Stereoselective Carbocyclization of Vinyloxiranes Catalyzed by Lewis Acids: Construction of the Musellarin Tricyclic Core

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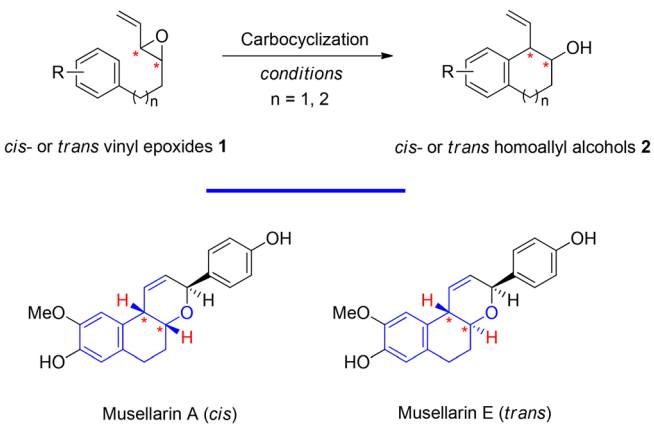
Stereoselective carbocyclizations of vinyloxiranes were efficiently catalyzed by Lewis acids to provide cyclic homoallyl alcohols as single isomers. The choice of Lewis acid, $B(C_6F_5)_3$ was crucial for the stereoselective transformation in the case of *cis* vinyloxiranes, whereas $BF_3{\cdot}OEt_2$ was proven to be an effective catalyst for *trans* substrates. The method was well implemented in the synthesis of seven-membered rings and six-membered rings with functional group tolerance. Utility of the resulting *trans*- and *cis* homoallyl alcohols was demonstrated to concisely build the tricyclic core of musellarin A and E.

Keywords: carbocyclization, vinyloxirane, Lewis acid, stereoselectivity, musellarin

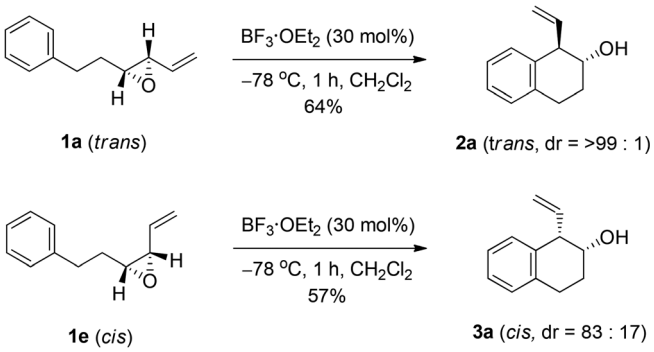
Vinyl epoxides have become versatile building blocks due to their unique reactivity arising from the combination of the vinyl and the epoxide.[1] It is interesting that each individual functional group cannot offer the same or comparable characteristics to vinyl epoxides. A number of reactions using these epoxides have accumulated over the past years including radical[2] and cycloaddition[3] reactions as well as nucleophilic openings.[1] Various nucleophiles are introduced to the openings of vinyl epoxides, and one of the nucleophiles is electron-rich π system as a carbon nucleophile.[4] This type of transformations are defined as Friedel–Craft reactions in which the epoxide can be activated by Lewis or Brønsted acids. Typically, Friedel–Crafts type alkylations are proven to be useful for construction of polycyclic compounds.[5]

In the view of a novel method targeted to bioactive natural products, musellarins A–E have been recognized as potential anticancer agents according to the cytotoxicity against several cancer cell lines such as HL-60 and A-549 since their isolation in 2002.[6,7] These natural products represent the bicyclic tetrahydropyran skeleton bearing seven-carbon unit between two aromatic groups. Despite increasing attention to the natural products, only few studies toward structural confirmation and their syntheses were found in the literature.[7] In the previous report, musellarin A-C having a *cis* relationship of the bicyclic tetrahydropyran were synthesized in 15–16 steps. However, the known synthetic routes are only available to prepare the *cis* ring system and selectivity issues still remained to be improved. There is no literature precedent regarding syntheses of musellarin D and E containing a *trans* ring junction to the tetrahydropyran distinct from the other natural products (Supporting Information S1).

We envisioned that both *cis*- and *trans* ring skeletons in musellarins can be rapidly built up through a cyclization of



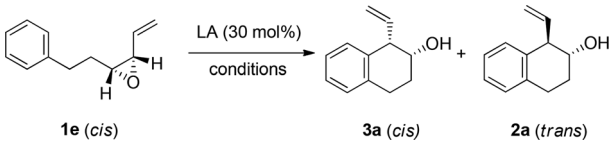
Scheme 1. Synthetic strategy.



