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A Stereoselective Formal Synthesis of Leucascandrolide A

Kiyoun Lee, Hyoungsu Kim,[†] and Jiyong Hong*

Department of Chemistry, Duke University, Durham, North Carolina 27708, United States

jiyong.hong@duke.edu

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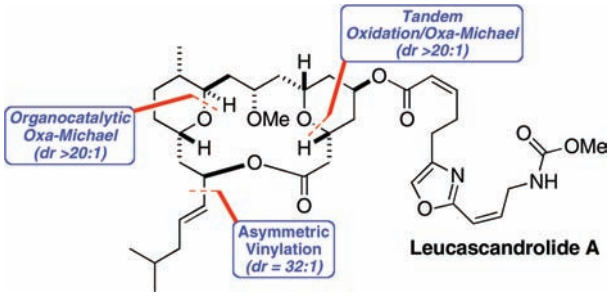
ABSTRACT



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.[1] Leucascandrolide A (**1**) is an extremely potent inhibitor of tumor cell proliferation (IC_{50} values: 71 nM for KB and 357 nM for P388)[1] and has attracted considerable interest from a number of synthetic groups.[2] Recently, Kozmin and co-workers suggested that **1** may elicit its potent antiproliferative activity via inhibition of mitochondrial ATP synthesis.[3] With an interest in facilitating access to biologically important natural products with tetrahydropyrans,[4] 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.

[†] Current address: Ajou University, College of Pharmacy, Suwon 443-749, Korea.

(1) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51–60.

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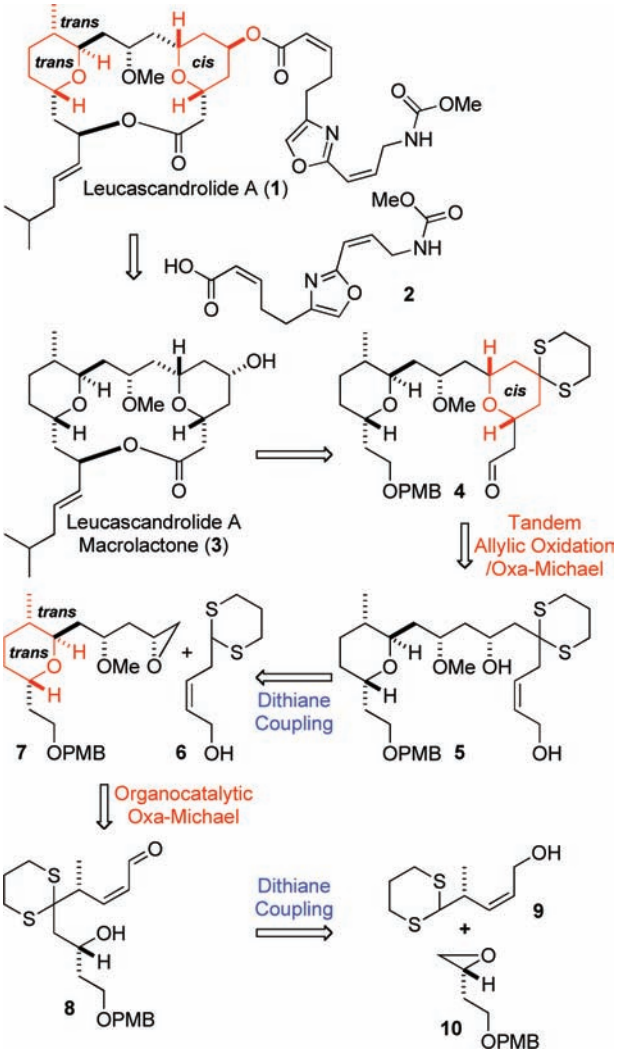
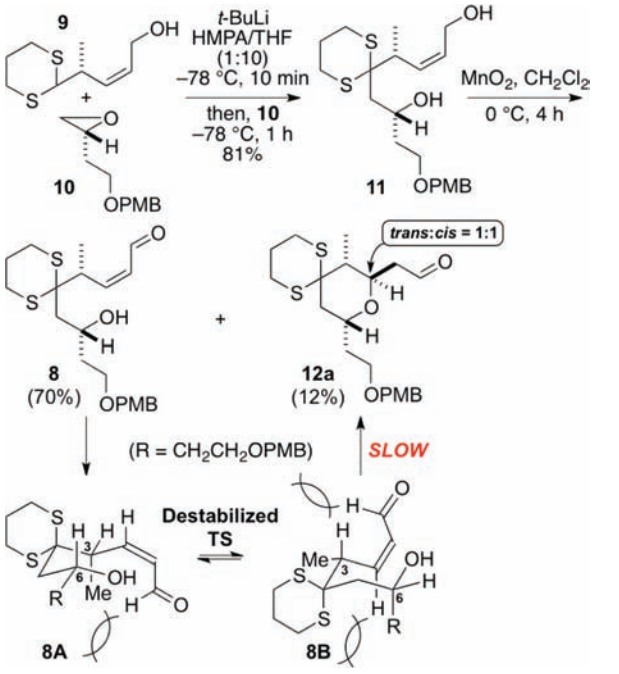
Scheme 1. Retrosynthetic Plan for Leucascandrolide A (**1**)



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



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[4b] 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 with amine and acid (Table 1). The organocatalytic oxa-Michael reaction[7,8] 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).[9] 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**[10] 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 α,β-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

(6) Ying, Y.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 796–799.

