

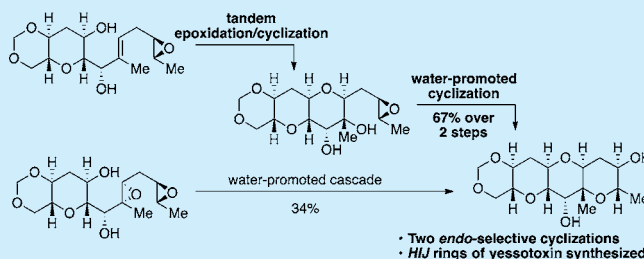
Hydroxyl-Substituted Ladder Polyethers via Selective Tandem Epoxidation/Cyclization Sequence

Lara C. Czabaniuk and Timothy F. Jamison*

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139, United States

Supporting Information

ABSTRACT: A new and highly selective method for the synthesis of hydroxyl-substituted tetrahydropyrans is described. This method utilizes titanium(IV) isopropoxide and diethyl tartrate to perform a diastereoselective epoxidation followed by in situ epoxide activation and highly selective *endo*-cyclization to form the desired tetrahydropyran ring. The *HIIJ* ring fragment of the marine ladder polyether yessotoxin was synthesized using this two-stage tactic that proceeds with high efficiency and excellent regioselectivity.

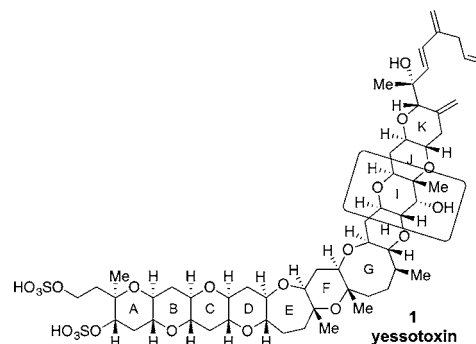


Marine ladder polyethers are natural products produced by dinoflagellate algae that comprise harmful algal blooms. Displaying a diverse range of biological activity, these polyethers have been targeted in numerous synthetic studies.¹ The prevailing proposed biogenesis for this family of molecules invokes an “all-*endo*” epoxide-opening cascade to construct the fused polycyclic core.² However, *exo*-cyclization to form the smaller sized ring is favored in electronically unbiased epoxy alcohols as predicted by Baldwin’s rules.³ In this paper, we report an approach to the synthesis of hydroxyl substituted tetrahydropyrans (THPs) that utilizes a tandem directed epoxidation followed by regioselective cyclization.

Various strategies have been developed to favor formation of the desired THP moiety. Appropriately positioned directing groups can introduce electronic bias by stabilizing partial positive charge buildup in the cyclization transition state.⁴ Additionally, Murai has demonstrated that a methoxymethyl group can direct *endo*-cyclization through Lewis acid chelation.⁵ Templating⁶ allows for highly selective THP formation without the need for directing groups, and we have reported the use of a preformed THP⁷ or 1,3 dioxane⁸ in water-promoted cyclizations. This approach has enabled the synthesis of THPs bearing methyl substituents at the ring junctions⁹ as well as marine ladder polyether fragments via polyepoxide cascades.^{7b}

While most THPs in the marine ladder polyethers contain an unsubstituted methylene between the ring junctions, hydroxyl substitution is found in a number of instances such as the I ring of yessotoxin (**1**).¹⁰ Isolated in 1987,¹¹ this marine ladder polyether is acutely neurotoxic¹² and has also been demonstrated to induce apoptosis in a number of cell lines.¹³ The yessotoxins have been targeted for fragment synthesis by Oishi¹⁴ and Rainier,¹⁵ but no total synthesis has been reported. Our interest in forming hydroxyl-substituted THPs via an epoxide-opening cascade was inspired by the need for efficient synthetic access to these natural products. Furthermore, we envisioned that the proposed methodology would provide

