the tandem and organocatalytic oxa-Michael reactions, which were promoted by the gem-disubstituent effect, in conjunction with the dithiane coupling reaction.

The marine macrolide leucascandrolide A (1, Scheme 1) was isolated from the calcareous sponge *Leucascandra caveolata* by Pietra and co-workers.<sup>1</sup> Leucascandrolide A (1) is an extremely potent inhibitor of tumor cell proliferation (IC<sub>50</sub> values: 71 nM for KB and 357 nM for P388)<sup>1</sup> and has attracted considerable interest from a number of synthetic groups.<sup>2</sup> Recently, Kozmin and co-workers

suggested that 1 may elicit its potent antiproliferative activity via inhibition of mitochondrial ATP synthesis.<sup>3</sup> With an interest in facilitating access to biologically important natural products with tetrahydropyrans,<sup>4</sup> we sought to develop an efficient and facile synthetic route for 1 that would be amenable to the synthesis of analogues for further biological studies. Herein, we report a stereoselective formal synthesis of 1 through the tandem and organocatalytic oxa-Michael reactions in conjunction with the dithiane coupling reaction.

Our retrosynthetic plan for **1** relies on the tandem and organocatalytic oxa-Michael reactions for the stereoselective synthesis of the 2,6-*cis*-tetrahydropyran and the 2,3-*trans*-2,6-*trans*-tetrahydropyran embedded in **1** (Scheme 1). Due to the poor thermodynamic stability of 2,6-*trans*-tetrahydropyrans, we expected that the stereoselective synthesis of 2,3-*trans*-2,6-*trans*-tetrahydropyran **7** would be challenging.

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Scheme 1. Retrosynthetic Plan for Leucascandrolide A (1)



The synthesis of 1 started with the preparation of 2, 3-*trans*-2,6-*trans*-tetrahydropyran 12a (Scheme 2). The coupling of 9 and  $10^5$  proceeded smoothly to afford allyl alcohol 11. The tandem allylic oxidation/oxa-Michael reaction<sup>4b</sup> of 11 provided aldehyde 8 as the major product (70%) due to the stereochemical mismatch between the C3 methyl group and the C6 alkyl group in 8A and 8B and resulted in complete decomposition after the prolonged reaction time (72 h).

We hypothesized that the iminium activation of the conjugate acceptor in the oxa-Michael reaction would help overcome the stereochemical mismatch in transition states and promote the oxa-Michael step by increasing the reactivity of aldehyde  $8.^6$  To test this hypothesis, we converted 8 to the corresponding iminium ion by treating

Scheme 2. Synthesis of 2,3-trans-2,6-trans-Tetrahydropyran 12a



with amine and acid (Table 1). The organocatalytic oxa-Michael reaction<sup>7,8</sup> of **8** in the presence of pyrrolidine or piperidine at 25 °C dramatically promoted the oxa-Michael reaction but afforded the undesired 2,3-cis-2, 6-cis-tetrahydropyran 12b as a single diastereomer (entries 1 and 2). Surprisingly, when the reaction was attempted at -40 °C, the stereoselectivity was reversed to provide 2.3-trans-2.6-trans-tetrahydropyran 12a as the major diastereomer (dr = 7-10:1, entries 3 and 4).<sup>9</sup> Encouraged by these results, we decided to test chiral organocatalysts to further improve the stereoselectivity of the oxa-Michael reaction. When 8 was treated with (S)-13<sup>10</sup> at -40 °C, the organocatalytic oxa-Michael reaction proceeded smoothly to provide 12a with excellent stereoselectivity and yield (dr > 20:1, 98%, entry 7). To the best of our knowledge, this is the first report for the synthesis of 2,3-trans-2,6-trans-tetrahydropyrans through the oxa-Michael reaction of  $\alpha,\beta$ -unsaturated aldehydes. It is also noteworthy that both 2,3-trans-2,6-trans- and 2, 3-cis-2,6-cis-tetrahydropyrans could be prepared from the

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Table 1. Organocatalytic Oxa-Michael Reaction for theStereoselective Synthesis of 2,3-*trans*-2,6-*trans* Tetrahydropyr-an 12a



entry	amine	temp (°C)	time (h)	yield $(\%)^a$	$\mathrm{d} \mathrm{r}^b$
1	pyrrolidine	25	1	98	12b only
2	piperidine	25	1	98	<b>12b</b> only
3	pyrrolidine	-40	5	94	7:1
4	piperidine	-40	24	96	10:1
5	(S)- <b>13</b>	0	3	96	6:1
6	(S)-13	-20	6.5	97	10:1
7	(S)-13	-40	13	98	>20:1
8	(R)- <b>13</b>	0	3	95	1.5:1

<sup>*a*</sup> Combined yield of the isolated **12a** and **12b**. <sup>*b*</sup> The diastereomeric ratio (**12a/12b**) was determined by integration of the <sup>1</sup>H NMR of the crude product.

common substrate through oxa-Michael reactions depending on reaction temperature and the secondary amine catalyst.

