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Synthesis of stereotetrads by regioselective cleavage of diastereomeric MEM-protected 2-methyl-3,4-epoxy alcohols with diethylpropynyl aluminum

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Abstract

The regioselectivity of the epoxide ring opening of 2-methyl-3,4-epoxy alcohols with diethylpropynylalane has been studied as a function of the C1 alcohol protecting group. An efficient selective method was developed using MEM as the protecting group. The reaction proceeded in a highly regioselective manner providing the useful 1,3-diol motif. The undesired 1,4-diol product produced by some free alcohol diastereomers was not observed. This highly stereoselective method provides access to termini-differentiated stereotetrads, which are essential building blocks for polypropionate synthesis.

Keywords

cleavage; epoxides; aluminum; stereotetrads; 3, 4-epoxy alcohols

Alkynyl aluminum compounds have been used as valuable reagents for the addition of carbon nucleophiles to epoxy alcohols.¹ In this regard, while developing an epoxide-based methodology for polypropionate construction, we have paid close attention to the cleavage of electronically unbiased disubstituted epoxides in an attempt to understand and identify the factors that influence the regioselectivity of the epoxide ring opening reaction. In our approach, diastereomeric 2-methyl-3,4-epoxy alcohols (**1**) were reacted with alkynyl aluminum reagents with the anticipation that the corresponding 5-alkynyl-1,3-diol products (**2**) would be obtained (Scheme 1). In spite of this, the diethylpropynylalane mediated cleavage of *trans*- and *cis*-2-methyl-3,4-epoxy alcohols gave alkynyl substitution products with variable regioselectivities and yields, where the required 1,3-diol and the unwanted 1,4-diol (**3**) were obtained depending on the *cis/trans* epoxide geometry and the *syn, anti* configuration of the epoxy alcohol substituents (Scheme 1).² This limitation hinders the generality of our methodology as only 1,3-diols are useful as precursors for polypropionate synthesis.

It is well recognized that for 2,3- and 3,4-epoxy alcohols or ethers, the coordination of the organoaluminum reagent with the epoxide oxygen and other coordinating groups can play an important role in the regioselectivity of the epoxide ring opening reaction,^{3–5} Most studies on the cleavage of epoxy alcohols with organoaluminum reagents have focused on

2,3-epoxy alkanols, where the hydroxy can be free or protected as an ether derivative.⁶ These studies have provided the broadly accepted notion that the regioselectivity of the epoxide ring opening of 2,3-epoxy alcohols with alkyl or alkynyl alane reagents proceeds through a bidentate complex, which coordinates the aluminum with both, the epoxide and alcohol (or alkoxy) oxygen atoms. The regiochemical outcome of the cleavage reaction is controlled by the *syn/anti* epoxide-alcohol relationship and the *cis/trans* geometry of the epoxide.

The reaction of 3,4-epoxy alcohols with organoaluminum reagents has been less explored. Flippin et al. studied the regioselectivity of the epoxide ring opening of diastereomeric 1-alkoxy-3,4-epoxides with mixed alkyl organoaluminum/organoaluminate reagents.³ These studies suggested a preference for attack at the C4 epoxide carbon in systems amenable to chelation control (bidentate complexes II and IV, Scheme 2). Maruoka studied the reaction of 1-alkoxy and 1-fluoro-3,4-epoxides with trialkylaluminum reagents employing NMR techniques.^{4,7} In these studies, they found that a pentacoordinate aluminum chelate was the active intermediate in the cleavage of these epoxides.

Based on the work with 2,3-epoxy ethers, we explored the modification of the C1 free hydroxy functionality of the 3,4-epoxy alcohols employing different protecting groups. We envisaged that changing the hydroxy to an ether would greatly change the nature of the aluminum-oxygen coordination (Scheme 2). The reaction of the free alcohol with the alane reagent produces a dialkyl aluminum alkoxide that cannot be formed in the case of the ether derivative. In addition, the protecting group can increase the steric demand in the substrate, potentially promoting the attack at the external less hindered C4 carbon. Furthermore, from the perspective of polypropionate synthesis, the early protection of the alcohol can provide useful orthogonality for hydroxyl group differentiation that may be required at later stages of a synthetic sequence of a specific polypropionate target.

