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

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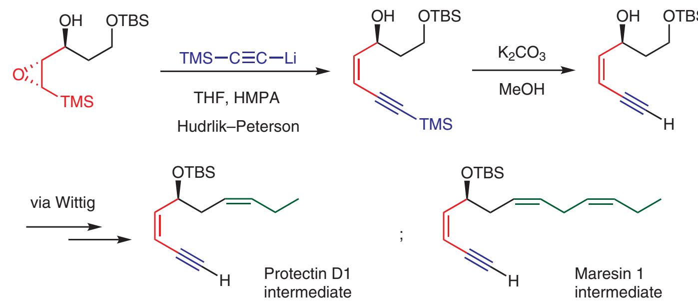

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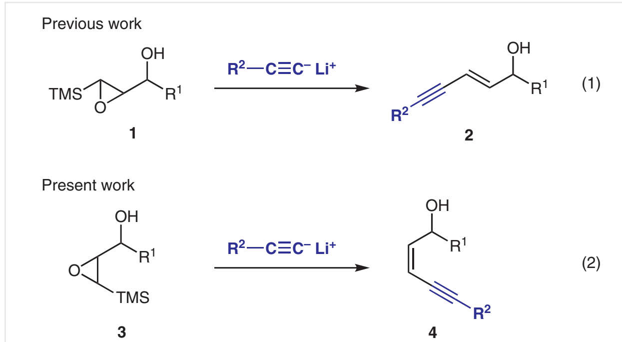
Abstract As an extension of the study on the Hudrlik–Peterson reaction of *trans*-TMS-epoxy alcohols with lithium acetylides, four *cis*-TMS-epoxy alcohols possessing different alkyl substituents were subjected to the reaction with TMS-acetylide. The reaction completed in 1 h at 0 °C to afford *cis*-enynyl 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 B_4.

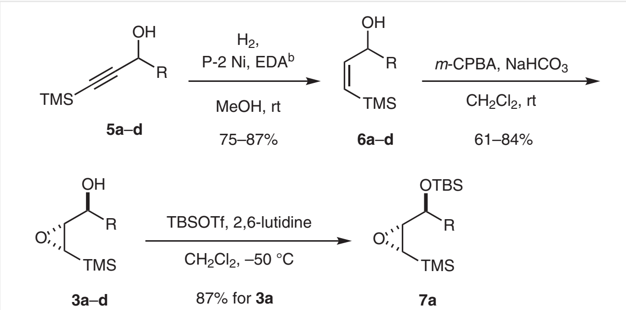
Key words epoxy alcohol, trimethylsilyl, acetylene, enyne, protectin D1, maresin 1, resolvin E1

The epoxide ring opening of a TMS-epoxide followed by the elimination of the TMS-oxy group is a process known as the Hudrlik–Peterson reaction.[1,2] Although the reaction with alkynyl anions has been limited to sterically less congested TMS epoxides,[3] we were able to extend the reaction to secondary *trans*-TMS-epoxy alcohols **1** in THF/HMPA to afford *trans*-enynyl alcohols **2** (Scheme 1, eq. 1).[4] The reaction was combined with the asymmetric epoxidation/kinetic resolution of racemic *trans*-TMS-epoxy alcohol[5] to develop a synthesis of 18*R*-HEPE. As an extension, we conceived the Hudrlik–Peterson reaction of *cis*-TMS-epoxy alcohols **3**. The products **4** possessing the TMS group as R^2 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[6] with *trans*-iodo olefins.[7] 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.[8,9] 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.



Scheme 1 Hudrlik–Peterson reaction of epoxy alcohols

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-acetylides to the corresponding aldehydes and reduced stereoselectively by using P-2 nickel[10] as a catalyst under hydrogen to afford **6a–d** with 94–97% stereoselectivity, which was stereoselectively converted into *syn*-epoxides **3a–d** with *m*-CPBA in CH_2Cl_2 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.[11] 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.[12] Epoxidation of the TBS ether of **6a** gave **7a**



Scheme 2 Preparation of racemic substrates **3a–d**[a] and **7a**. [a] R: **a**, C_5H_{11}; **b**, $(CH_2)_2OTBS$; **c**, $(CH_2)_3OTBS$; **d** $(CH_2)_4OTBS$. [b] Ethylenediamine.