With the key 2,3-*trans*-2,6-*trans*-tetrahydropyran **12a** in hand, we turned our attention to the stereoselective synthesis of 4-hydroxy epoxide **16** for our second dithiane coupling reaction (Scheme 3). Desulfurization of the 1,3-dithiane group in **12a** with Raney Ni, Parikh–Doering oxidation, and Brown asymmetric allylation<sup>11</sup> provided homoallyl alcohol **14**. Direct epoxidation of homoallyl alcohol **14** (VO(acac)<sub>2</sub>, TBHP, CH<sub>2</sub>Cl<sub>2</sub>, 0 to 25 °C) provided epoxide **16**, but in no stereoselectivity (dr = 1:1).<sup>12</sup> After an extensive investigation of epoxidation conditions, we adopted the IBr-induced cyclization of a homoallylic carbonate.<sup>13</sup> Boc protection of **14**, iodocyclization, and methanolysis afforded the desired 4-hydroxy epoxide **16** with excellent stereoselectivity (dr = 16:1, 71%).

Methylation of **16** followed by the coupling with **6**<sup>4b</sup> proceeded smoothly to set the stage for the key tandem allylic oxidation/oxa-Michael reaction. The tandem oxa-Michael reaction of **5** (MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 12 h) stereoselectively provided the desired 2,6-*cis*-tetrahydropyran aldehyde **4** (dr > 20:1 86%).<sup>4b,9</sup> It is noteworthy that the synthesis of both the 2,3-*trans*-2,6-*trans*- and 2,6-*cis*-tetrahydropyrans through the same type of reaction has been achieved only once in the synthesis of **1**.<sup>21</sup>

Scheme 3. Synthesis of Bis-Tetrahydropyran 4



Having successfully assembled both the tetrahydropyran units in leucascandrolide A (1), we embarked on the final stage of the synthesis of 1 (Scheme 4). The installation of the C17 appendage in a stereoselective manner has been problematic in the previous syntheses of 1. The direct addition of various vinyl groups to aldehydes provided the corresponding alcohols, but in low to modest stereoselectivities (dr = 1-6:1).<sup>2a,b,d,g,l,p,q</sup> To solve this challenge, we decided to utilize the (–)-MIB-catalyzed asymmetric vinylation reaction previously reported by Walsh and co-workers because of the great success of the reaction in this area.<sup>14</sup>

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Compound **4** was transformed into **18** via acetal formation, PMB deprotection, and TPAP oxidation. To our

delight, the (–)-MIB-catalyzed asymmetric vinylation reaction of **18** (4-methyl-1-pentyne, Cy<sub>2</sub>BH, Et<sub>2</sub>Zn, (–)-MIB, toluene,  $-5 \,^{\circ}$ C, 1.5 h) afforded the desired (17*R*)alcohol **19** with excellent stereoselectivity (dr = 32:1).<sup>15</sup> Acetal deprotection of **19** smoothly provided the corresponding hydroxy aldehyde which was spontaneously transformed into macrolactol **20** (49% for two steps from **18**) as previously observed by Kozmin and coworkers.<sup>2c</sup> Deprotection of the dithiane group in **20**, PCC oxidation,<sup>2c</sup> and NaBH<sub>4</sub> reduction<sup>21</sup> accomplished the synthesis of leucascandrolide A macrolactone (**3**), constituting a formal synthesis of leucascandrolide A (**1**).<sup>2c</sup>

In summary, the stereoselective formal synthesis of leucascandrolide A (1) was accomplished through the oxa-Michael reaction promoted by the *gem*-disubstituent effect. We demonstrated that both the 2,6-*cis*- and 2, 3-*trans*-2,6-*trans*-tetrahydropyrans embedded in leucas-candrolide A (1) can be assembled through the tandem and organocatalytic oxa-Michael reactions with excellent stereoselectivities. We also showed that the (–)-MIB-catalyzed asymmetric vinylation reaction is a highly effective method for the stereoselective installation of the C17 stereocenter. Our efficient synthetic route established by the tandem and organocatalytic oxa-Michael reactions in conjunction with the dithiane coupling reaction would be applicable to the synthesis of analogues of 1 for further biological studies.

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**Supporting Information Available.** General experimental procedures including spectroscopic and analytical data along with copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

<sup>(15)</sup> The diastereomeric ratio was determined by HPLC separation (Phenomenex Luna  $C_{18}$  (5 $\mu$ m, 4.60 mm  $\times$  250 mm), flow rate: 1 mL/min, 80% MeOH in H<sub>2</sub>O) of the crude product (see the Supporting Information for details).