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Enantioselective Synthesis of the C18–C25 Segment of Lasonolide A by an Oxonia-Cope Prins Cascade

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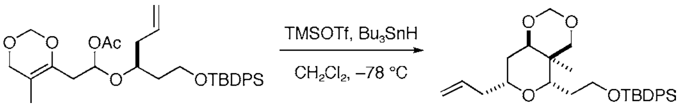
ABSTRACT



A 2-oxonia-Cope Prins cascade was developed that led to a facile and stereoselective synthesis of the C18–C25 segment of lasonolide A. The strategy nicely handles the introduction of the quaternary center in the tetrahydropyran ring, and all of the stereogenic centers in the product arise from a single stereocenter introduced in a catalytic enantioselective reaction.

Tetrahydropyran rings are common structural motifs in marine natural products. Enantioselective synthesis of such rings has been a topic of interest in recent years, and general solutions to this problem include enantioselective hetero-Diels−Alder reactions,[1] Prins cyclizations,[2] and intramolecular etherification of a suitable acyclic precursor.[3] Quaternary centers make the synthesis of tetrahydropyran rings more challenging. The first two strategies are not well suited to tetrahydropyrans with quaternary centers, and the final approach is hampered by the synthesis of acyclic quaternary centers. We describe a tandem oxonia−Cope Prins cyclization[4,5] that nicely meets this challenge and illustrate the concept with a synthesis of the C18 to C25 segment of lasonolide A (Figure 1).

Lasonolide A was isolated from a shallow water Caribbean sponge, species *Forcepia*.[6] It shows potent activity against A-549 human lung carcinoma. Lee's seminal synthetic work included a correction of the structure and a reassignment of the absolute configuration.[7] Lee prepared the C18−C25 segment of lasonolide through a radical cyclization with a silyl tether. More recently, Kang has reported an efficient total synthesis of lasonolide A.[8] Kang prepared the C15−C25 segment through a clever desymmetrization strategy to introduce the quaternary center prior to tetrahydropyran cyclization.[8b] Several other groups have synthesized the C19−C23 tetrahydropyran of lasonolide A.[9] Lasonolide A's interesting structure, potent anticancer activity, and natural

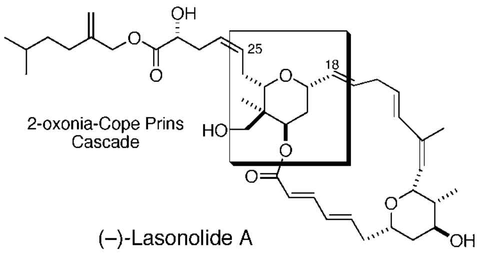


Figure 1. Structure of (−)-lasonolide A (**1**) and the C18−C25 tetrahydropyran segment.

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[1] (a) Taylor, M. S.; Jacobsen, E. N. *PNAS* **2004**, *101*, 5368−5373. (b) Paterson, I.; Luckhurst, C. A. *Tetrahedron Lett.* **2003**, *44*, 3749−3754.

[2] (a) Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499−1502. (b) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429−2432. (c) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919−3922. (d) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217−1219.

[3] For example, see: Ye, T.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 319−322.

[4] Dalgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662−15663.

[5] For a related tetrahydropyran synthesis, see: (a) Petasis, N. A.; Lu, S. P. *Tetrahedron Lett.* **1996**, *37*, 141−144. (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942−10953. (c) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216−12217.

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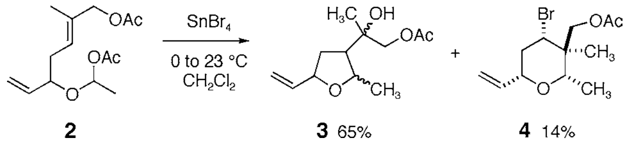
scarcity have made it an attractive target for synthetic chemists.

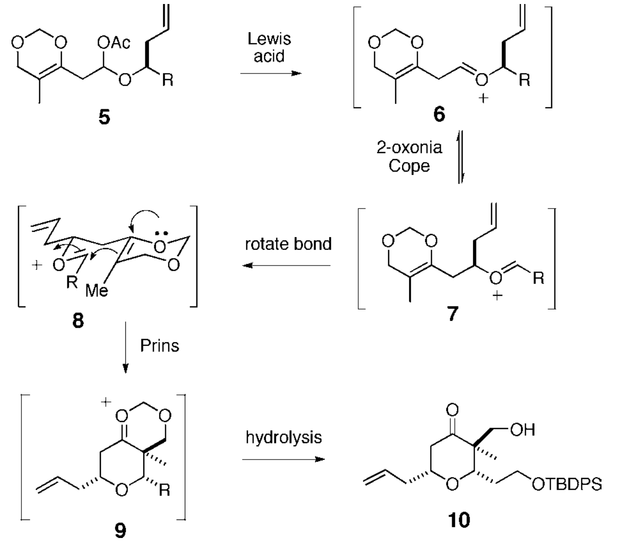
The segment-coupling Prins cyclization strategy is versatile and allows diverse cyclizations to be investigated.[10] A simple approach to the requisite C19−C23 tetrahydropyran of lasonolide might arise from cyclization of a trisubstituted alkene as shown in Scheme 1. Not unexpectedly, this strategy fails. A trisubstituted alkene such as **2** favors cyclization on the less substituted position to produce the undesired tetrahydrofuran **3**.[11] We had hoped that inclusion of electron-withdrawing groups on the alkene, such as the acetate in **2**, would favor the other regioisomer in the cyclization. The effect is real, but the best outcome only led to 14% yield of the tetrahydropyran **4**. Prins cyclizations with trisubstituted alkenes are not useful for the synthesis of tetrahydropyrans with quaternary centers at C3.