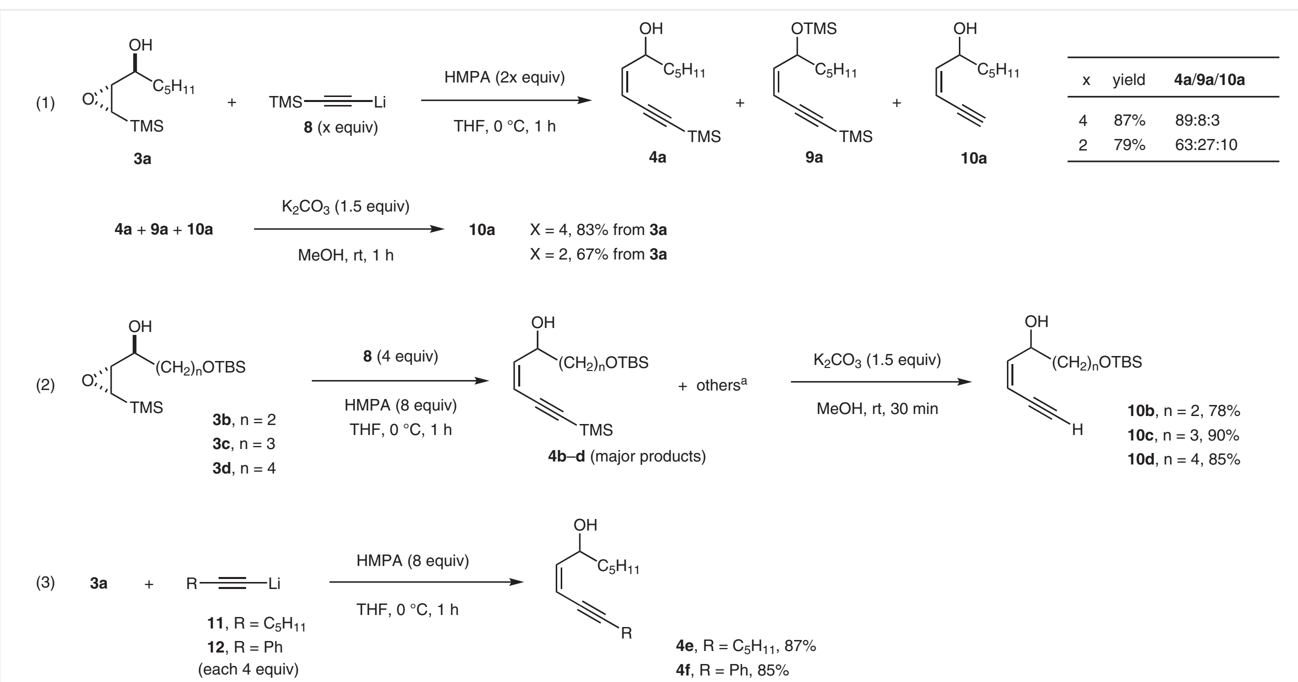
and the stereoisomer in an 81:19 ratio. Consequently, **3a–d** and **7a** were substrates of the present investigation.

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 K_2CO_3 in MeOH to afford *cis*-enynyl alcohol **10a** in 83% yield from **3a**. The use of less equivalents of **8** (2 equiv) produced **10a** in a 67% yield. The reaction did not proceed without HMPA.