Scheme 2. Preliminary investigations.

vinyloxiranes tethered with arenes in stereoselective manners (Scheme 1). In this respect, we set out to explore a method to access key cyclic intermediates. First, *cis*- and *trans* vinyl epoxides were readily prepared from propargyl alcohols through reductions[8] and epoxidations[9] followed by

Table 1. Orienting experiments for the carbocyclization of *cis*-vinyloxirane **1e**.[a]



1e (*cis*) **3a** (*cis*) **2a** (*trans*)

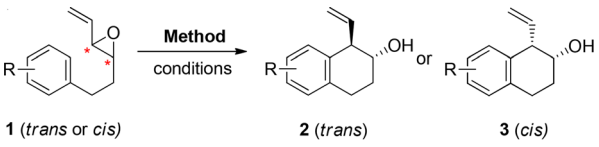
Entry	LA	Solvent	T (°C)	dr (*cis*:*trans*)[b]	Yield (%)[c]
1	$Ti(OiPr)_4$	CH_2Cl_2	−78	–	NR
2	$Ti(OiPr)_2Cl_2$	CH_2Cl_2	−78	45:55	21
3	$SnCl_4$	CH_2Cl_2	−78	85:15	57[c]
4	$TiCl_4$	CH_2Cl_2	−78	80:20	51[d]
5	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0	80:20	55
6	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	83:17	57
7	$B(C_6F_5)_3$	CH_2Cl_2	−78	*cis* only	67
8	$B(C_6F_5)_3$	Toluene	−78	*cis* only	53

[a] Reactions were carried out under dried nitrogen atmosphere.
[b] Ratios of **3a** and **2a** (*cis*:*trans*) were determined by ^{1}H NMR analysis of the crude mixture.
[c] Isolated yield after purification by SiO_2 chromatography.
[d] Corresponding chlorohydrines were also formed (<10%).

one-pot oxidations/Wittig olefinations as modified procedures in the literature.[10] Treatment of *trans* vinyloxirane **1a** with 30 mol % of $BF_3{\cdot}OEt_2$ at −78 °C resulted **2a** in 64% yield with excellent diastereoselectivity (>99: 1 *dr*). In the case of *cis* vinyloxirane **1e**, **3a** was produced in moderate yield under the same conditions with somewhat lower diastereoselectivity (83: 17 *dr*) (Scheme 2).

This observation can be explained by assumption that the partial generation of rotatable allylic carbocation from the complex of *cis*-**1e**-BF_3. Therefore, it was required that a Lewis acid catalyst keeps the intermediate free from a partial carbocation preventing from isomerization.[10] Consequently, we turned our attention to improve stereoselectivity of the cyclization in the case of *cis* vinyloxirane **1e**. After investigating various Lewis acids, $Ti(OiPr)_4$ and $Ti(OiPr)_2Cl_2$ turned out to be inefficient for the cyclization (Table 1, entries 1 and 2). Using $SnCl_4$ or $TiCl_4$ provided the diastereomeric mixtures slightly in favor

Table 2. Stereospecific carbocyclization of vinyloxirane **1.**

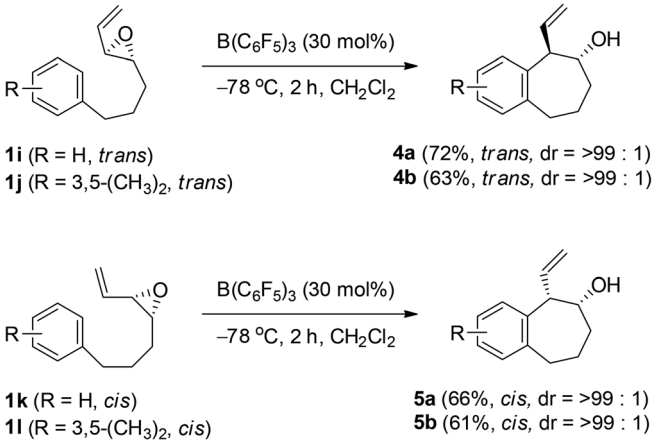


1 (*trans* or *cis*) **2** (*trans*) **3** (*cis*)

