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Regiocontrolled ring opening of monoprotected 2,3-epoxy-1,4-diols using alkynyl aluminum reagents. Synthesis of differentially monoprotected alkynyl triol derivatives

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Abstract

The regioselectivity of the epoxide ring opening reaction of *cis* and *trans* TIPS-monoprotected 2,3-epoxy-1,4-diols with diethylalkynyl aluminum reagents was studied. Alane and alanate conditions in toluene or dichloromethane were explored. The alkynyl attack at the C2 epoxide carbon was favored for both, the alane and alanate conditions in toluene, while in dichloromethane the C3 attack was preferred. The best regioselectivities were obtained using the alanate conditions in toluene. This methodology provides access to differentially monoprotected alkynyl triols with high diastereoselectivity. These compounds are useful building blocks for polypropionate synthesis and are precursors for the introduction of the hydroxymethyl moiety found in some polyketide systems.

Graphical Abstract

Keywords

epoxide cleavage; epoxy alcohols; alkynyl aluminum; polypropionates; propargylic alkynol

Synthetic chemists maintain extensive interest in epoxide ring opening reactions due to their proven utility in carbon-carbon bond formation reactions. Among the different organometallic approaches for epoxide cleavage, alkynyl aluminum reagents have shown to be the most effective for the transfer of the acetylenic moiety, providing access to homopropargylic alkynols.¹ In this regard, we have developed and further employed a three-step reiterative sequence for polypropionate synthesis based on the preparation and cleavage of epoxy alcohols with alkynyl aluminum derivatives.²

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This first-generation methodology employs diethylalkynyl aluminum reagents for the ring opening of *cis* or *trans* TIPS-protected 2,3-epoxy alcohols (**1-cis** and **1-trans**) to produce *anti* or *syn* homopropargylic alcohols (**2**), respectively (Scheme 1). This reaction provides good yields and excellent regioselectivities with the propynyl (R = Me) and other aluminum reagent favoring the C3 attack. The reaction of **1-trans** with diethyl[(trimethylsilyl)ethynyl]aluminum (R = TMS) also favors the epoxide ring opening product **2**, however, this reagent showed a lower (60:40) **2:3** regioselectivity when reacted with epoxy alcohol **1-cis**. (Scheme 1).^{2c}

To further expand this approach, and to seek a solution to this limitation, a second-generation sequence was studied where the monoprotected 2,3-epoxy-1,4-diols **4-cis** and **4-trans** were explored (Scheme 1).³ In this instance, and contrary to the first-generation epoxides **1-cis** and **1-trans**, the regioselective cleavage of epoxides **4** at the C2 or the C3 position produces monoprotected the alkynyl triols **5** or **6**, respectively. These derivatives are equally useful for the synthesis of propionates as they are differentially protected stereoisomeric triols.⁷ In addition, the incorporation of the primary hydroxy directing group in **4** provides a new diastereoselectivity manifold that can assist in directing the subsequent epoxidation and epoxide cleavage reiterative steps. In this regards, we recently prepared several challenging C2 *syn* epoxy alcohols not previously available with the first-generation method.³

Considering the importance of the ring opening reaction of epoxy alcohols for the stereoselective elaboration of polypropionate architectures, we further investigated other alane and alanate variations. These studies broaden the scope and usefulness of the second-generation epoxide-based approach.

The ring opening reaction of epoxides **4-cis** and **4-trans** with diethylpropynyl aluminum was initially explored. Two complementary reaction conditions: the traditional electron deficient alane reagents (protocol I),^{2a} and the electron rich aluminum ate complexes (protocol II) were studied.^{1d} Solvent effects were also explored, as it has been found that nonpolar solvents such as toluene, exhibit opposite regioselectivities compared to dichloromethane in the alkyl and alkynyl substitution reaction of epoxides with organoaluminum reagents.^{1e,5} These studies showed that in toluene, a preference for the C2 attack is favored producing the 1,3-diol, while the C3 attack is observed in dichloromethane yielding the isomeric 1,2-diol.

