The Hudrlik–Peterson Reaction of Secondary cis-TMS-Epoxy Alcohols and its Application to the Synthesis of the Fatty Acid Intermediates

Shun Saito
Yutaro Nanba
Masao Morita
Yuichi Kobayashi*

Department of Bioengineering, Tokyo Institute of Technology, Box B-52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan
ykobayashi@bio.titech.ac.jp

Abstract
As an extension of the study on the Hudrlik–Peterson reaction of trans-TMS-epoxy alcohols with lithium acetylides, four cis-TMS-epoxy alcohols possessing different alkyl substituents were subjected to the reaction with TMS-acetylide. The reaction completed in 1 h at 0 °C to afford cis-enynyl alcohols in good yields. The results indicated that cis-TMS-epoxy alcohols had higher reactivity than the trans-isomers. Anions derived from 1-heptyne and phenylacetylene participated in the reaction as well. The reaction was applied to optically active cis-TMS-epoxy alcohols, and the resulting enynyl alcohols were transformed to the synthetic intermediates of protectin D1, maresin 1, resolvin E1, and leukotriene B4.

Key words epoxy alcohol, trimethylsilyl, acetylene, enyne, protectin D1, maresin 1, resolvin E1

The epoxide ring opening of a TMS-epoxide followed by the elimination of the TMS-oxyl group is a process known as the Hudrlik–Peterson reaction. Although the reaction with alkynyl anions has been limited to sterically less congested TMS epoxides, we were able to extend the reaction to secondary trans-TMS-epoxy alcohols in THF/HMPA to afford trans-enynyl alcohols (Scheme 1, eq. 1). The reaction was combined with the asymmetric epoxidation/kinetic resolution of racemic trans-TMS-epoxy alcohol to develop a synthesis of 18R-HEPE. As an extension, we conceived the Hudrlik–Peterson reaction of cis-TMS-epoxy alcohols. The products possessing the TMS group as R2 would be desilylated to enynyl alcohols without the TMS group, which have been used as synthetic intermediates of metabolites of fatty acids via the Suzuki–Miyaura coupling with trans-iodo olefins. Previously, 4 have been synthesized from trans-TMS-allylic alcohols by bromination, desilylation of the resulting bromine adducts with TBAF, and the Sonogashira coupling of cis-bromoallylic alcohols with acetylenes. Consequently, the different accesses to 4 by the previous and present methods would complement each other in organic synthesis. Herein, we report the results of this investigation and its application to the synthesis of the intermediates.

Preparation of cis-epoxy alcohols 3a–d and the TBS ether of 3a is summarized in Scheme 2. The propargylic alcohols 5a–d were synthesized by addition of lithium TMS-acetylide to the corresponding aldehydes and reduced stereoselectively by using P-2 nickel as a catalyst under hydrogend to afford 6a–d with 94–97% stereoselectivity, which was stereoselectively converted into syn-epoxides 3a–d with m-CPBA in CH2Cl2 at room temperature (rt) in good yields. The epoxides were purified by column chromatography on silica gel, and small quantities of the stereoisomers were removed. The stereochemistry of the epoxides was assigned as depicted based on the literature results. Alcohol 3a was converted into TBS-ether 7a, which was a substrate of the present reaction as well. An attempted Mitsunobu inversion of 3a afforded compounds other than the expected stereoisomer. Epoxidation of the TBS ether of 6a gave 7a.
and the stereoisomer in an 81:19 ratio. Consequently, 3a–d and 7a were substrates of the present investigation.

