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Regioselective cleavage of *cis*- and *trans*-2-methyl-3,4-epoxy alcohols with diethylpropynyl aluminum

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Abstract—The regioselectivity of the reaction of diethylpropynyl aluminum with diastereomeric 2-methyl-3,4-epoxy alcohols was studied. The preferred side of attack (1,3-diol vs 1,4-diol product) depends on the stereochemical disposition of the substituents. NMR studies showed that the regiochemistry of this reaction is governed by the aluminum coordination pattern. Protection of the alcohol with MEM provides the 1,3-diol product in systems where the free alcohol produced the 1,4-diols.

The stereoselective cleavage of an epoxide with a carbon nucleophile has become an important C–C bond formation strategy in organic and natural products synthesis.[1] Among the different organometallic reagents that have been used for this purpose, organoaluminum reagents have become a popular alternative.[2–7] This type of reagent has been applied to a variety of epoxide substrates including 2,3-epoxy alcohols,[3] γ,δ-epoxy unsaturated esters,[4] epoxy sulfides,[5] and selenides,[6] and very recently to epoxy alkanes.[7] On the contrary, the application of organoaluminum chemistry to 3,4-epoxy alcohols, unlike their 2,3-epoxy alcohol counterparts, has been less studied.[8] Nonetheless, when disubstituted epoxides are used (similar to other organometallic approaches), the regioselectivity of the oxirane ring cleavage becomes a critical concern.

We are specifically interested in 2-methyl-3,4-epoxy alcohols as precursors for the stereoselective elaboration of a series of stereotetrads, which may have potential uses in polypropionate synthesis (Fig. 1).[9] In this regard, over the past several years we have been working on the development of effective methods for the preparation of polypropionates based on epoxides using diethylpropynylalane[10] as the oxirane cleaving agent (Scheme 1).[11] In our three-step approach, an epoxide (**1**) is submitted to a sequence of diethylpropynylalane-mediated oxirane cleavage, alkyne reduction and stereoselective epoxidation to yield a 3,4-epoxy alcohol (**2**). Cleavage of **2** with the propynyl aluminum reagent produces a second propionate unit (**3**). This methodology could be repeated on **3**, a homopropargylic alcohol, to produce a new 3,4-epoxy alcohol (**4**), which allows for chain elongation in a reiterative fashion. The configuration of the newly formed hydroxy functionality is controlled by the initial epoxide configuration, while the *syn*/*anti* relative configuration of the methyl and hydroxy groups results from the *cis*/*trans* geometry of the epoxide. The regioselective cleavage of the resulting 3,4-epoxy alcohols is the key step in this sequence.

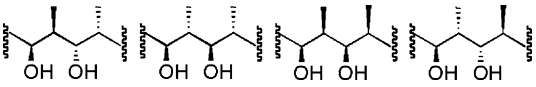
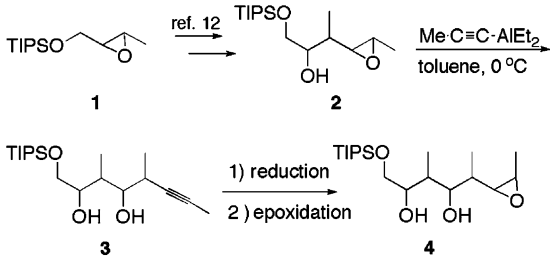


Figure 1. Examples of stereotetrads.

Consequently, when the 2-methyl-3,4-epoxy alcohol **2a** was treated with diethylpropynylalane in toluene, the



Scheme 1. Reiterative epoxide sequence to polypropionates.

Keywords: Epoxide cleavage; Alkynyl aluminum; Stereotetrads; Polypropionate synthesis.
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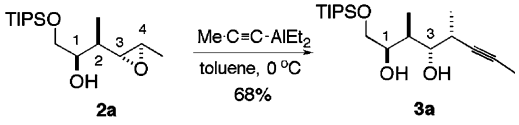
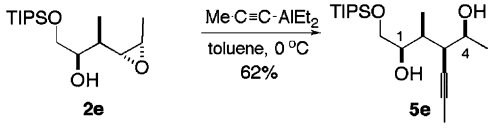
syn, *anti*, *syn* stereotetrad **3a** was isolated as the major product in 68% yield (Eq. 1). This 1,3-diol was the expected product based on steric considerations. Surprisingly, when the same reaction was extended to the *cis*-epoxy alcohol diastereomer **2e**, the 1,4-diol regioisomer **5e** was obtained as the exclusive product (Eq. 2). This intriguing result led us to examine further the reaction of 2-methyl-3,4-epoxy alcohols with alkynyl aluminum. Herein we report our findings on the regioselectivity of the diethylpropynylalane cleavage of *trans*- and *cis*-2-methyl-3,4-epoxy alkanols and present a solution to the regioselectivity problem to demonstrate the synthetic utility of alkynyl aluminums in polypropionate synthesis.