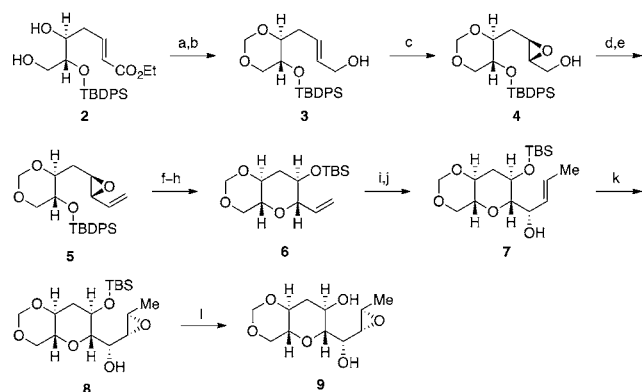
additional insight into substrate substituent effects on templated cyclizations.



Initial studies investigated the monocyclization of bicycle **9**, which was synthesized from known 1,3-diol **2**⁸ in 11 steps (Scheme 1). We hypothesized that the introduction of an electron-withdrawing hydroxyl group would favor *endo*-cyclization, as it would destabilize partial positive charge buildup at the *exo*-site during cyclization. However, under aqueous conditions, 5-*exo* product **11** formed in a 2.2:1 ratio to the desired *endo* product **10** (Table 1, entry 1).¹⁶ A similar ratio was observed under buffered conditions at pH 7 (Table 1, entry 2). The high *endo* selectivity from THP-templated cyclizations is hypothesized to arise from a highly ordered transition state involving multiple water molecules.^{6b} The cyclization results of **9** under aqueous conditions suggest that the hydroxy substituent disrupts or destabilizes this transition state, thus favoring *exo*-selective cyclization. The use of base resulted in a nonselective cyclization (Table 1, entry 3). Further decreases in *endo*-selectivity were observed under both Brønsted and Lewis

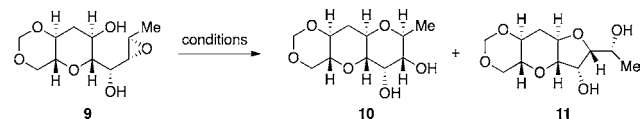
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Scheme 1. Synthesis of 9^a

^aReaction conditions: (a) $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , rt; (b) DIBALH, CH_2Cl_2 , -78°C , 75% over two steps; (c) (–)-DET, $\text{Ti}(\text{O}-i\text{-Pr})_4$, $t\text{-BuOOH}$, CH_2Cl_2 , -20°C , 71%; (d) $\text{SO}_3 \cdot \text{py}$, NEt_3 , CH_2Cl_2 , DMSO , 0°C ; (e) MePPh_3Br , NaHMDS , THF, 0°C , 79% over two steps; (f) TBAF, THF, rt; (g) PPTS, CH_2Cl_2 , rt; (h) TBSCl, imidazole, DMF, rt, 65% over three steps; (i) O_3 , CH_2Cl_2 , -78°C , then PPh_3 , -78°C to rt; (j) (*E*)- $\text{H}_3\text{CCH}=\text{CHMgBr}$, THF, -78°C , 39% over two steps; (k) $\text{VO}(\text{acac})_2$, $t\text{-BuOOH}$, CH_2Cl_2 , 0°C , 80%, 3:1 dr; (l) TBAF, THF, rt, 83%.