We began this study using 3,4-epoxy alcohol **1b**, which yields exclusively the 1,4-diol regioisomer **3b** when submitted to the diethylpropynylalane reaction conditions. When **1b** was protected with the bulky TBS group, no reaction occurred. Similar results were obtained with the coordinating Bn and MOM protecting groups, recovering only the starting epoxide. These results were surprising since the benzyl protecting group does not affect the reactivity or the regioselectivity of 2,3-epoxy alkanols with organoalane reagents.⁸ The first glimpse of the desired C4 attack was observed when SEM was employed as the protecting group, but the reaction yield was only 15% as other byproducts, resulting from alane attack at the acetal carbon, also formed. Previous preliminary results have indicated that epoxides **4b** and **4d**, the MEM ether of epoxides **1b** and **1d**, produced exclusively the corresponding monoprotected 1,3-diol products **5b** and **5d** with complete regioselectivity (Scheme 3).²

To ascertain if this observation represented a general trend and not a fortuitous event, the remaining six diastereomeric *trans*- and *cis*-2-methyl-3,4-epoxy MEM ethers **4a**, **c-h** were prepared starting from the free epoxy alcohols **1a**, **c-h** (Scheme 4). The yield of the reaction ranged from 53% for **4f** to 85% for **4c**.⁹

Having all diastereomeric MEM-protected epoxy alcohols **4** in hand, their propynylalane mediated cleavage reaction was carried at 0 °C to rt with five equivalents¹⁰ of the *in situ* prepared diethylpropynylalane reagent (Table 1). The most significant feature of this study was that for all MEM-protected 3,4-epoxy alcohol diastereomers **4**, the epoxide ring opening occurred regioselectively at the external C4 carbon. When compared with the free epoxy alcohols **1**,² a dramatic reversal was observed for epoxides **4d** and **4f**, where the desired monoprotected 1,3-diol was produced exclusively. Previously, the corresponding free alcohol precursors **1d** and **1f** provided a mixture of regioisomers (entries 4 and 6). Notably,

the C4 regioselectivity was maintained for epoxy alcohol **4a** and **4e**, which already favored the C4 attack as the free alcohol (entries 1 and 5).

Although all eight MEM-protected epoxy alcohols **4**, were cleaved at the C4 carbon, diastereomers **4c**, **4g** and **4h** produced disappointingly low yields (entries 3, 7 and 8). The lower reactivity exhibited by these substrates, allowed the formation of other byproducts. These included MEM deprotection with concomitant cyclization to the furan, propynyl addition to the acetal carbon, and propynyl addition to the methyl ketone resulting from epoxide rearrangement. (see the supporting Information). Being that the alane reaction conditions are Lewis acidic, the formation of these byproducts are conceivable in systems with lower reactivity.⁹ Attempts to improve these results by varying the stoichiometry of the alane reagent or the reaction temperature were unsuccessful. Is it important to stress that although three MEM-protected systems gave low yields, the combination of the free and MEM protected alcohols can be used for at least six of the eight diastereomeric possibilities providing access to these termini differentiated stereotetads.

The regioselectivity of the epoxide opening reaction was established by ¹³C and ¹H NMR spectroscopy. The COSY spectrum of a 1,4-diol, such as **3b**, showed cross peaks between the C4 methine at 3.90 ppm, and the C5 methyl at 1.24 ppm (-CH(OH)CH₃), while both methyl groups in the external C4 opening product **2a** exhibit cross peaks with non-oxygenated methines. Also, the ¹³C NMR spectra for the MEM monoprotected 1,3-diols revealed methine peaks around 39.8–35.8 for the C2 carbons, and 29.5–30.7 for C4. Conversely, the 1,4-diols displayed signals at 41.6–45.1 and 34.6–36.4 ppm for the C2 and C3 carbon atoms respectively. These trends are consistent and can be used as a reliable tool to assess the regioselectivity of the epoxide cleavage.

