



Stereospecific interconversion of *cis*- and *trans*- γ,δ -epoxy α,β -unsaturated ester systems

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ABSTRACT

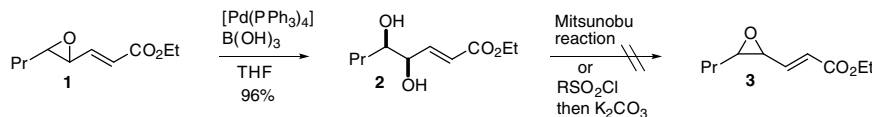
The unprecedented, stereospecific interconversion of *cis*- and *trans*- γ,δ -epoxy α,β -unsaturated ester systems has been realized, which involves the palladium-catalyzed stereospecific alkoxy or hydroxy substitution reaction with double inversion of configuration at the γ -position as the key step. The new methodology is not only applicable to various disubstituted and trisubstituted epoxy unsaturated esters, but also these interconversions proceed with an extremely high degree of stereoselectivity and efficiency.

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Stereoselective, epoxide-opening reactions with nucleophiles have played very important roles in organic synthesis, particularly in the stereoselective synthesis of biologically important target molecules in natural product and in medicinal research.¹ It is well known that the epoxide-opening reaction via an S_N2 process occurs stereospecifically, that is, the reaction of a *trans*-epoxide with a nucleophile gives an *anti*-product stereoselectively, while that of a *cis*-epoxide produces a *syn*-product exclusively. Therefore, if stereospecific interconversion between *cis*-epoxides and *trans*-epoxides is realized, both *anti* and *syn* products should be available from the same epoxide in a highly stereoselective manner. However, such transformation has been known to be methodologically very difficult, although *cis*–*trans* isomerization of epoxides in a few particular cases such as thermal isomerization of α -cyanostilbene oxide,² ruthenium-catalyzed isomerization,³ and that of α,β -epoxy amides⁴ have been reported, most of which produced the thermodynamically more stable *trans*-isomers predominantly.

As a program of acyclic stereocontrol based on the stereospecific epoxide-opening reactions, we already reported the highly stereoselective interconversion between *cis*- and *trans*-epoxy sulfides.⁵ Our recent studies on a number of stereospecific substitution reactions of γ,δ -epoxy α,β -unsaturated esters with carbon,⁶ nitrogen,⁷ and oxygen nucleophiles⁸ call for an efficient and highly stereoselective interconversion of *cis*- and *trans*-epoxy unsaturated ester systems, which would provide very useful transformations in organic synthesis.

We first explored an interconversion route via the palladium-catalyzed stereospecific hydroxy substitution reaction of γ,δ -epoxy α,β -unsaturated esters with boric acid ($B(OH)_3$) which was recently developed by us^{8b} (Scheme 1). Thus, the palladium-catalyzed reaction of ethyl *trans*-4,5-epoxy-2-octenecarboxylate (**1**) with $B(OH)_3$ in THF smoothly occurred giving rise to *syn*-diol **2** with double inversion of configuration at the γ -position in excellent yield. We presumed that stereoselective interconversion of *cis*- and



Scheme 1. Attempts to convert *trans*-epoxy unsaturated ester **1** to *cis*-congener **3** via *vic*-diol **2**.

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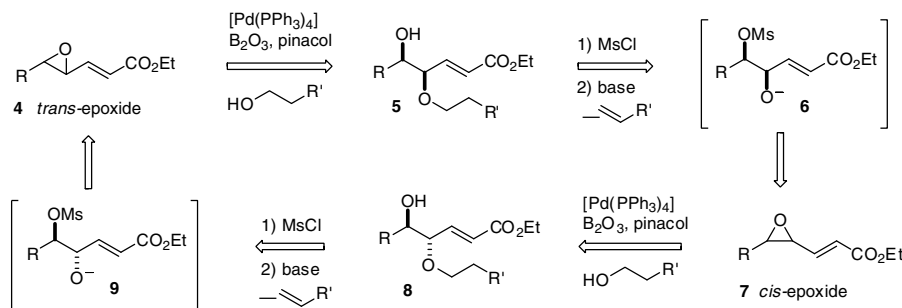
trans- γ,δ -epoxy α,β -unsaturated esters might be possible, if the diol **2** was to be stereoselectively converted to the corresponding *cis*-epoxide **3**. However, neither the Mitsunobu dehydration reaction⁹ of **2** nor the two-step reaction sequence via mono-sulfonate followed by treatment with a base was fruitful under various conditions (Scheme 1). These results suggest that ingenuity to differentiate vicinal hydroxyl groups in **2** is of critical importance for interconversion of the *trans*-epoxide **1** and the *cis*-epoxide **3**.