TIPS ethers have been traditionally employed in our methodology for polypropionate synthesis. Therefore, the TIPS protected alcohols **4-cis** and **4-trans** were subjected to the diethylpropynyl aluminum cleavage conditions in toluene (protocol IA) and dichloromethane (protocol IB) at 0 °C. The reaction of epoxide **4-cis** in toluene produced the expected C2 regioselectivity yielding the 1,3-diol product **5a** (R = Me) in 82% and a 73:27 regioselectivity. However, when epoxide **4-trans** was subjected to the same conditions, no regiochemical preference was observed. As anticipated, in dichloromethane (protocol IB), the reaction favored the C3 attack on both **4-cis** and **4-trans** producing the 1,2 diol products **6a** and **6b** with moderate regioselectivities (21:79 and 23:77), respectively. The yield was very low for the *trans* system (34%) compared to *cis* epoxide (85%).

These mixed results employing the alane reagent prompted us to study the alanate conditions (protocol II). This reaction first requires a pre-treatment of the free alcohol with *n*-BuLi, prior to the reaction with the alkynyl aluminum reagent. Epoxides **4-cis** and **4-trans** were subjected to the alanate conditions employing toluene as solvent (protocol IIA). The results are summarized in Table 1. This reaction provided the 1,3-diols **5a** and **5b** with good regioselectivities (90:10 and 82:18, respectively) and yields (entries 1, and 4). This contrast with the results obtained for epoxide **4-trans** under protocol IA in toluene, where a lack of regioselectivity was observed. We then explored the aluminum ate complexes using dichloromethane as solvent (protocol IIB). This time, the regioisomeric 1,2-diols **6a** and **6b**, resulting from C3 attack, were obtained (entries 2 and 5). Overall, the alanate protocol IIA showed better regioselectivities than protocol IIB for both, the *cis* and *trans* monoprotected epoxy diols **4**. Nonetheless, protocol IIB provides preparative access to the 1,2-diols as the regioisomers can be readily separated by flash chromatography (entries 2 and 5).

We continued the epoxide ring opening study with the diethyl[(trimethylsilyl)ethynyl] alanate complex (R = TMS) employing the most selective conditions (i.e., protocol IIA). Cleavage of epoxides **4-cis** and **4-trans** under these conditions favored the epoxide cleavage at C2, producing 1,3-diols **7a** and **7b** as the major isomers (entries 3 and 6). These systems showed excellent to good regioselectivities (>95:5, 82:18). Once again, the *cis* epoxide exhibited better regioselectivity than its *trans* counterpart. These results showcase the increased efficacy provided by the second-generation approach for the (trimethylsilyl)ethynyl alanate and present a solution to the poor regiochemical discrimination observed for the first generation epoxide **1-cis**. In addition, the (trimethylsilyl)ethynyl moiety conveys greater flexibility to our reiterative polypropionate synthetic sequence. This functionality can be converted into a terminal alkyne via TMS removal, which can be further transformed into the allylic alcohol via carbethoxylation/reduction for subsequent epoxidation.^{2c}

As previously stated, a salient feature of this second-generation approach is that the regioselective attack at the C2 or C3 position produces useful products for the synthesis of propionates (Scheme 2). In the case of epoxide **4-trans**, both regioisomeric products **5b** and **6b** converge to the same enantiomer upon removal of the silyl protecting group. Even more appealing, for epoxide **4-cis**, the regioisomeric products **6a** and **6b** correspond to enantiomers upon desilylation, thus providing access to the propionate antipode. This progression provides a complementary entry to hydroxymethyl analogues that are commonly found in naturally occurring polypropionate compounds (vide supra).