The procedure established for trans-epoxy alcohols\(^4\) was applied to 3a with lithium TMS-acetylide 8 (4 equiv) with HMPA (8 equiv) in THF at 0 °C (Scheme 3, eq. 1). The reaction completed in 1 h, which was less time than for the trans-epoxy isomer of 3a, and produced a mixture of 4a, the TMS-ether of 4a (i.e., 9a) and 10a in an 89:8:3 ratio in an 87% combined yield. Then, the mixture was exposed to \( \text{K}_2\text{CO}_3\) in MeOH to afford 4a, 9a, and 10a in 87% for 3a. A plausible transition state (TS) 17 for the reaction of 3a and 8 is depicted in Scheme 5 (eq. 1), in which the oxygen atom in the epoxide group is necessarily coordinated to the lithium cation to assist the Hudrlik reaction. Since the conformation of 3a is fixed with \( \text{C}_5\text{H}_11\) in a distal position from TMS, the conformation is ready to move to the TS with little conformational change, and hence, the TS energy is lower than that for the trans epoxy alcohols. Similarly, the conformation of TBS ether 7a is fixed for the chelation to the lithium cation (Scheme 5, eq. 2). In contrast, steric congestion between TMS and \( \text{C}_5\text{H}_11\) groups in the diastereomer of 3a apparently disfavors TS 19 for the reaction to proceed (Scheme 5, eq. 3), and thus the TS energy for 19 would be high, whereas 20 in the equilibrium was thought to be less

**Scheme 3** The Hudrlik–Peterson reaction of cis-epoxy alcohols with lithium acetylides. \(^4\) TMS ethers of 4b–d and 10b–d.

**Table 1**

<table>
<thead>
<tr>
<th>Reaction Details</th>
<th>Yield (x)</th>
<th>4a/9a/10a</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a + 9a = 10a</td>
<td>4</td>
<td>87%</td>
</tr>
<tr>
<td>8 (x equiv)</td>
<td>2</td>
<td>79%</td>
</tr>
<tr>
<td>THF, 0 °C, 1 h</td>
<td>3</td>
<td>63:27:10</td>
</tr>
<tr>
<td>K(_2)CO(_3) (1.5 equiv)</td>
<td>10a</td>
<td></td>
</tr>
<tr>
<td>MeOH, rt, 1 h</td>
<td>X = 4, 83% from 3a</td>
<td></td>
</tr>
<tr>
<td>X = 2, 67% from 3a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Scheme 2** Preparation of racemic substrates 3a–d and 7a. \(^5\) R: a, \( \text{C}_5\text{H}_11\); b, (\( \text{CH}_2\))\(_2\)OTBS; c, (\( \text{CH}_2\))\(_3\)OTBS; d, (\( \text{CH}_2\))\(_4\)OTBS. \(^6\) Ethylenediamine.
reactive because of the absence of chelation by Li. With these speculations in mind, we made no effort to find a method to prepare diastereomer 3a after the failure of the Mitsunobu inversion of 3a under the standard conditions.

In conclusion of the above study, cis-epoxy alcohols 3a–d were good substrates for the Hudrlik–Peterson reaction with TMS-acetylide 8 to produce cis-enynyl alcohols 10a–d after the TMS desilylation with K₂CO₃ in MeOH. The reaction of 3a with lithium acetylides 11 and 12 afforded 4e and 4f in good yields. TBS-ether 7a was also a substrate for the reaction, but lower reactivity was observed for the reactions with lithium acetylides 11 and 12. In consideration of all these results, we recommend the use of free alcohols because of their higher reactivity compared to TBS-ethers.