Very recently, we developed the novel palladium-catalyzed alkoxy substitution reaction by combination of a γ,δ -epoxy α,β -unsaturated ester, boron oxide, and pinacol, which proceeds with double inversion of the configuration at the γ -position to afford a γ -alkoxy- δ -hydroxy- α,β -unsaturated ester in a stereospecific manner and in high yield.¹⁰ Since a variety of γ -alkoxy- δ -hydroxy- α,β -unsaturated esters **5** are easily obtainable by this method, we envisioned that stereospecific interconversion between *cis*- and *trans*-epoxy unsaturated esters might be possible, if the key alkoxide ion **6** could effectively be generated in situ by use of a γ -alkoxy substituent after introduction of a mesyloxy group at the δ -position, as shown in Scheme 2. Based on this concept, we studied the following three-step reaction sequence, which involves the palladium-catalyzed stereospecific alkoxy substitution reaction of a *trans*-epoxy unsaturated ester **4**, mesylation of the resulting alcohol **5** followed by the key generation of the alkoxide ion **6** leading to a *cis*-epoxide **7**.

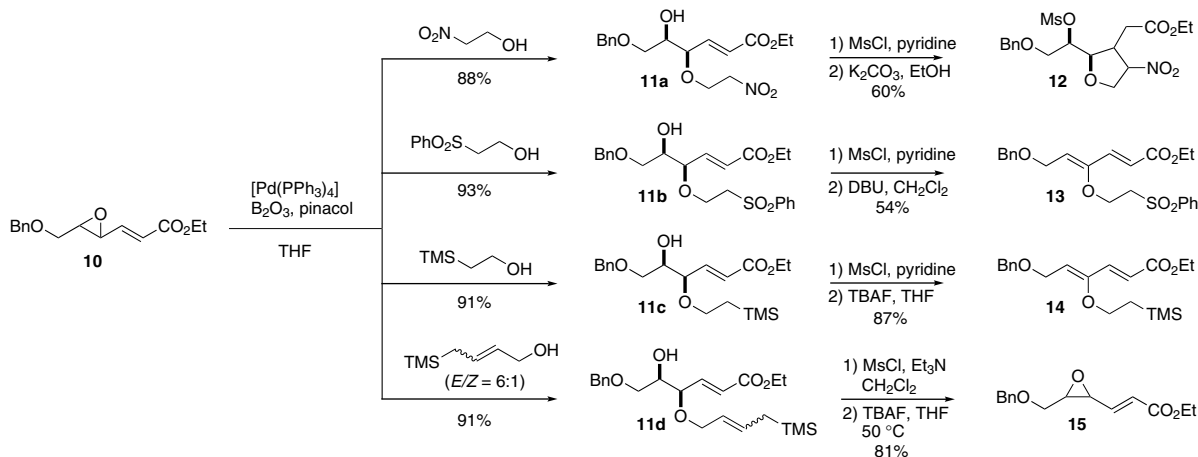
Initially, a number of alcohol nucleophiles were examined to find out which type of an alkoxy substituent in **5** is most suitable for in situ generation of the alkoxide ion **6**. For this purpose, we selected 2-nitroethanol, 2-(phenylsulfonyl)ethanol, 2-trimethylsilylethanol, and 4-(trimethylsilyl)-2-buten-1-ol^{11,12} as alcohol counterparts, and carried out the palladium-catalyzed alkoxy sub-

stitution reactions of ethyl 6-benzyloxy-*trans*-4,5-epoxy-2-hexenoate (**10**) with these alcohols. The substitution reactions smoothly occurred at room temperature to afford *syn*- γ -alkoxy- δ -hydroxy- α,β -unsaturated esters **11a–d**, the products with retention of configuration, in excellent yields, as shown in Scheme 3. After each product was treated with methanesulfonyl chloride, the crude mesylate was subjected to the key epoxide-forming reaction. Upon treatment of the mesylate derived from **11a** with K_2CO_3 in EtOH, only tetrahydrofuran derivative **12**¹⁴ was formed, and the *cis*-epoxide **15** was not detected at all. On the other hand, treatment of the mesylate prepared from **11b** with DBU resulted in formation of the elimination product **13**. Next, we focused on the reactions of **11c** and **11d** in expectation to generate of alkoxide ions by treatment with a mild fluoride ion. Thus, treatment of the mesylate derived from **11c** with TBAF in THF merely resulted in formation of diene **14**. On the contrary, upon treatment of the mesylate prepared from **11d** with TBAF in THF at 50 °C, much to our pleasure, the *cis*-epoxide **15** was produced as a single product in 81% isolated yield. These outcomes demonstrate that only 4-(trimethylsilyl)-2-buten-1-ol serves as the alcohol counterpart for this particular transformation that allows efficient generation of the key alkoxide ion by elimination of 1,3-butadiene from the 4-(trimethylsilyl)-2-butenyl ether moiety on treatment with TBAF.