Establishing of the structural or electronic features that govern the regiochemical outcome of the diethylpropynylalane reaction with 3,4-epoxy alcohol derivatives is not apparent by examination of the examples in Table 1. The favored external carbon regioselectivity observed for the MEM ethers may conceivably arise from several factors including: an intrinsic electronic difference between C3 and C4, conformational differences, and a persistent contribution from a chelation-control pathway.³ In order to better rationalize the reversal in the regioselectivity and gain insight on the nature of the aluminum coordination, the MEM-protected epoxides were treated with 1–4 equivalents of Et₃Al and analyzed by ²⁷Al and ¹³C NMR spectroscopy. All ²⁷Al resonances are broad and lie in a narrow range from 128–135 ppm, being on the boundary of aluminum tetra- and pentacoordination.^{11–13} Therefore, unambiguous assignment of the type of aluminum species is not possible based on the ²⁷Al chemical shifts alone.

We turned our attention to the ¹³C NMR data for the epoxide MEM ethers **4a–h** in the presence of Et₃Al. We found that the C4 epoxide and C8 methoxy carbons bear the greater chemical shift displacement (), suggesting coordination to the organoalane reagent (Figure 1). Interestingly, the acetal oxygen atoms do not appear to play a role in the complexation, which explains the lack of reactivity of the MOM protected derivative **9**. An average change of 5.4 ppm downfield for C4, and of 2.8 ppm for C3 for all MEM epoxides was observed.⁹ These changes remained constant regardless of the number of Et₃Al equivalents added. The lower field at C4 for the MEM protected epoxide **4b** suggests a higher electrophilic character for this carbon, different from that observed for the free epoxy alcohol **1b** and the MOM ether **9**. This observation is in agreement with the observed regioselectivity for all MEM-protected systems **4a–h**. Interestingly, the SEM protected substrate **10**, which also favored the C4 attack, showed a similar to **4b** for the epoxide C3 and C4 carbons.

In summary, the reaction of *trans*- and *cis*-2-methyl-3,4-epoxy MEM ethers with diethylpropynylalane produces the 1,3-diol products with excellent regioselectivity, suppressing the production of the unwanted 1,4-diols. This outcome allows the preparation of otherwise unavailable polypropionate stereotetrads, such as **5b**, **5c** and **5f**. While the actual intermediates of the reaction remain unknown, the NMR data discards the formation of an aluminum bidentate complex and suggest a higher electrophilicity of the C4 carbon, thus favoring the alane reagent attack.

General procedure for the protection of epoxy alcohols with 2-methoxyethoxymethyl chloride (MEM-Cl)

The epoxy alcohol **1** (1.0 g, 3.31 mmol) was added to 11 mL of DCE (0.3 M) in a flame-dried flask equipped with a reflux condenser. The temperature was lowered to 0 °C and 1.15 mL (6.61 mmol) of DIPEA was added. The reaction was stirred at 0 °C for 30 min prior to the addition of 0.42 mL (3.64 mmol) of MEM-Cl. The ice bath was removed and the reaction mixture was heated at reflux (~3–5 h). After completion (TLC), the reaction was diluted with ether followed by addition of satd aqueous NH₄Cl. The aqueous phase was extracted with ether. The combined organic phase was washed with H₂SO₄ (5%), dried over MgSO₄ and concentrated under reduced pressure. The crude product **4** was purified by column chromatography (4:1 hexane/EtOAc).