We envisaged the synthesis of 26, 28, and 32 using the above reaction. These compounds are intermediates for the synthesis of protectin D1,7b maresin 1,7a resolvin E1,7c and leukotriene B₄.7d Addition of lithium acetylide 8 to aldehyde 21 followed by oxidation with PCC gave ketone 22 in 80% yield (Scheme 6). Subsequently, the asymmetric transfer hydrogenation11 produced (S)-5b with 96% ee as determined by chiral HPLC analysis. The four-step conversion developed for racemic 5b was applied to (S)-5b to afford (S)-10b in 47% overall yield, which was similar to the yield for 5b (44.1%). Silylation of (S)-10b with TBSCI followed by regioselective desilylation of the resulting bis-TBS ether with PPTS in MeOH and subsequent oxidation of alcohol 23 gave aldehyde 24 in a good yield. Finally, aldehyde 24 was subjected to the Wittig reaction with the ylide derived from n-Pr phosphonium salt 25 and NaHMDS (NaN(TMS)),. Since the elimination of the TBS-oxy group was expected, HMPA was added according to the previous results,14 and the protectin D1 intermediate 26b was produced in 94% yield. Similarly, the Wittig reaction of 24 with 27|NaHMDS afforded 28, which is the synthetic fragment of maresin 1.15 The synthesis of 32, the intermediate of RvE1 and LTβ,7d commenced with the addition of acetylide 8 to aldehyde 29, followed by oxidation and subsequent asymmetric reduction to afford alcohol (S)-5d, which was subjected to the key transformation to afford (S)-10d in 62% yield via (S)-3d. (S)-5d TBS protection/deprotection produced alcohol 30 uneventfully. Finally, a two-step oxidation followed by esterification of the resulting acid with CH₂N₂ gave 32 in a good yield. The 1H NMR and 13C NMR spectra of 26, 28, and 32 confirmed the high chemical and stereoisomeric purity and were consistent with the spectra reported previously.7

In conclusion, the Hudrlik–Peterson reaction of four cis-TMS-epoxy alcohols 3a–d possessing different alkyl substituents with TMS-acetylide 8 and anions 11 and 12 derived from l-heptyloxy and phenylacetylenic completed in 1 h to afford cis-enynyl alcohols in good yields.15 The TBS...
ether 7a was a substrate for the reaction with 8, although the reactions with anions 11 and 12 required more time (2–5 h). The reaction was applied to cis-TMS-epoxy alcohols in optically active forms, and the resulting enynyl alcohols were transformed to the synthetic intermediates of protecin D1, maresin 1, resolvin E1, and leukotriene B4. Furthermore, the method would give compounds for the study of structure and activity relationship.

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Supporting Information
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References and Notes
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(12) The 1H NMR analysis suggested the trans-olefin formed formally by dehydration of 3a and the cis-olefin derived by the oxy-Hudrik–Peterson reaction with p-NO2C6H4CO2H.
(15) To an ice-cold solution of trimethylsilylacetylene (0.29 mL, 2.10 mmol) in THF (0.8 mL) was added n-BuLi (1.57 M in hexane, 1.20 mL, 1.88 mmol) dropwise. After 30 min of stirring at 0 °C, HMPA (0.64 mL, 3.68 mmol) and a solution of epoxy alcohol 3a (101 mg, 0.467 mmol) in THF (0.7 mL) were added. The solution was stirred at 0 °C for 1 h and diluted with saturated NH4Cl solution to afford a mixture of 4a, 9a, and 10a (total 93 mg). A mixture of the products and K2CO3 (95 mg, 0.687 mmol) in MeOH (1.6 mL) was stirred at rt for 1 h and diluted with saturated NH4Cl solution. The mixture was extracted EtOAc three times and purified by chromatography on silica gel (hexane/EtOAc, 4:1) to afford 10a (59 mg, 83% from 3a): liquid; Rf = 0.50 (hexane/EtOAc, 4:1). 1H NMR (400 MHz, CDCl3); δ = 0.87 (t, J = 7.2 Hz, 3 H), 1.22–1.67 (m, 8 H), 2.21 (br s, 1 H), 3.12 (dd, J = 2.2 Hz, 3 H), 1.22–1.67 (m, 8 H), 2.21 (br s, 1 H). 13C–APT NMR (100 MHz, CDCl3); δ = 14.1 (+), 22.6 (–), 24.8 (–), 31.7 (–), 36.5 (–), 70.0 (+), 79.6 (–), 82.7 (–), 108.8 (+), 147.6 (+).

HRMS (EI+): m/z calcd for C10H16O [M + ]: 152.1201; found: 152.1206.

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