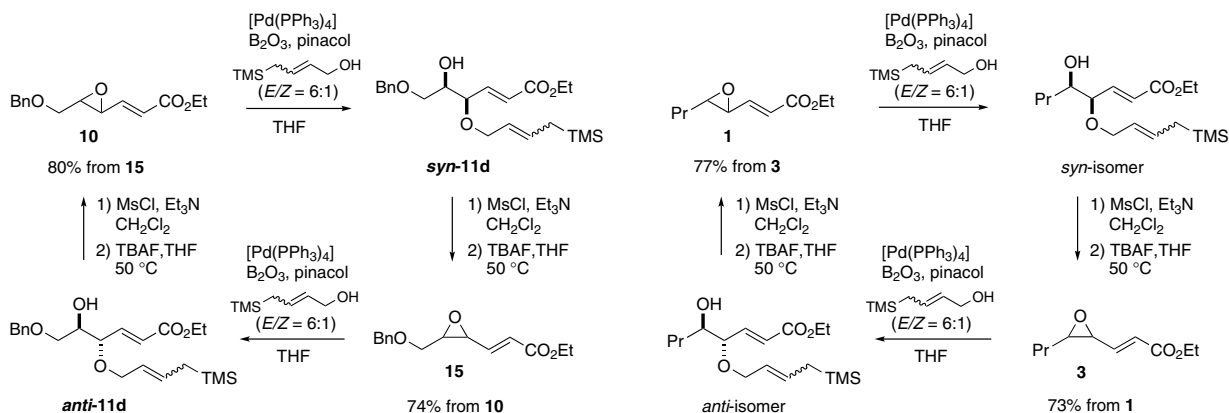
Efficient conversion of the *trans*-epoxide **10** to the *cis*-congener **15** with complete diastereoselectivity prompted us to investigate the scope of this methodology. To our expectation, the opposite transformation from the *cis*-epoxide **15** to the *trans*-isomer **10** also occurred stereospecifically in three steps in 80% overall yield (Scheme 4). Similarly, interconversion of *cis*- and *trans*-epoxy unsaturated esters **3** and **1** that bear no ether oxygen atom on the side chain was performed with complete stereoselectivity, as



Scheme 2. Strategy for stereospecific interconversion of *cis*- and *trans*-epoxy unsaturated esters.



Scheme 3. Pd(0)-catalyzed substitution reactions of **10** with various alcohols and subsequent epoxide-forming reactions.

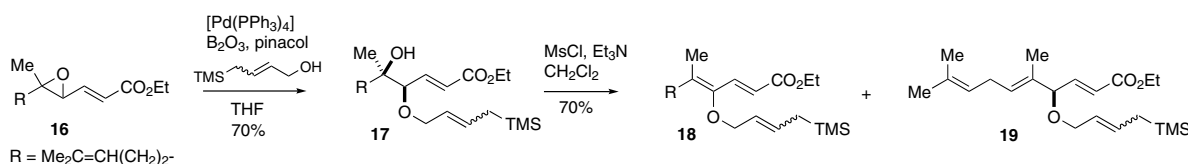


Scheme 4. Stereospecific interconversion cycle of **10** and **15** and that of **1** and **3**.

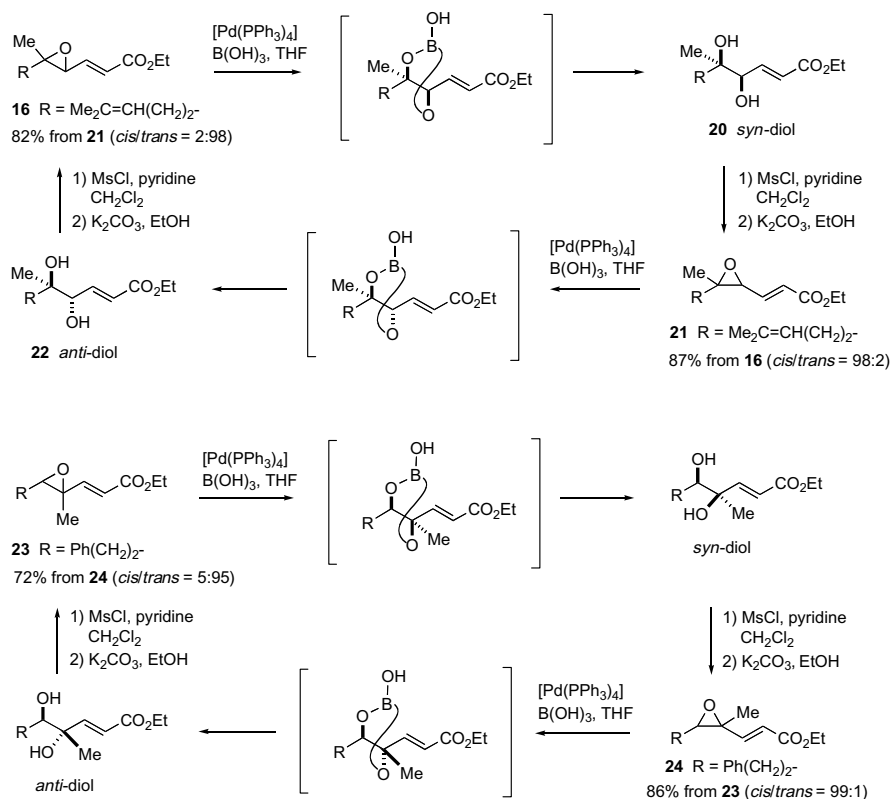
shown in **Scheme 4**. In this way, the stereospecific interconversion of the disubstituted γ,δ -epoxy α,β -unsaturated ester systems was established.