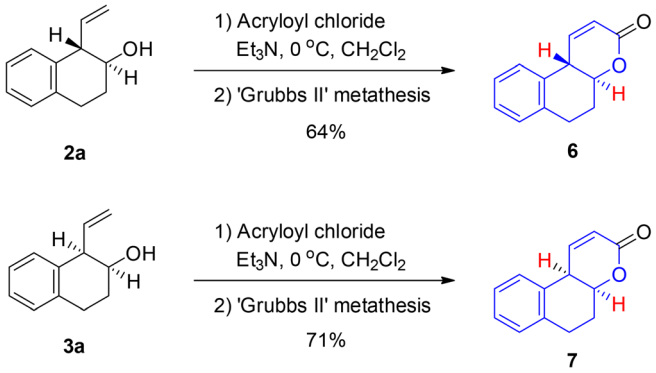
Method A: $BF_3{\cdot}OEt_2$ (50 mol%), –78 °C, 2 h, CH_2Cl_2
Method B: $B(C_6F_5)_3$ (30 mol%), –78 °C, 2 h, CH_2Cl_2

Entry	1	R	Method	Product	dr (2:3)[a]	Yield[b]
1	**1a** (*trans*)	H	**A**	**2a**	>99:1	71
2	**1b** (*trans*)	4-CH_3	**A**	**2b**	>99:1	75
3	**1c** (*trans*)	4-Br	**A**	**2c**	>99:1	63
4	**1d** (*trans*)	3-OMe	**A**	**2d**	>99:1	77
5	**1e** (*cis*)	H	**A**	**3a**	1:>99	67
6	**1f** (*cis*)	4-CH_3	**B**	**3b**	1:>99	65
7	**1g** (*cis*)	4-Br	**B**	**3c**	1:>99	63
8	**1h** (*cis*)	3-OMe	**B**	**3d**	1:>99	75

[a] Ratios of **2** and **3** (*trans*:*cis*) were determined by the analysis of 300 MHz ^{1}H NMR.
[b] Isolated yield after purification by SiO_2 chromatography.



Scheme 3. Extension to seven-membered ring system.



Scheme 4. Construction of the musellarin skeleton.

of *cis* **3a** (85:15–80:20 *dr*, Table 1, entries 3 and 4). Fortunately, we were delighted to find that unique catalyst $B(C_6F_5)_3$ can be efficiently catalyzed the stereoselective cyclization in CH_2Cl_2 at −78 °C affording *cis* **3a** as a single isomer (Table 1, entry 7).

With these observations in hand, *cis*- and *trans* substrates varying substitutions of arenes were evaluated to establish optimal conditions. Based on the preliminary results, cyclizations of *trans* vinyloxiranes in the presence of 50 mol % $BF_3{\cdot}OEt_2$ at −78 °C for 2 h (Table 2, entries 1–4, **Method A**) led to high levels of diastereoselectivity in all cases.

In addition, $B(C_6F_5)_3$ was successfully employed to the *cis* substrates for the transformations providing *cis* adducts **3** in good yields with excellent stereoselectivity regardless of electronic effect from the substituents of arenes (Table 2, entries 5–8, **Method B**).

This result prompted us to explore an extension to seven-membered ring system. According to the conditions for *trans* vinyloxiranes, we first examined *trans* **1i** with 50 mol % of $BF_3{\cdot}OEt_2$ (**Method A**), but isolated **4a** in only marginal results. Although cyclized product **4a** was produced during the reaction, problems of low yield (30%) and formation of several unidentified side products remained to be solved. Gratifyingly, we found that treatment of **1i** with 30 mol% of $B(C_6F_5)_3$ was effective to form **4a** as a single isomer (**Method B**). Under the same conditions, dimethyl-substituted arene **1j** was also converted to **4b** with comparable results. It is noteworthy mentioning that *cis* vinyloxiranes **1k** and **1l** were cyclized to **5a** and **5b**, respectively, without scrambling stereochemistry under the same conditions as *trans* vinyloxiranes (Scheme 3).

To demonstrate the potential use of resulting cyclic compounds as key intermediates in the synthesis of musellarins, we carried out each diastereomers **2a** and **3a** to form the corresponding acrylic ester. Then, ring-closing metathesis of the esters afforded the γ-lactones with the requisite *cis*- and *trans* stereochemistry for the construction of musellarin A and E (Scheme 4).[11]

In conclusion, we described efficient catalytic system for regio- and stereoselective carbocyclizations of *cis*- and *trans*-vinyloxiranes. The carbocyclization delivered six- and seven-membered rings with a wide range of substrate scope. The synthetic utility of this method was demonstrated in the concise synthesis of the tricyclic core of musellarins. Further investigations for asymmetric method and syntheses of musellarin A and E are in progress.

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Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

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