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Synthesis of α,α′-*trans*-Oxepanes through an Organocatalytic Oxa-conjugate Addition Reaction

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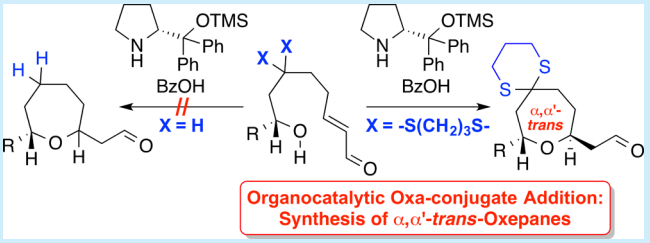
Supporting Information

ABSTRACT: Oxepanes are found in a wide range of natural products; however, they are challenging synthetic targets due to enthalpic and entropic barriers. Organocatalytic oxa-conjugate addition reactions promoted by the *gem*-disubstituent (Thorpe−Ingold) effect stereoselectively provided α,α′-*trans*-oxepanes. In addition, the potential of an organocatalytic tandem oxa-conjugate addition/α-oxidation was demonstrated in a rapid generation of molecular complexity. These organocatalytic oxa-conjugate addition reactions would provide powerful tools for the synthesis of natural products that contain highly functionalized oxepanes.



Architecturally complex 7-membered cyclic ethers (oxepanes) are found in a wide range of structurally or biologically interesting natural products (Figure 1).[1] Relative to tetrahydrofurans and tetrahydropyrans, oxepanes are challenging synthetic targets due to enthalpic and entropic barriers.[2]

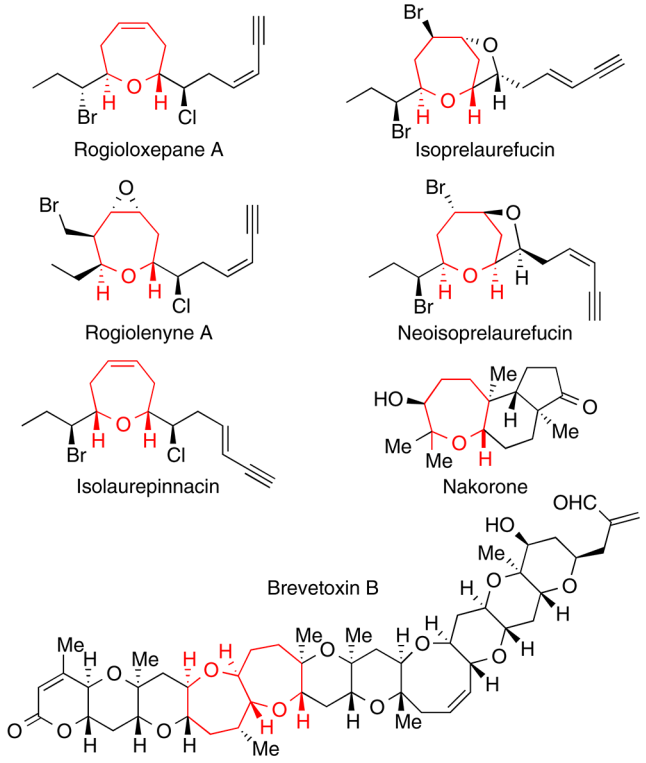


Figure 1. Examples of natural products containing 7-membered cyclic ethers.

Given the continued interest and challenges these molecules present as potential synthetic targets, the number of methods available for the construction of oxepanes has steadily increased.[3,4] Despite progress toward this goal, currently available methods for the synthesis of oxepanes possess several limitations. For example, with the notable exception of ring-closing metathesis (RCM),[3c,k] catalytic methods remain scarce. In addition, the stereoselective synthesis of α,α′-*trans*-oxepanes remains a challenging task since they are thermodynamically less favorable than the corresponding *cis* isomers.[5] Further limitations include the challenges associated with preparation of chiral substrates with preinstalled stereocenters, limited substrate scope, and competitive formation of smaller size rings according to Baldwin's rules.[6] Therefore, despite the advances of the past decade, there still exists a great need for synthetic approaches toward α,α′-*trans*-oxepanes that address these limitations.