We next focused on interconversion of trisubstituted γ,δ -epoxy α,β -unsaturated esters. As a result, although the palladium-cata-

lyzed alkoxy substitution reaction of *trans*-epoxide **16** with 4-(trimethylsilyl)-2-buten-1-ol smoothly occurred to furnish alcohol **17**, the corresponding mesylate could not be isolated because of the concomitant elimination reactions that are yielding a mixture of dienes **18** and **19** (**Scheme 5**). These preliminary results suggest



Scheme 5. Application to trisubstituted epoxy ester **16**.



Scheme 6. Stereospecific interconversion cycle of trisubstituted epoxides **16** and **21**, and that of **23** and **24** with the different substitution patterns.

that the successful methodology for disubstituted epoxides is not applicable to trisubstituted epoxides.

Although the first strategy for interconversion of **1** and **3** via mono-sulfonate was unsuccessful as described in Scheme 1, we hopefully anticipated that this methodology should be applicable to interconversion of trisubstituted epoxy esters, because of different steric hindrance and reactivity of the secondary and the tertiary hydroxyl groups in the products. Indeed, the palladium-catalyzed substitution reaction of **16** with B(OH)₃ yielded *syn*-diol **20** quantitatively, and subsequent mesylation of the secondary hydroxyl group followed by treatment of the resulting mesylate with K₂CO₃ in EtOH produced *cis*-epoxide **21** with remarkably high stereoselectivity (*cis/trans* = 98:2) in three steps in 87% yield (Scheme 6). As well, the opposite conversion from the *cis*-epoxide **21** to the *trans*-isomer **16** was performed in an efficient and highly stereoselective manner (*cis/trans* = 2:98).

Furthermore, we found that this methodology was also applicable to alternative trisubstituted epoxy unsaturated ester **23** with the different substitution pattern (Scheme 6). Namely, the *trans*-epoxide **23** bearing a methyl group at the γ -position was successfully transformed into *cis*-congener **24** (*cis/trans* = 99:1) in 86% overall yield as shown in Scheme 6, while **24** could be converted to **23** (*cis/trans* = 5:95) in 72% isolated yield. Thus, stereospecific interconversion cycle of *cis*- and *trans*-trisubstituted γ,δ -epoxy α,β -unsaturated ester systems with the different substitution patterns has been established. To the best of our knowledge, this is the first case in interconversion between trisubstituted epoxides.

In conclusion, we developed the new methodologies for interconversion of *cis*- and *trans*- γ,δ -epoxy α,β -unsaturated ester systems. Interconversion of disubstituted *cis*- and *trans*-epoxy unsaturated esters was achieved by the three-step reaction sequence involving the palladium-catalyzed stereospecific alkoxy substitution reaction with 4-(trimethylsilyl)-2-buten-1-ol, mesylation of the resulting alcohol followed by treatment with TBAF. On the other hand, interconversion of trisubstituted epoxy unsaturated esters was performed by the different three-step reaction sequence that involves the palladium-catalyzed hydroxy substitution reaction with B(OH)₃, selective mesylation of the secondary hydroxyl group followed by treatment with K₂CO₃. Since these interconversions proceed with remarkably high diastereoselectivity and efficiency, the present methodologies should provide very useful transformations in organic synthesis, particularly in natural product synthesis and in medicinal research. Application of these methodologies to the synthesis of complex natural products is in progress in our laboratory.

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Supplementary data

Typical experimental procedures and characterization data are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.084.

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