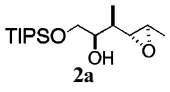
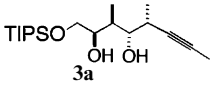
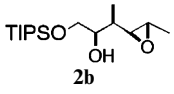
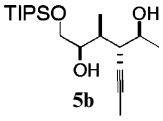
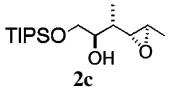
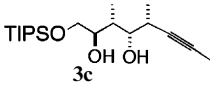
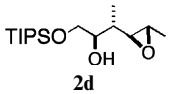
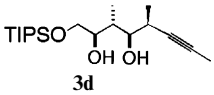
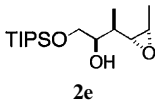
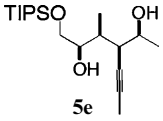
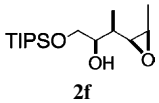
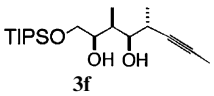
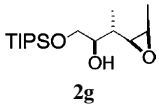
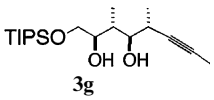
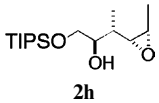
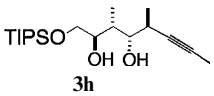
(1)



(2)

All eight diastereomeric *trans*- and *cis*-2-methyl-3,4-epoxy alcohols were prepared[12] and allowed to react with diethylpropynylalane. The results are summarized in Table 1. All epoxides gave alkynyl substitution products in variable yields and regioselectivities. In the cases in which the epoxides were cleaved at the C4 carbon atom (1,3-diol products), *syn*-propionate units were obtained from *trans*-epoxy alcohols, whereas *anti*-propionate products were produced from *cis*-epoxy alcohols. Therefore, for the *trans*-epoxide series (**2a**–**d**), treatment of epoxy alcohols **2a**,**c**, and **2d** afforded the 1,3-diol products **3a**,**c**, and **3d** in moderate to low yields (entries 1, 3, and 4). Conversely, when epoxy alcohol **2b** was treated under similar conditions, the 1,4-diol **5b** was

Table 1. Reaction of 3,4-epoxy alcohols with diethylpropynylalane

Entry	Epoxide[a]	Major diol product	**3**:**5** Ratio[b]	Yield[c]
1	 **2a**	 **3a**	89:11	78
2	 **2b**	 **5b**	15:85	39[d]
3	 **2c**	 **3c**	56:44	28[d,e]
4	 **2d**	 **3d**	67:33	52
5	 **2e**	 **5e**	<5:95[f]	62[e]
6	 **2f**	 **3f**	71:29	56[d]
7	 **2g**	 **3g**	<95:5[f]	52[g]
8	 **2h**	 **3h**	<95:5[f]	17[g,h]

[a] Prepared by published procedures (Ref. 12).
[b] Determined by ^{1}H and ^{13}C NMR spectroscopy.
[c] Combined yield (%) of isolated 1,3- and 1,4-diol products.
[d] Epoxide rearrangement (to ketone) followed by propynyl addition product (9% for **2b**, 8% for **2c**, and 27% for **2f**) was also observed.
[e] A furan (from internal alkoxide attack at C4) was also isolated (14%).
[f] Only one isomer was observed by NMR analysis.
[g] Yield of the isolated acetonide starting from the epoxide.
[h] An oxetane (from internal alkoxide attack at C3) was also isolated (36%).

the major isomer, although obtained in low yield, as a result from an attack at the more hindered C3 carbon (entry 2). For the *cis*-epoxide series (**2e**–**h**), the introduction of a propynyl group at the C4 position was observed in moderate to good regioselectivity (entries 6–8). The reaction of the corresponding epoxy alcohol **2e**, however, resulted in substitution at the C3 position, again to afford the 1,4-diol **5e** exclusively (entry 5).