The second-generation epoxide cleavage studies were further extended to other protecting groups and alkynyl aluminum reagents (Table 2). Again, the superior alanate in toluene conditions (IIA) were used. To assess the influence of the protecting group, the propynyl substitution reaction of the TBS and Bn protected epoxides were studied. The TBS-monoprotected epoxy diol **9-trans** gave results similar to those of the TIPS-ether **4-trans** producing the expected 1,3-diols **10b** with a slight increase in the C2 regioselectivity and yield (90:10, 88%, entry 1). An increase in regioselectivity (95:5) was observed for the Bn-protected epoxide **12-trans** (entry 2). The *cis* epoxides **9-cis** and **12-cis** provided similar regioselectivities with a decrease in reaction yields when subjected to the same propynyl

alanate condition (not shown in the table). When the TBS and Bn protected epoxy alcohols **9-*cis***, **9-*trans*** and **12-*trans*** were subjected to the cleavage reaction using the alkynyl-TMS derivative, excellent to good regioselectivities were obtained. For example, **9-*cis*** produced the 1,3-diol exclusively in a 76% yield (entry 3). The results employing the TBS and Bn protected epoxides **9-*trans*** and **12-*trans*** (entries 4 and 5) are in line with Miyashita's findings reporting similar regioselectivities using the TMS-alanate conditions on related epoxides.^{1d}

To further explore the alkynyl aluminum mediated epoxide cleavage reaction, epoxy alcohols **4-*cis*** and **4-*trans***, were reacted with several 3-*O*-substituted alkynyl aluminum derivatives.^{2c} The reaction with the R = CH₂OTBS and CH₂OBn aluminum reagents gave exclusive C2 attack producing the propargyl protected alkynol **19a** and **21a**, respectively, with moderate yields (entries 6 and 7).

We also studied the unsymmetrically protected epoxy diol **23**. This epoxide highly favored the C2 attack (93:7) under the diethylpropynylalane conditions IA, producing the TBS protected primary alcohol derivative **24** in a 57% yield (Scheme 3). This high C2 regioselectivity was also observed for the 1-OTES derivative.

The regioselectivity of the epoxide cleavage reaction was established by ¹H and ¹³C NMR spectroscopy. Representative acetonides were formed from the 1,3- and 1,2-diols (Scheme 4). The formation of a five-membered acetonide supports the alkynyl attack at the C3 position, while the six-membered acetonides corroborates the C2 attack. The ¹³C NMR spectra showed peaks near 29 and 19 ppm for the *gem*-dimethyl carbons of the six-membered acetonide, while the more flexible five-membered acetonide showed two signals in the range between 26-27 ppm. Also, the ¹³C chemical shifts for the six-membered acetonide ketal carbons below 99 ppm and between 108-109 ppm for the five-membered isomer are in agreements with the predicted ring size.⁶ In addition, the vicinal methine protons H_a and H_b of the six-membered acetonides also corroborated the *syn/anti* relationship of the diol precursors, showing coupling constants *J*_{ab} around 3–4 Hz for the axial-equatorial relationship of the *anti* stereoisomer, while a *J*_{ab} = 8–10 Hz was obtained for the *syn* relationship. These results are consistent with an attack and an inversion of configuration at the C2 epoxide carbon.

Once more, a salient feature of this second-generation approach is the incorporation of a hydroxymethyl moiety into the polypropionate framework, exemplified by the related tedanolide and myriaporone families, among many others.⁷ In this regard, epoxy alcohol **27**, prepared from **4-*cis***,³ was reacted with the TMS-ethynyl aluminum reagent producing the alkynyl diol **28** in 71% yield and excellent regioselectivity (Scheme 5). This compound represents the termini-differentiated C14-C17 tedanolide, and the C6-C9 myriaporone 3/4 polypropionate fragments with the correct relative configuration. This outcome further demonstrates the utility of our second-generation epoxide based approach for polypropionate synthesis. In addition, the TMS alkynyl moiety of **28** allows for further propagation of the second-generation sequence.^{2c}