Scheme 1. Segment-Coupling Prins Cyclization with Trisubstituted Alkene Favors Tetrahydrofurans



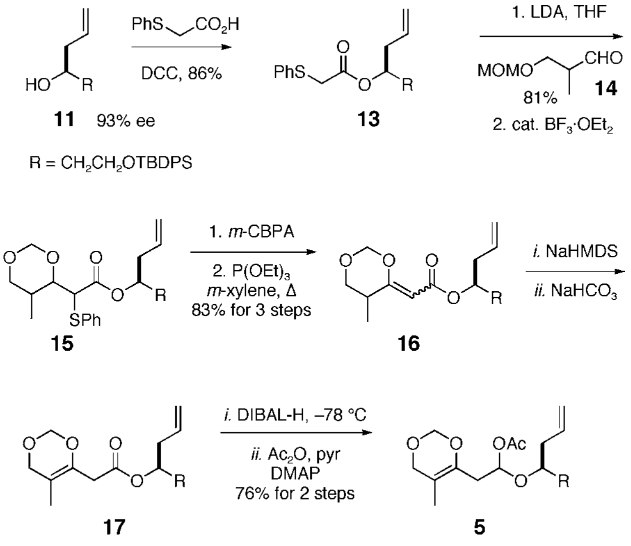
We developed a new approach to the lasonolide A tetrahydropyran based on a tandem carbenium ion reaction.[4] Scheme 2 illustrates the proposed 2-oxonia-Cope Prins cyclization cascade. If one solvolyzed α-acetoxy ether **5**, the resulting oxocarbenium ion would undergo a facile 2-oxonia Cope rearrangement to produce oxocarbenium ion **7**.[12] Both **6** and **7** could react in a standard Prins cyclization. However, the much more nucleophilic enol ether should react more rapidly, particularly if a favorable geometry could be achieved. The rearrangement to **7** sets up a very favorable cyclization of chair conformer **8** that leads to oxocarbenium ion **9**. Hydrolysis of **9** would produce **10**, the ketone corresponding to the C18−C25 segment of lasonolide A. This proposal, though speculative, was attractive in that all of the stereogenic centers of **10** would arise from a single stereogenic center.

Scheme 2. Proposed 2-Oxonia-Cope Prins Cyclization Cascade To Produce C18−C25 Tetrahydropyran of Lasonolide A



Substrate **5** was prepared as illustrated in Scheme 3. Optically active **11** was prepared by Keck allylation of the corresponding aldehyde.[13] Esterification with phenylsulfanylacetic acid led to **13**. Aldol reaction with racemic **14**, followed by MOM cyclization on Lewis acid treatment, gave 1,3-dioxane **15**. Oxidation of thiophenyl ether **15** to the sulfoxide and elimination generated the alkene **16**. Decon-

Scheme 3. Synthesis of the Optically Active Cyclization Substrate **5**



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(6) Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O. J. *J. Am. Chem. Soc.* **1994**, *116*, 6015−6016.

(7) (a) Lee, E.; Song, H. Y.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Joo, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 384−385. (b) Lee, E.; Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D. S.; Jung, C. K.; Hong, C. Y.; Jeong, S.; Jeon, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3519−3520. (c) Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. Y.; Jeong, S.; Jeon, K.; Park, J. H. *J. Org. Chem.* **2003**, *68*, 8080−8087.

(8) (a) Kang, S. H.; Kang, S. Y.; Kim, C. M.; Choi, H.-w.; Jun, H.-S.; Lee, B. M.; Park, C. M.; Jeong, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 4779−4782. (b) Kang, S. H.; Choi, H.-W.; Kim, C. M.; Jun, H.-S.; Kang, S. Y.; Jeong, J. W.; Youn, J.-H. *Tetrahedron Lett.* **2003**, *44*, 6817−6819. (c) Kang, S. H.; Kang, S. Y.; Choi, H.-w.; Kim, C. M.; Jun, H.-S.; Youn, J.-H. *Synthesis* **2004**, 1102−1114.

(9) (a) Gurjar, M. K.; Kumar, P.; Rao, B. V. *Tetrahedron Lett.* **1996**, *37*, 8617−8620. (b) Nowakowski, M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1997**, *38*, 1001−1004. (c) Hart, D. J.; Patterson, S.; Unch, J. P. *Synlett* **2003**, 1334−1338. (d) Yoshimura, T.; Bando, T.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2004**, *45*, 9241−9244.