Table 1. Epoxy Alcohol Cyclizations



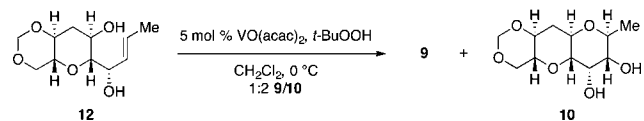
entry	conditions	10/11/9 ^a
1 ^b	D_2O , 70°C	31:69:0
2 ^b	pH 7 KP_1 buffer, 70°C	34:66:0
3 ^c	Cs_2CO_3 , MeOH, rt	48:52:0
4 ^c	(±)-CSA, CH_2Cl_2 , rt	24:76:0
5 ^d	$\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C	29:71:0
6 ^e	$\text{La}(\text{OTf})_3$, 3 Å MS, CH_2Cl_2 , rt	48:24:28

^aRatio determined by ^1H NMR analysis of the crude reaction mixture. ^bConducted at 0.02 M for 72 h. ^cConducted at 0.02 M for 16 h. ^dConducted at 0.02 M for 1 h. ^eConducted at 0.015 M for 36 h.

acidic conditions (Table 1, entries 4 and 5). Based on Murai's work with chelation-directed cyclizations^{5b} we anticipated that the vicinal alcohol and epoxide of 9 could direct selective *endo*-cyclization. Under these Lewis acidic conditions modest selectivity for 10 was observed, but the reaction did not proceed to completion (Table 1, entry 6).

As an alternate means to access 9, a directed epoxidation was performed on diol 12. Upon performing this reaction we were pleasantly surprised to observe formation of the desired *endo* cyclization product 10 as the major product. (Scheme 2). Notably, 10 was the only cyclized product detected; no 5-*exo* cyclization product 11 was formed in this reaction sequence. Lewis acidic conditions promote epoxy alcohol cyclizations, but

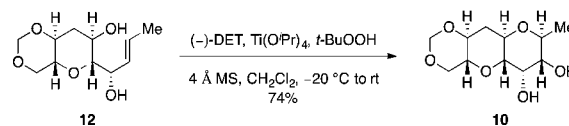
Scheme 2. Vanadium-Catalyzed Epoxidation Followed by Partial Cyclization



these reactions typically form mixtures of THFs and THPs.⁸ The presence of the neighboring hydroxyl group is proposed to enable epoxide activation and concomitant chelation to direct *endo*-selectivity. Sharpless has demonstrated that the addition of a chelating Lewis acid increases regioselectivity for epoxide opening distal to the alcohol in both inter-¹⁷ and intramolecular¹⁸ cases. Additionally, Oishi has reported partial *endo*-cyclization to form a THP following epoxidation, but this cyclization proceeded on an electronically biased epoxide.^{14d}

Attempts to optimize the vanadium-catalyzed process were plagued by modest diastereoselectivity in the epoxidation event (3:1 dr)¹⁹ in addition to incomplete cyclization. For this reason, we turned our attention to Sharpless asymmetric epoxidation, which enables reagent control for complete diastereoselectivity (Scheme 3).²⁰ The reaction required stoichiometric $\text{Ti}(\text{O}-i\text{-Pr})_4$

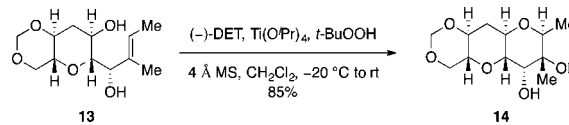
Scheme 3. Tandem Sharpless Asymmetric Epoxidation/Cyclization



to achieve complete conversion, as has been observed in the epoxidation of 1,2-diols.²¹ Under these conditions, desired tricycle 10 was isolated in 74% yield as the sole product.