Analytical and NMR data for compound **4b** (For all other compounds see the supporting information). ¹H NMR (500 MHz, CDCl₃): 4.93 (d, *J* = 6.8 Hz, 1H), 4.83 (d, *J* = 6.8 Hz, 1H), 3.82 (dd, *J* = 11.4, 7.7 Hz, 1H), 3.80 (ddd, *J* = 7.7, 4.7, 3.4 Hz, 1H), 3.75 (dd, *J* = 11.4, 4.7 Hz), 3.73 (dt, *J* = 10.3, 4.2 Hz, 1H), 3.71 (dt, *J* = 10.3, 4.2 Hz, 1H), 3.54 (dt, *J* = 9.8, 4.2 Hz, 2H), 3.38 (s, 3H), 3.08 (dq, *J* = 5.4, 4.3 Hz, 1H), 2.87 (dd, 9.6, 4.3 Hz, 1H), 1.70 (ddq, 9.6, 7.0, 3.4 Hz, 1H), 1.29 (d, *J* = 5.4 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.05 (m, 21H), ¹³C NMR (125 MHz, CDCl₃): 96.4, 79.9, 71.8, 67.2, 64.1, 59.0, 58.5, 52.6, 33.0, 17.9, 13.1, 11.9, 10.5. Anal. Calcd for C₂₀H₄₂O₅Si: C, 61.49; H, 10.84. Found: C, 61.72; H, 10.89.

General procedure for the ring opening of MEM-protected epoxy alcohols 4a–h with diethylpropynylalane

A flame-dried flask, equipped with a dry-ice condenser, was charged with 9 mL of dry toluene (0.13 M) and cooled to 0 °C. Then, 2.55 mL (5.76 mmol) of *n*-BuLi (2.27M in hexane) was added. Propyne gas was bubbled into the solution until the reaction turned milky white. After 30 min, 3.21 mL (5.76 mmol) of diethylpropynylalane chloride (1.8M in toluene) was added via syringe and the solution was stirred at 0 °C for 4 h. Then, 0.45 g (1.15 mmol) of the MEM-protected epoxide **4** was added and the reaction was allowed to reach rt while stirring overnight. The reaction was quenched at 0 °C by careful dilution with 6 mL of a 5% H₂SO₄ solution. The aqueous phase was extracted with hexane or ether. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product **5** was purified by column chromatography (4:1 hexane/EtOAc).

Analytical and NMR data for compound **5b** (For all other compounds see the supporting information). ¹H NMR (500 MHz, CDCl₃): 4.93 (d, *J* = 6.8 Hz, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 4.15 (ddd, *J* = 7.2, 5.6, 1.9 Hz, 1H), 3.85 (dd, *J* = 10.1, 5.6 Hz, 1H), 3.79 (dt, *J* = 10.0, 5.3 Hz, 1H), 3.68 (dd, *J* = 10.1, 7.2 Hz, 1H), 3.54 (dt, *J* = 10.0, 5.3 Hz, 1H), 3.57 (dt, *J* = 10.7, 5.3 Hz, 2H), 3.37 (s, 3H), 3.29 (dd, *J* = 9.4, 2.3 Hz, 1H), 2.64 (dq, 7.0, 2.4, 2.3 Hz, 1H), 2.02 (ddq, 9.4, 7.0, 1.9 Hz, 1H), 1.80 (d, *J* = 2.4 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.05 (m, 21H), 0.81 (d, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): 96.1, 79.1, 78.7, 77.5,

74.6, 71.6, 67.1, 64.6, 58.8, 38.5, 29.5, 18.7, 17.9, 11.8, 10.2, 3.5. Anal. Calc for $C_{23}H_{46}O_5Si$: C, 64.14; H, 10.77. Found: C, 63.93; H, 10.81.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and Notes