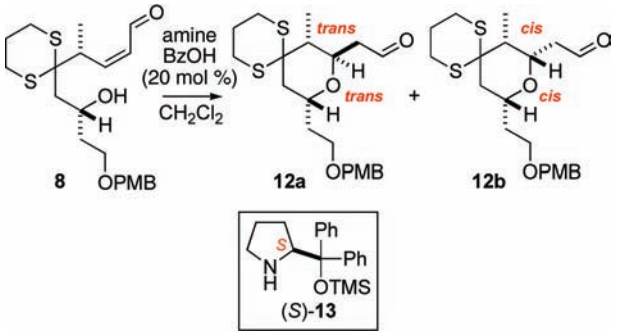
(7) For examples of the organocatalytic intramolecular oxa-Michael reaction, see: (a) Wang, H.-F.; Cui, H.-F.; Chai, Z.; Li, P.; Zheng, C.-W.; Yang, Y.-Q.; Zhao, G. *Chem.—Eur. J.* **2009**, *15*, 13299–13303. (b) Díez, D.; Núñez, M. G.; Benéitez, A.; Moro, R. F.; Marcos, I. S.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Synlett* **2009**, 390–394.

(8) For recent examples of the organocatalytic intermolecular oxa-Michael reaction, see: (a) Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536–1537. (b) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 507–509. (c) Sundén, H.; Ibrahem, I.; Zhao, G. L.; Eriksson, L.; Córdova, A. *Chem.—Eur. J.* **2007**, *13*, 574–581. (d) Rueping, M.; Sugiono, E.; Merino, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3046–3049. (e) Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tetrahedron Lett.* **2009**, *50*, 704–707. (f) Andersen, N. R.; Hansen, S. G.; Bertelsen, S.; Jørgensen, K. A. *Adv. Synth. Catal.* **2009**, *351*, 3193–3198.

(9) The relative stereochemistry was determined by 2D NMR studies (see the Supporting Information for details).

(10) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215.

Table 1. Organocatalytic Oxa-Michael Reaction for the Stereoselective Synthesis of 2,3-*trans*-2,6-*trans* Tetrahydropyran **12a**



entry	amine	temp (°C)	time (h)	yield (%)[a]	dr[b]
1	pyrrolidine	25	1	98	**12b** only
2	piperidine	25	1	98	**12b** only
3	pyrrolidine	−40	5	94	7:1
4	piperidine	−40	24	96	10:1
5	(*S*)-**13**	0	3	96	6:1
6	(*S*)-**13**	−20	6.5	97	10:1
7	(*S*)-**13**	−40	13	98	>20:1
8	(*R*)-**13**	0	3	95	1.5:1

[a] Combined yield of the isolated **12a** and **12b**. [b] The diastereomeric ratio (**12a**/**12b**) was determined by integration of the ^{1}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[11] provided homoallyl alcohol **14**. Direct epoxidation of homoallyl alcohol **14** ($VO(acac)_2$, TBHP, CH_2Cl_2, 0 to 25 °C) provided epoxide **16**, but in no stereoselectivity (dr = 1:1).[12] After an extensive investigation of epoxidation conditions, we adopted the IBr-induced cyclization of a homoallylic carbonate.[13] Boc protection of **14**, iodocyclization, and methanolysis afforded the desired 4-hydroxy epoxide **16** with excellent stereoselectivity (dr = 16:1, 71%).