During the last century, considerable progress has been made in the conjugate addition of carbon nucleophiles to a diverse set of acceptors for C−C bond formation.[7] However, there has been far less interest in the analogous conjugate addition of alcohols to α,β-unsaturated carbonyl compounds (oxa-conjugate addition reaction) and its application to the stereoselective synthesis of acyclic and cyclic ethers.[8] This is especially true with respect to the synthesis of medium-sized cyclic ethers. This can be attributed to the low reactivity of oxygen nucleophiles, the reversibility of the reaction, and the lack of control in the stereoselectivity.[8] To date, there have been only a few reports on the synthesis of medium-sized cyclic ethers through an intramolecular oxa-conjugate addition reaction.[9] As an example, Martin and co-workers reported the synthesis of an oxepane through the oxa-conjugate addition reaction of a

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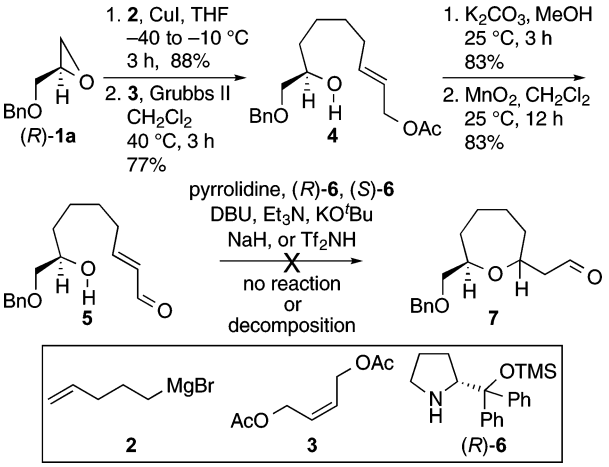
hydroxy ester.[9a] However, the reaction suffered from competing tetrahydropyran formation, required an internal (*Z*)-double bond to achieve good yields, and had a narrow substrate scope. Despite the scarcity of successful examples, however, the oxa-conjugate addition reaction has the potential to be a highly straightforward and efficient method for the synthesis of medium-sized cyclic ethers. Herein, we describe our investigation of the organocatalytic oxa-conjugate addition reaction promoted by the *gem*-disubstituent (Thorpe–Ingold) effect in the stereoselective synthesis of *α,α′-trans*-oxepanes.

To test the feasibility of the oxa-conjugate addition reaction for the stereoselective synthesis of oxepanes, we prepared *α,β*-unsaturated aldehyde **5** and subjected it to the conditions shown in Scheme 1. Our initial attempts at the oxa-conjugate

Scheme 1. Initial Attempts for the Oxa-conjugate Addition Reaction

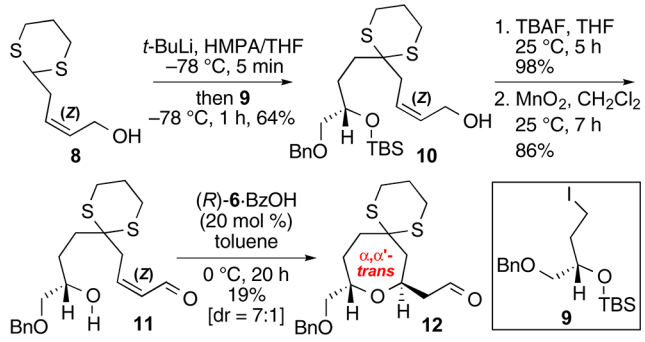


addition reaction, under a variety of reaction conditions (pyrrolidine, (*R*)-**6**, (*S*)-**6**, DBU, Et_3N, KO^{t}Bu, NaH, or Tf_2NH), failed to provide the desired oxepane **7**. We attributed the unsuccessful results to the low reactivity of the oxygen nucleophile, entropic factors, and/or transannular and torsional strain.

To overcome these obstacles, we envisioned the introduction of a structural element that would promote conformational preorganization of *α,β*-unsaturated aldehydes for an intramolecular oxa-conjugate addition reaction. We hypothesized that a 1,3-dithiane group installed on *α,β*-unsaturated aldehydes could satisfy these requirements on the basis of the *gem*-disubstituent effect (Thorpe–Ingold effect).[10] The *gem*-disubstituent effect has been shown to have a profound effect on the formation of medium-sized rings.[10,11] Among the functional groups used to elicit the *gem*-disubstituent effect, the 1,3-dithiane group is one of the most effective.[12] The 1,3-dithiane group is an acyl anion equivalent with impressive reactivity which allows umpolung-based strategies and serves as a latent functional group for a carbonyl, hydroxy, or olefinic group or hydrogen atoms.[13]

To explore the feasibility of the oxa-conjugate addition reaction promoted by the *gem*-disubstituent effect in the synthesis of oxepanes, we prepared the *α,β*-unsaturated aldehyde **11** with a 1,3-dithiane group by coupling dithiane **8** with alkyl iodide **9** followed by MnO_2 oxidation (Scheme 2).[14] Aldehyde **11** was then subjected to a secondary amine-catalyzed oxa-conjugate addition reaction. We anticipated that the *gem*-