1. Pena PCA, Roberts SM. *Current Organic Chemistry*. 2003; 7:555–571.
2. Tirado R, Torres G, Torres W, Prieto JA. *Tetrahedron Lett*. 2005; 46:797–801.
3. Flippin LA, Brown PA, Jalali-Araghi K. *J Org Chem*. 1989; 54:3588–3596.
4. Ooi T, Kagoshima N, Ichikawa H, Maruoka K. *J Am Chem Soc*. 1999; 121:3328–3333.
5. Skrydstrup T, Benecchie M, Khuonghuu F. *Tetrahedron Lett*. 1990; 31:7145–7148.
6. (a) Sasaki M, Tanino K, Hirai A, Miyashita M. *Org Lett*. 2003; 5:1789–1791. [PubMed: 12735778]
(b) Sasaki M, Hatta M, Tanino K, Miyashita M. *Tetrahedron Lett*. 2004; 45:1911–1913. (c) Chini M, Crotti P, Flippin LA, Gardelli C, Giovani E, Macchia F, Pineschit M. *J Org Chem*. 1993; 58:1221–1227. (d) Tanino K, Sasaki M, Miyashita M. *Org Lett*. 2001; 3:1765–1767. [PubMed: 11405706]
7. Ooi T, Kagoshima N, Ichikawa H, Maruoka K. *J Am Chem Soc*. 1997; 119:5754–5755.
8. Di Bussolo V, Fiasella A, Frau I, Favero L, Crotti P. *Tetrahedron Lett*. 2010; 51:4937–4941.
9. All products were isolated and fully characterized by 1D and 2D 1H and ^{13}C NMR spectroscopy. Compounds **4a–h** and **5a–h** showed purities = 95%. See the supporting information.
10. The reaction can be carried out with two to seven equivalents of the alane reagent. Five equivalents were optimal in terms of product yield.
11. (a) Magnusson G. *Organic Preparations and Procedures International*. 1990; 22:547–574. (b) Morgans DJ, Sharpless KB, Traynor SG. *J Am Chem Soc*. 1981; 103:462–464.
12. Benn R, Rufinska A, Lehmkuhl H, Janssen E, Kruger C. *Angew Chem Int Ed Engl*. 1983; 22:779–780.
13. Muller G, Lachmann J, Rufinska A. *Organometallics*. 1992; 11:2970–2972.

Figure 1. Selected ^{13}C NMR data (, ppm) and ^{27}Al NMR data (in parenthesis) for the aluminum complexes formed by the reaction of epoxy alcohol **1b** and epoxy ethers **9**, **10** and **4b** with Et_3Al .

Scheme 1.

Diethylpropynylalane cleavage of selected diastereomeric 2-methyl-3,4-epoxy alcohols **1a–c**.

Scheme 2. Coordination complexes of protected *trans* and *cis*-3,4-epoxy-1-alkanols with R_3Al

Scheme 3.
Diethylpropynyl aluminum cleavage of the MEM-protected 2-methyl-3,4-epoxy alcohol derivative **4b**

Scheme 4. Preparation of diastereomeric 3,4-epoxy MEM ethers **4a-h**

Table 1Reaction of diastereomeric 3,4-epoxy MEM ethers with diethylpropynylalane.¹¹

Entry	Epoxide	Product 5	Ratio ^a (Yield)	Free alcohol 2:3 ratio (Yield) ^b
1	4a	 5a	>95:5 (67)	1a, 89:11 (78)
2	4b	 5b	>95:5 (76) ^b	1b, >5:95 (62)
3	4c	 5c	>95:5 (19) ^{c,d}	1c, 15:85 (39)
4	4d	 5d	>95:5 (49) ^b	1d, 67:33 (52)
5	4e	 5e	>95:5 (50)	1e, >95:5 (52)
6	4f	 5f	>95:5 (57)	1f, 56:44 (28)
7	4g	 5g	>95:5 (15) ^{d,e}	1g, >95:5 (56)

Entry	Epoxide	Product 5	Ratio ^a (Yield)	Free alcohol 2:3 ratio (Yield) ^b
8	4h	5h	>95:5 (9.1) ^d	1h, >95:5 (17)

^aEstablished by ¹H NMR spectroscopy.

^bData from reference 2.

^cDeprotection of the MEM group with concomitant cyclization to the furan was isolated (50%).

^dPropynyl addition at the acetal carbon followed by epoxide ring opening with the CH₃O(CH₂)₂O[−] leaving alkoxide was observed (entries 3 (8%), 7 (11%) and 8 (37%).

^eEpoxide hydrolysis product (23%), and addition of the rearranged methyl ketone (6%) were observed.