In summary, we have successfully applied the aluminum mediated epoxide ring opening reaction to the second-generation TIPS-monoprotected 2,3-epoxy-1,4-diols **4-cis** and **4-trans** and other related epoxides employing alkynyl aluminum chemistry. The alkynyl nucleophilic attack occurred at the C2 position producing the 1,3-diol with high regioselectivity when toluene was used as solvent. A reversal of the regioselectivity was obtained in dichloromethane, favoring the substitution at the C3 position producing the 1,2-diol. The alanate/toluene conditions (protocol IIA) provided the best regioselectivities among the conditions explored. This approach solves the regioselectivity problem observed for the first-generation method and provides access to termini differentiated diastereomeric or antipodal polypropionate fragments containing the hydroxymethyl moiety. This methodology is currently being extended to the elaboration of the tedanolide and myriaporone polypropionate chains.

General procedure for the alkynyl substitution reaction of epoxy alcohols with diethylalkynyl aluminum (Protocol I, alane procedure)

A flame-dried flask, equipped with a dry-ice condenser, was charged with 12.0 mL of toluene (protocol IA) or dichloromethane (protocol IB) and cooled to 0 °C. Then, 2.1 mL (4.6 mmol, 3.8 equiv) of *n*-BuLi was added and an excess of propyne gas was bubbled through the soln. After stirring for 30 min, 2.6 mL (4.6 mmol, 3.8 equiv) of Et₂AlCl was added and stirred for 3 h at 0 °C. To the reaction mixture was added 0.30 g (1.2 mmol, 1.0 equiv) of the epoxide and stirred overnight. The reaction was quenched by the slow addition of aq 5% H₂SO₄ (9.2 mL) at 0 °C. The reaction mixture was transferred to a separatory funnel and the phases were separated. The aqueous phase was extracted with hexane (3 × 10 mL) and the combined organic extracts were dried over MgSO₄. The solvent was removed in vacuo and the crude product mixture was purified by column chromatography (4:1 hexane/EtOAc).

Analytical and NMR data for compound **6b** (for all other compounds, see the Supporting Information). ¹H NMR (500 MHz, CDCl₃): δ = 4.02 (dd, *J* = 9.9, 4.2 Hz, 1 H), 3.91–3.70 (m, 4 H), 2.75 (dtq, *J* = 9.4, 6.6, 2.4 Hz, 1 H), 1.77 (d, *J* = 2.4 Hz, 3 H), 1.11 (m, 21 H). ¹³C NMR (500 MHz, CDCl₃): δ = 80.5, 75.4, 74.9, 67.1, 65.1, 36.4, 17.9, 11.6, 3.5. Anal. Calcd for C₁₆H₃₂O₃Si: C, 63.95; H, 10.73. Found: C, 63.94; H, 10.73.

General procedure for the alkynyl substitution reaction of epoxy alcohols with diethylalkynyl aluminum (Protocol II, alanate procedure)

A flame-dried flask equipped with a dry-ice condenser was charged with 23.0 mL of dry toluene (protocol IIA) and the flask was cooled to 0 °C. Then, 3.1 mL (6.9 mmol, 4.0 equiv) of *n*-BuLi was added and an excess of propyne gas was bubbled through the solution. After stirring for 30 min, 3.8 mL (6.9 mmol, 4.0 equiv) of Et₂AlCl was added at 0 °C. In a separate flash, a solution of the lithium alkoxide of the epoxy alcohol was prepared from 0.26 g (1 mmol, 1.0 equiv) of the alcohol in 7.7 mL of toluene (0.15 M final soln) and *n*-BuLi (0.6 mL, 1.7 mmol, 1.1 equiv) stirred at 0 °C for 30 min. The alane reaction mixture was cooled to –78 °C and the lithium alkoxide soln was transferred via a double-ended

needle and stirred overnight as it reached r.t. The reaction was quenched by the slow addition of aq 5% H₂SO₄ at 0 °C. The reaction mixture was transferred to a separatory funnel and the phases were separated. The aqueous layer was extracted with hexane (3 × 20 mL) and the combined organic extracts were dried over MgSO₄. The solvent was removed in vacuo and the crude product was purified by column chromatography (5:1 hexane/EtOAc).