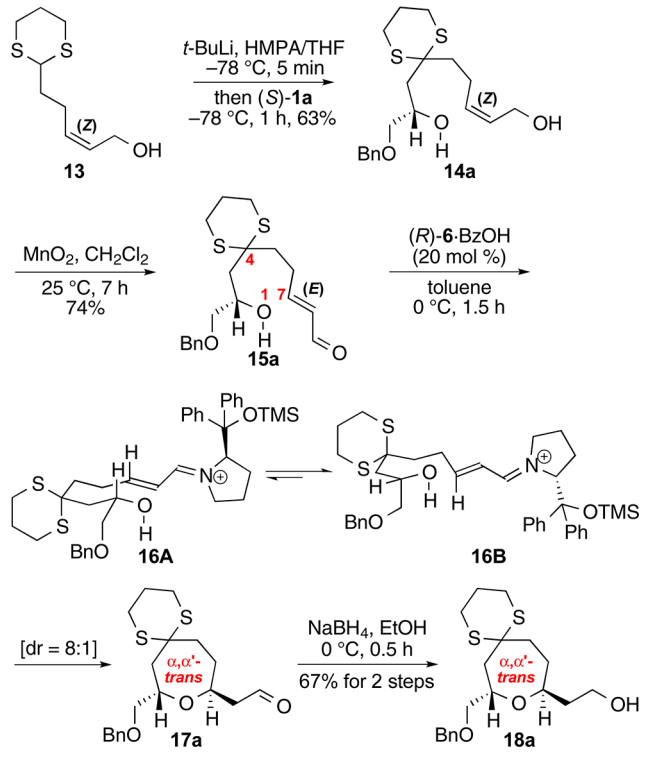
Scheme 2. Effect of the 1,3-Dithiane Group on the Oxa-conjugate Addition Reaction



disubstituent effect as well as the iminium activation would help overcome the ring strain and accelerate the cyclization step.[15,16] After an extensive search for reaction conditions, treatment of **11** with (*R*)-**6** (20 mol %) and BzOH provided the *α,α′-trans*-oxepane **12** as the major diastereomer[17] in good stereoselectivity (*α,α′-trans*:*α,α′-cis* = 7:1), but in low yield (19%).[18]

Encouraged by this initial success in the stereoselective synthesis of *α,α′-trans*-oxepane **12**, we decided to test the hypothesis that the position of 1,3-dithiane group might effect the reactivity and stereoselectivity.[19] We prepared *α,β*-unsaturated aldehyde **15a** with the 1,3-dithiane group at the C4 position by coupling **13** with (*S*)-glycidyl benzyl ether ((*S*)-**1a**) followed by MnO_2 oxidation (Scheme 3). We were delighted to find that the organocatalytic oxa-conjugate addition reaction of **15a** in the presence of (*R*)-**6** (20 mol %) and BzOH followed by $NaBH_4$ reduction successfully provided the desired *α,α′-trans*-oxepane **18a** through the more favorable iminium intermediate **16B**[20] (dr = 8:1, 67% for two steps).[21−24]

Scheme 3. Synthesis of an *α,α′-trans*-Oxepane via the Organocatalytic Oxa-conjugate Addition Reaction



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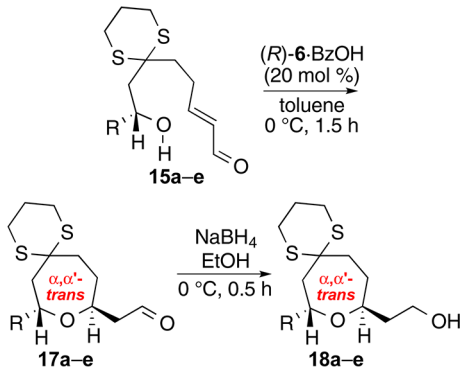
Surprisingly, when the reaction was run for a prolonged period, the stereoselectivity was reduced to provide a 1:1 mixture of **17a** and the corresponding *α,α′-cis*-oxepane, suggesting that the organocatalytic oxa-conjugate addition reaction was reversible. Probing the reaction further, **15a** was treated with (*R*)-**6** and BzOH and monitored for the formation and ratio of *α,α′-trans*- and *α,α′-cis*-oxepanes at different time points using NMR. We observed that the *α,α′-trans*-oxepane **17a** was initially formed as the major diastereomer. However, after 24 h, the reaction provided a 1:1 mixture of **17a** and the corresponding *α,α′-cis*-oxepane. This data suggests that the formation of the *α,α′-trans*-oxepane **17a** through the organocatalytic oxa-conjugate addition is a kinetically controlled process.