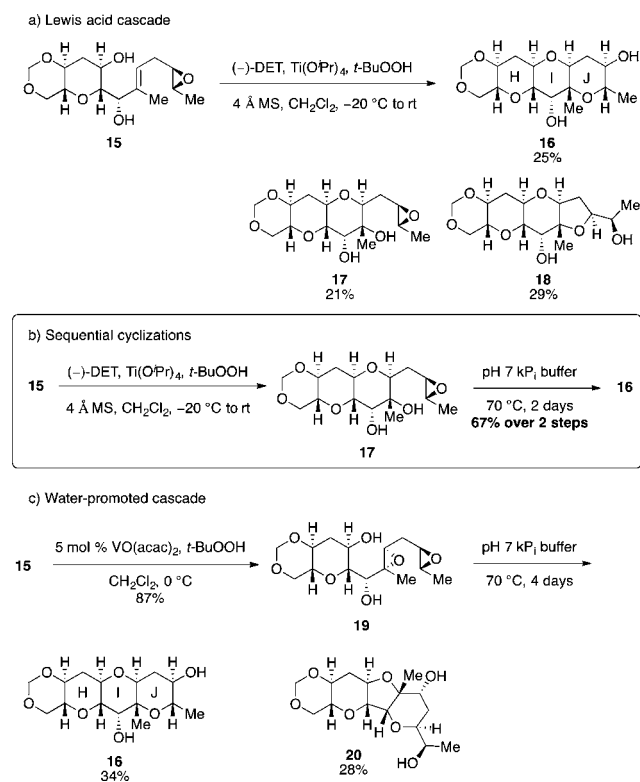
To explore the scope of this tandem epoxidation/cyclization methodology further, trisubstituted alkene 13 was prepared. Previous work with substrates containing this additional group at the proximal position demonstrate decreased selectivity in templated water-promoted epoxy alcohol cyclizations as the methyl is believed to stabilize the transition state leading to *exo*-cyclization.⁹ Remarkably, however, under the tandem epoxidation/cyclization conditions, the only product observed was the desired *endo* product 14, which was isolated in excellent yield (Scheme 4).

Scheme 4. Tandem Sharpless Asymmetric Epoxidation/Cyclization of Alkene Bearing Proximal Methyl Group



The excellent yield and regioselectivity observed in the cyclization of 14 prompted an investigation into extension of the method to a diepoxide cascade to synthesize a fragment of yessotoxin. To this end, allylic alcohol 15 was subjected to the newly developed methodology. Tetracycle 16 was obtained in 25% yield (Scheme 5). This result represents an average of 63% yield per transformation (epoxidation, cyclization, and cyclization), and the tetracycle contains the *HIJ* rings of yessotoxin. Additionally, epoxy alcohol 17 and *endo/exo*-cyclized product 18 were isolated in significant amounts. The ratio of 18 to 16 indicates a 1:1.2 *endo/exo* selectivity for the second ring closing event. This ratio is consistent with previous findings for templated epoxy alcohol cyclizations under Lewis acidic conditions.⁸ However, because templated water-promoted cyclizations are known to proceed with excellent *endo*-selectivity, we decided to decouple the two cyclizations to capitalize on the individual needs of each cyclization event.

Scheme 5. Synthesis of HIJ Fragment of Yessotoxin



Thus, the epoxidation/cyclization methodology was performed at a shorter reaction time to form tricycle **17** (Scheme 5b). Without any additional purification, this material was then heated in a neutral aqueous phosphate buffer to yield **16** in 67% yield over two steps, which corresponds to an average of 87% yield per transformation. To compare the two-step procedure to a single diepoxide cascade, **19** was prepared from **15** and then heated under aqueous conditions (Scheme 5c). The desired tetracycle **16** was isolated in 34% yield or 30% over the two steps. The product of *S-exo* followed by *6-exo* cyclization (**20**) was obtained from the reaction mixture in 28% yield, as well as numerous products arising from epoxide hydrolysis. The efficiency of the decoupled cyclization procedure is evident as it proceeds to one product in greater than 2-fold isolated yield.

In conclusion, a tandem epoxidation/cyclization approach to hydroxyl-substituted tetrahydropyrans has been developed. We have demonstrated that this method is applicable to different alkene substitution patterns, and the methodology has been utilized in a cascade to yield the HIJ rings of the marine ladder polyether yessotoxin. Further investigations into the formation of other ring systems by this method are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for all unknown compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tfj@mit.edu.

Notes

The authors declare no competing financial interest.

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