Analytical and NMR data for compound **5b** for all other compounds, see the Supporting Information). ¹H NMR (500 MHz, CDCl₃): δ = 3.93 (dd, *J* = 9.8, 3.2 Hz, 1 H), 3.85–3.77 (m, 3 H), 3.72 (ddd, *J* = 8.3, 5.6, 2.7 Hz, 1 H), 2.87 (d, *J* = 3.6 Hz, 1 H), 2.82 (bs, 1 H), 2.65 (m, 1 H), 1.65 (d, *J* = 2.4 Hz, 3 H), 1.10 (m, 21 H). ¹³C NMR (125 MHz, CDCl₃): δ = 80.3, 75.9, 73.8, 65.6, 64.5, 37.5, 17.9, 11.9, 3.5. Anal. Calcd for C₁₆H₃₂O₃Si: C, 63.95; H, 10.73. Found: C, 63.66; H, 10.96.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

First and second-generation 2,3-epoxy alcohols ring opening with alkynyl aluminum reagents.

Scheme 2.

Stereochemical outcome of the regioselective opening of epoxides **4-*trans*** and **4-*cis***

Scheme 3.

Diethylpropynyl aluminum mediated cleavage of unsymmetrically protected epoxy diol **23**.

Scheme 4.

¹³C NMR resonances of the ketal and *gem*-dimethyl carbons for the six- and five-membered acetonide.

Scheme 5.
Preparation of hydroxymethyl TMS-alkyne **28**

Table 1

Second-generation epoxide ring opening of **4-cis** and **4-trans** using alkynyl aluminum reagents

entry	epoxide	R	protocol ^a	major diol	1,3/1,2 ratio (yield) ^b
1	4-cis	Me	IIA	5a	90:10 (80)
2	4-cis	Me	IIB	6a	33:67 (86) ^c
3	4-cis	TMS	IIA	7a	>95:5 (81) ^d
4	4-trans	Me	IIA	5b	82:18 (83)
5	4-trans	Me	IIB	6b	24:76 (69)
6	4-trans	TMS	IIA	7b	82:18 (94)

^aThe epoxy alcohol was pretreated with 1.1 equiv of *n*-BuLi at 0 °C in toluene (IIA) or DCM (IIB) using 4 equiv of the aluminum reagent.

^bIsolated product. Ratio of 1,3- to 1,2-diol determined by ¹H NMR spectroscopy.

^cCrude product.

^dOnly one isomer was observed by NMR analysis

Second-generation epoxide ring opening of other epoxides using alkynyl aluminum reagents

Table 2

entry	Epoxide	PG	R	1,3-/1,2-Diols	Ratio ^a Yield (%) ^b
1	9- <i>trans</i>	TBS	Me	10b/11b	90:10 (88)
2	12- <i>trans</i>	Bn	Me	13b/14b	95:5 (84)
3	9- <i>cis</i>	TBS	TMS	15a/16a	>95:5 ^c (76)
4	9- <i>trans</i>	TBS	TMS	15b/16b	82:18 (94)
5	12- <i>trans</i>	Bn	TMS	17b/18b	84:16 (84)
6	4- <i>cis</i>	TIPS	CH ₂ -OTBS	19a/20a	>95:5 ^c (54)
7	4- <i>cis</i>	TIPS	CH ₂ -OBn	21a/22a	>95:5 ^c (57)

^aRatio of 1,3-: 1,2-diol determined by ¹H NMR spectroscopy.

^bIsolated product.

^cOnly one isomer was observed