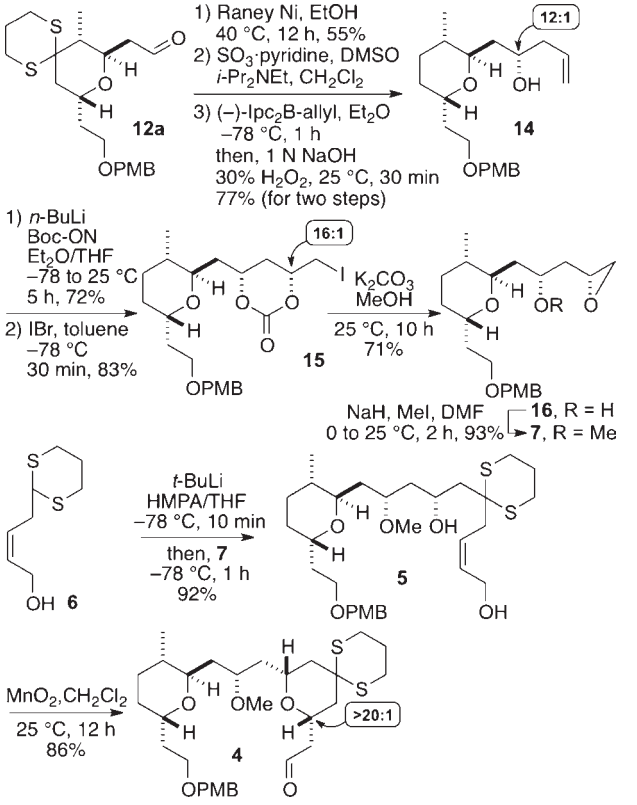
(11) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432–439.

(12) (a) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690–7692. (b) Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707–3711.

(13) (a) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Chem. Commun.* **1981**, 465–466. (b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626–4633. (c) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013–4018. (d) Duan, J. J.-W.; Smith, A. B., III. *J. Org. Chem.* **1993**, *58*, 3703–3711.

Methylation of **16** followed by the coupling with **6**[4b] proceeded smoothly to set the stage for the key tandem allylic oxidation/oxa-Michael reaction. The tandem oxa-Michael reaction of **5** (MnO_2, CH_2Cl_2, 25 °C, 12 h) stereoselectively provided the desired 2,6-*cis*-tetrahydropyran aldehyde **4** (dr >20:1 86%).[4b,9] 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**.[21]

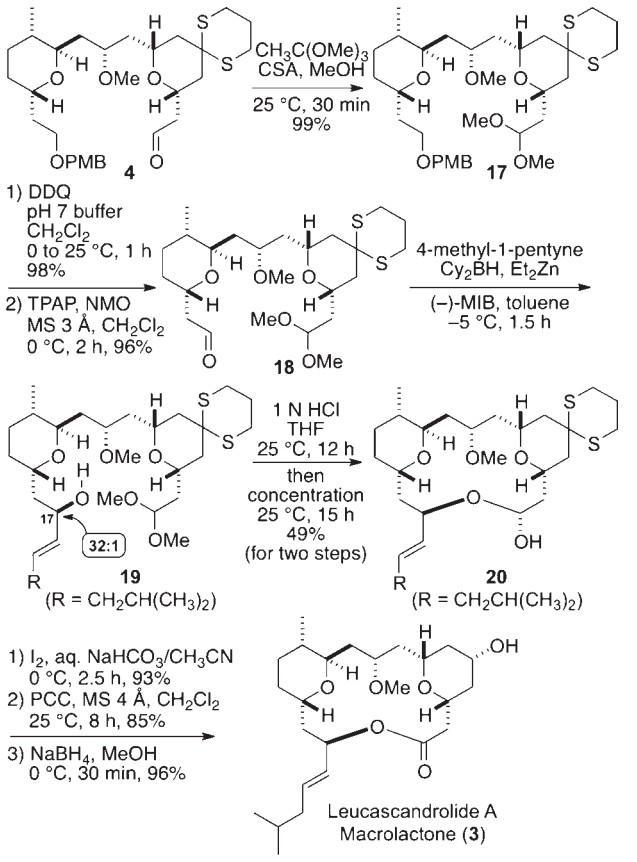
Scheme 3. Synthesis of Bis-Tetrahydropyran **4**



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).[2a,b,d,g,l,p,q] 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.[14]

(14) (a) Nugent, W. A. *Chem. Commun.* **1999**, 1369–1370. (b) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225–12231. (c) Garcia, C.; Libra, E. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 3210–3211. (d) Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 10677–10683. (e) Chen, Y. K.; Jeon, S. J.; Walsh, P. J.; Nugent, W. A. *Org. Synth.* **2005**, *82*, 87–92.

Scheme 4. Completion of the Formal Synthesis of Leucascandrolide A (**1**)



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_2BH, Et_2Zn, (−)-MIB, toluene, −5 °C, 1.5 h) afforded the desired (17*R*)-alcohol **19** with excellent stereoselectivity (dr = 32:1).[15] 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.[2c] Deprotection of the dithiane group in **20**, PCC oxidation,[2c] and $NaBH_4$ reduction[2l] accomplished the synthesis of leucascandrolide A macrolactone (**3**), constituting a formal synthesis of leucascandrolide A (**1**).[2c]

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 leucascandrolide 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 ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) The diastereomeric ratio was determined by HPLC separation (Phenomenex Luna C_{18} (5 μm, 4.60 mm × 250 mm), flow rate: 1 mL/min, 80% MeOH in H_2O) of the crude product (see the Supporting Information for details).