Establishment of the structural features that could govern the regiochemical outcome of the cleavage reaction is not apparent by examination of the examples in Table 1. When, however, the cis/trans geometry of the epoxide and the *syn*/*anti* relationship between the C1-hydroxy and the epoxide are analyzed, a general trend for the regiochemical outcome of the epoxide cleavage reaction is observed; For the *trans*-epoxy-alcohol series (entries 1–3), a *syn* hydroxy–epoxide relationship promotes the cleavage of the epoxide at C3, while an *anti* hydroxy–epoxide relationship favors the cleavage at C4. On the contrary, for the *cis*-epoxy alcohol series (entries 5–7), a *syn* hydroxy–epoxide relationship promotes the cleavage of the epoxide at C4, while an *anti* hydroxy–epoxide relationship induces the cleavage at C3. Still, epoxides **2d** and **2h** (entries 4 and 8) diverge from these trends. The *trans*-epoxy alcohol **2d**, which has a *syn* hydroxy–epoxide relationship, promoted the attack at C4. In the case of the *cis* alcohol **2h**, which has an *anti* hydroxy–epoxide relationship, again the 1,3-diol was favored. In both cases, the relative configuration of the 2-methyl group must be playing a controlling role. In addition, the reaction of **2h** produced an oxetane (from an internal alkoxide attack) as the major isolated product. This system constitutes the limitation of this methodology.

The regioselectivity of the epoxide cleavage was established by ^{13}C and ^{1}H NMR. For example, the COSY spectra of the 1,4-diol **5e** showed cross peaks between the C4 methyne at 3.90 ppm, and the C5 methyl at 1.24 ppm (–C*H*(OH)C*H*$_3$). Interestingly, the ^{13}C NMR spectra for the 1,3-diols (**3a**,**c**,**d**,**f**, and **3g** revealed methyne peaks around 35.2–39.5 for the C2 carbon atoms, and 30.2–31.0 ppm for the C4 carbon atoms. On the other hand, the 1,4-diols (**5b**,**e** and the other minor 1,4-diol products) presented peaks around 41.6–45.1 and 34.6–36.4 ppm for the C2 and C3 carbon atoms. These trends are consistent and may be used as a reliable tool to assess the regioselectivity of the epoxide cleavage. To establish the relative configuration of the stereotetrads, the 1,3-diols were converted to the six-membered ring acetonides and analyzed by NMR spectroscopy. The $J_{1,2}$ and $J_{1,3}$ values for the acetonides were in agreement with the proposed relative configuration, as shown in the examples in Figure 2.[13] In addition, the *syn* acetonides show ^{13}C NMR signals around 20 and 30 ppm for the *gem*-dimethyl carbon atoms, while the *anti* acetonides show both signals near 25 ppm.[14]

The importance of the oxygen–aluminum chelation between the alane reagent and the epoxy ether oxygen has been established as a fundamental factor in the regioselectivity of the oxirane ring cleavage in 2,3- and 3,4-epoxy-1-ethers.[15] In this regard, two chelation patterns

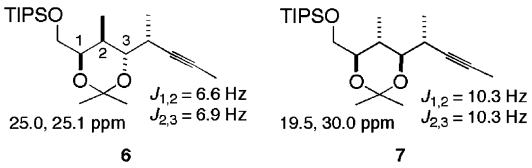


Figure 2. Selected NMR data for acetonides **6** and **7**.

have been proposed: In the bidentate pathway, one equivalent of the aluminum reagent coordinates to the alkoxy and oxirane groups to form a cyclic intermediate, while in the monodentate pathway, 1 equiv of the aluminum reagent coordinates with the epoxide and another coordinates the ether oxygen. We expect that related aluminum bidentate (**8**) and monodentate (**9**) chelation patterns could similarly apply to the hindered 2-methyl-3,4-epoxy alcohol systems **2a**–**h**, with the evident difference that the free alcohol initially forms an aluminum alkoxide with the first alkynyl alane equivalent through an acid–base reaction (Fig. 3). Consequently, the regioselectivity in the epoxide opening reaction of 2-methyl-3,4-epoxy alcohols depends on the nature of the aluminum chelates, that is, bidentate complexes produce the 1,3-diols favorably, while monodentate complexes afford 1,4-diols preferentially. Another aluminum reagent probably coordinates with the alkoxide oxygen in **9** and accelerates the intramolecular reaction to produce 1,4-diols preferentially.[15]