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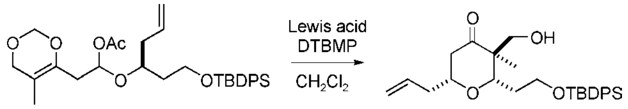
(12) (a) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815−3818. (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577−580.

jugation produced ester **17** and reductive acetylation delivered the α-acetoxy ether substrate **5**. The preparation of compound **5** is straightforward, and the substrate was easily prepared for further study.

The proposed rearrangement and cyclization of α-acetoxy ether **5** is presented in Table 1. All of the Lewis acids investigated led to significant quantities of the rearranged and cyclized product **10**. The 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was added to suppress proton-induced side reaction. Side products include the Prins cyclization products arising from cyclization of oxocarbenium ion **6** on the terminal alkene (not shown). The best results were found with TMSOTf (entry 4), which promotes oxocarbenium ion formation but does not encourage Prins cyclization, presumably due to the poorly nucleophilic counterion. TMSOTf treatment led to the formation of **10** as a single diastereomer in 74% yield. HPLC analysis demonstrated that the cyclization took place with no loss of optical activity, even though the original stereogenic center is lost in the course of the reaction.[14] The synthesis of the C18−C25 segment of lasonolide A was completed by L-Selectride reduction of the ketone to the axial alcohol **18** (Scheme 4). The configuration of alcohol **18** was confirmed by NOE analysis.

Table 1. Cascade Cyclization of α-Acetoxy Ether **5** with Different Lewis Acids

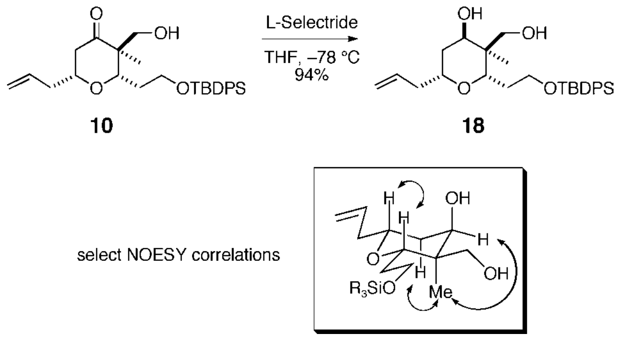


5 **10**

entry[a]	Lewis acid (equiv)	*T* (°C)	time (h)	yield (%)
1	$BF_3{\cdot}OEt_2$ (1.0)	−78	3	36
2	$TiCl_4$ (2.4)	−78 to −30	6	59
3	$TiBr_4$ (2.0)	−78	1	45
4	TMSOTf (3.0)	−78	2	74

[a] All reactions were conducted in the presence of 1.0−1.5 equiv of DTBMP.

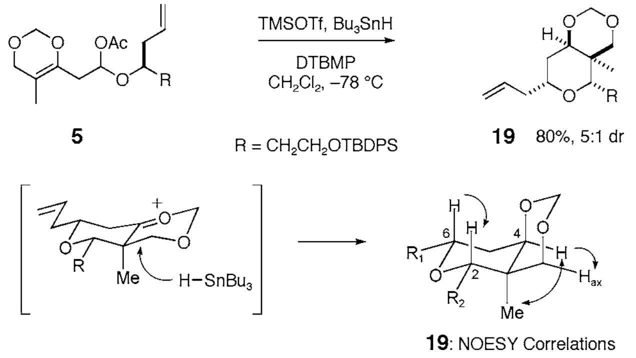
Scheme 4. Stereoselective Reduction and Stereochemical Assignment



10 **18**

A final variation of the cyclization was investigated. In situ reduction of oxocarbenium ion **9** would generate directly a protected form of the C18−C25 diol. There are many other oxocarbenium ions that might be reduced in the sequence, but surprisingly enough, they did not interfere. Treatment of α-acetoxy ether **5** with TMSOTf and tributyltin hydride in the presence of DTBMP led to the dioxane **19** in a remarkable 80% yield (Scheme 5). Even the 5:1 diastereoselectivity in the reduction favors the lasonolide A configuration.[15] Tributyltin hydride is a powerful reducing agent,[16] and the high yield suggests that this tandem rearrangement and cyclization reaction occurs very rapidly.

Scheme 5. In Situ Hydride Reduction of an Oxocarbenium Ion Intermediate with Bu_3SnH



We have developed a rapid and efficient route to the C18−C25 segment of lasonolide A based on a 2-oxonia-Cope Prins cyclization cascade. This strategy introduces the quaternary center with excellent diastereoselectivity and should be useful in the synthesis of other highly functionalized tetrahydropyran rings.

Acknowledgment. This work was supported by the National Institutes of Health (CA081635).

Supporting Information Available: Preparation and characterization of the described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468.

(14) See the Supporting Information for details of the HPLC analysis of **10**.

(15) The relative stereochemistry of **19** was confirmed by COSY and NOESY studies. A NOESY correlation was observed between the C4-H and the C3-methyl group. There was no observed correlation between the C4-H and the C2 and C6 hydrogens, which showed enhancements to each other. The coupling constants for the C4-H (3.19 ppm; t, *J* = 2.9 Hz) combined with the NOESY data confirm that it is an equatorial proton.

(16) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957.