To investigate the substrate scope and stereoselectivity of the reaction, *α,β*-unsaturated aldehydes **15b–e** with a variety of substituents at the C2 position were prepared[25] and subjected to the standard reaction conditions (Table 1). We were pleased

Table 1. Substrate Scope of the Organocatalytic Oxa-conjugate Addition Reaction



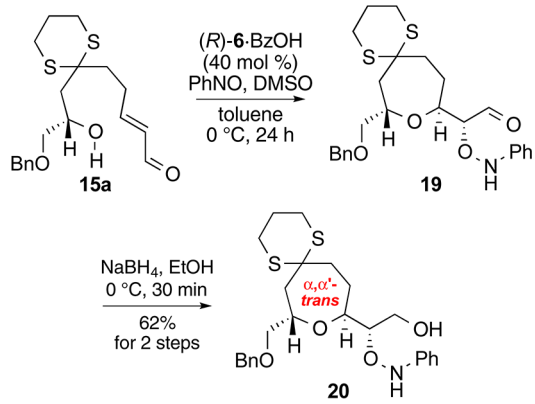
entry	R	yield[a] (%)	dr[b]
a	CH_2OBn	67	8:1
b	Et	87	6:1
c	Ph	56	6:1
d	$C(CH_3)_2CH_2OBn$	82	17:1
e	CH((*R*)-OPMB)CH_2OBn	64	20:1

[a]Combined yield of the isolated *α,α′-trans*- and *α,α′-cis*-oxepane alcohols after $NaBH_4$-reduction of the corresponding oxepane aldehydes. [b]The diastereomeric ratio (*α,α′-trans*/*α,α′-cis*) was determined by integration of relevant ^1H NMR spectroscopic signals of the crude oxepane aldehydes.

to find that the organocatalytic oxa-conjugate addition reaction of **15b–e** in the presence of (*R*)-**6** provided *α,α′-trans*-oxepanes **17b–e** in good-to-excellent stereoselectivities (dr = 6–20:1).

Recently, the organocatalytic tandem reaction, which carries out at least two reactions under the same reaction conditions, has drawn a considerable amount of attention.[26] It avoids time-consuming, costly protecting-group manipulations as well as the isolation of reaction intermediates. In this way, molecular complexity is achieved quickly and often accompanied by high levels of stereoselectivity. Building on the aforementioned work, we attempted an organocatalytic tandem oxa-conjugate addition/*α*-oxidation (Scheme 4).[27] The organocatalytic tandem oxa-conjugate addition/*α*-oxidation of **15a** in the presence of (*R*)-**6** and PhNO followed by $NaBH_4$ reduction afforded **20** (62% for two steps) as a single diastereomer.[28] The

Scheme 4. Organocatalytic Tandem Oxa-conjugate Addition/*α*-Oxidation



organocatalytic tandem reaction would provide a powerful tool for the rapid synthesis of natural products since these *α*-functionalized medium-sized cyclic ethers are abundant in natural products.

In summary, we have established an efficient method for the stereoselective synthesis of oxepanes based on the organocatalytic oxa-conjugate addition reaction promoted by the *gem*-disubstituent effect. It is noteworthy that the organocatalytic oxa-conjugate addition reaction of *α,β*-unsaturated aldehydes allows for the formation of *α,α′-trans*-oxepanes, which has proven challenging in other approaches. We have also demonstrated the potential of the organocatalytic tandem oxa-conjugate addition/*α*-oxidation in a rapid generation of molecular complexity. We plan to extend this organocatalytic oxa-conjugate addition reaction to the stereoselective synthesis of biologically important natural products.

■ ASSOCIATED CONTENT

Supporting Information

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.

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Notes

The authors declare no competing financial interest.

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(17) The relative stereochemistry of **12** was determined to be *trans* by 2D NMR spectroscopic studies (see the Supporting Information for details).

(18) An NMR kinetic experiment showed that during the initial 8 h, the isomerization of (*Z*)-enal **11** to the corresponding (*E*)-enal was observed with negligible formation of the desired oxepane **12**.

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(21) The relative stereochemistry of **18a** was determined to be *trans* by 2D NMR spectroscopic studies (see the Supporting Information for details).

(22) Lower loadings of (*R*)-**6** (5 and 10 mol %) reduced the reaction yield to 13% and 42%, respectively.

(23) The oxa-conjugate addition reaction of **15a** in the presence of pyrrolidine and BzOH (20 mol %, toluene, 0 °C, 1.5 h) provided *α,α′-trans*-oxepane as the major diastereomer (dr = 1.6:1).

(24) The oxa-conjugate addition reaction of **15a** in the presence of (*S*)-**6** and BzOH (20 mol %, toluene, 0 °C, 1.5 h) provided *α,α′-cis*-oxepane as the major diastereomer (dr = 1.8:1).

(25) For the synthesis of **15b−e**, see the Supporting Information for details.

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