NMR studies were performed in order to explore these possibilities. Thus, the diastereomeric 2-methyl-3,4-epoxy alcohols **2a**,**b**,**e**, and **2g** were treated with Et_3Al and analyzed by ^{27}Al and ^{13}C NMR in order to discern the nature of the aluminum coordination. The ^{27}Al NMR study was not conclusive, as all the detected signals ranged between 136 and 139 ppm at −33 °C in toluene-d_8. Nevertheless, the ^{13}C NMR spectra for the epoxide–aluminum complexes presented changes in the chemical shifts for the C1 carbon atoms, and the C3 and C4 epoxide carbon atoms (Table 2). Examination of the NMR data produced the following observations: The systems that favor the attack at the C4 position (**2a** and **2g**) show an 8.2 and 8.0 ppm downfield shift at the C1 carbon atom, while the cases that favor the C3 attack (**2b** and **2e**) exhibit smaller or upfield (+/−2.0 ppm) C1 chemical shift difference. In addition, all epoxide carbon atoms exhibit noticeable downfield shift differences ($\Delta\delta$ 4.3–10.8), which suggest a strong aluminum coordination with the epoxide. Although an unambiguous interpretation of these trends is not possible at this moment, these observations imply that the aluminum coordination pattern for the systems that produce the 1,3-diols

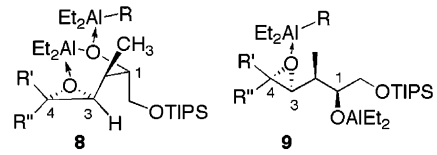


Figure 3. Bidentate and monodentate intermediates (R = propynyl).

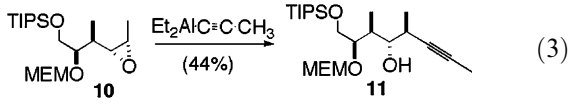
Table 2. ^{13}C NMR chemical shift differences for selected epoxy alcohol carbons (C1, C3, C4) after complexation with Et_3Al[a]

Epoxide	Attack	δC1	δC1[b]	$\Delta\delta$C1	δC3	δC3[b]	$\Delta\delta$C3	δC4	δC4[b]	$\Delta\delta$C4
2a	C4	73.9	82.2	8.2	61.7	69.3	7.6	53.5	61.1	7.6
2b	C3	73.5	75.5	2.0	61.6	65.9	4.3	53.9	61.7	7.1
2e	C3	74.2	72.9	−1.9	58.4	69.2	10.8	51.8	61.9	10.1
2g	C4	75.5	83.5	8.0	57.7	66.6	8.9	51.1	56.8	5.7

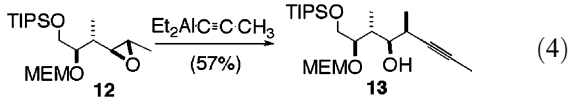
[a] In toluene-d_8.
[b] δ After Et_3Al addition.

is different from those that favor the 1,4-diols. This is consistent with a competition between different coordination pathways.

In order to find a solution to the regioselectivity problem, so that this methodology could be used for polypropionate synthesis, we explored the use of protecting groups as a means of modifying the aluminum coordination pattern. After exploring several hydroxy protecting groups, we found that **10** (the MEM ether of epoxide **2e**) produced exclusively the monoprotected 1,3-diol product **11** (Eq. 3). This reversal of regioselectivity suppresses the production of the undesired 1,4-diol and allows the preparation of the otherwise unavailable stereotetrad **11**. Similarly, the protection of **2d**, which gave a 2:1 diol mixture, produced 1,3-diol **13** as the only product in 57% yield. This finding solves the epoxide-cleavage regioselectivity problem and is currently under further exploration.



(3)



(4)

In conclusion, the regioselectivity of the cleavage of 2-methyl-3,4-epoxy alcohols with propynyl alane was evaluated and shown to give mechanistic insight into the factor that governs the preferred attack at the epoxide. This has allowed us to develop a methodology for the stereoselective preparation of a series of stereotetrads that should find use in polypropionate synthesis. Further studies, which include ab initio calculations, are being undertaken to understand better the aluminum coordination and to extend this concept to the preparation of all possible stereotetrads.

Acknowledgements

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Supplementary data

General experimental procedure and characterization data for representative 1,3-diol **3g**, 1,4-diol **5b**, and acetonide **7**. The supplementary data is available online with the paper in ScienceDirect. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.018.

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