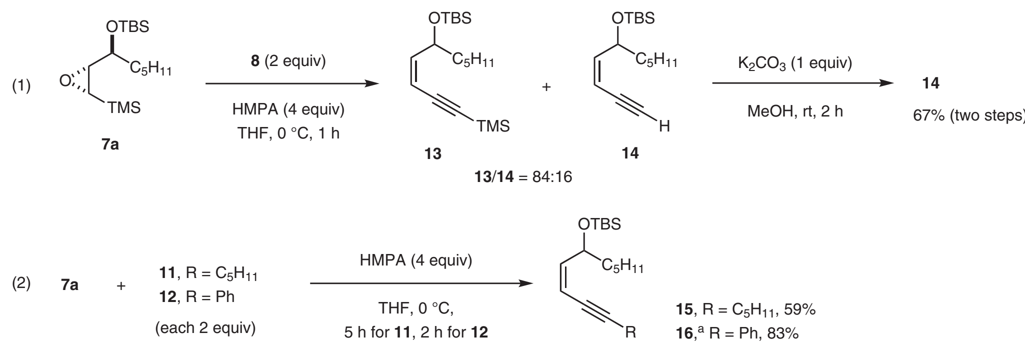
Epoxy alcohols **3b–d** with different methylene lengths and the TBS-oxy group were subjected to the Hudrlik–Peterson reaction. Production of **4b–d**, TMS ethers, and the TMS-desilylated enynes was confirmed by TLC, and the products were treated with K_2CO_3 in MeOH to give **10b–d** in good yields (Scheme 3, eq. 2). The reaction of **3a** with lithium acetylides **11** and **12** also afforded **4e** and **4f**, respectively (eq. 3).

TBS-ether **7a** derived from **3a** underwent the Hudrlik–Peterson reaction with acetylide **8** in THF/HMPA to afford a mixture of **13** and **14** in 84:16 ratio, and the subsequent reaction of the mixture with K_2CO_3 afforded **14** in 67% yield from **7a** (Scheme 4, eq. 1). The reaction of **7a** with anion **11** proceeded as well, but slowly, and completed in 5 h, giving **15** in 59% yield (Scheme 4, eq. 2). The reaction with acetylide **12** was also slow but produced **16** in 83% yield. Unfortunately, a ratio of **16** and the *trans*-isomer was 88:12 by ^{1}H NMR spectroscopy.

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 C_5H_{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 C_5H_{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

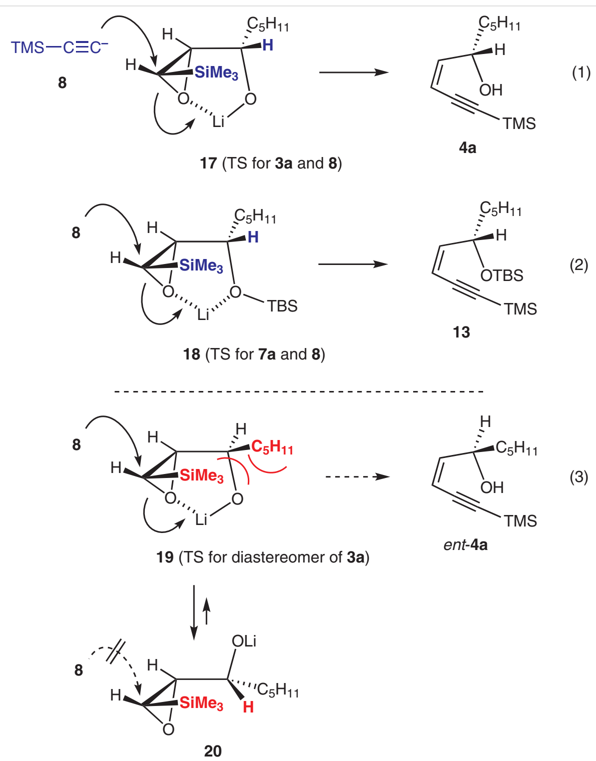


Scheme 3 The Hudrlik–Peterson reaction of *cis*-epoxy alcohols with lithium acetylides. [a] TMS ethers of **4b–d** and **10b–d**.



Scheme 4 The Hudrlik–Peterson reaction of the TBS ether with lithium acetylides. [a] Mixture of **16** and the *trans*-isomer (ratio 88:12).

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.

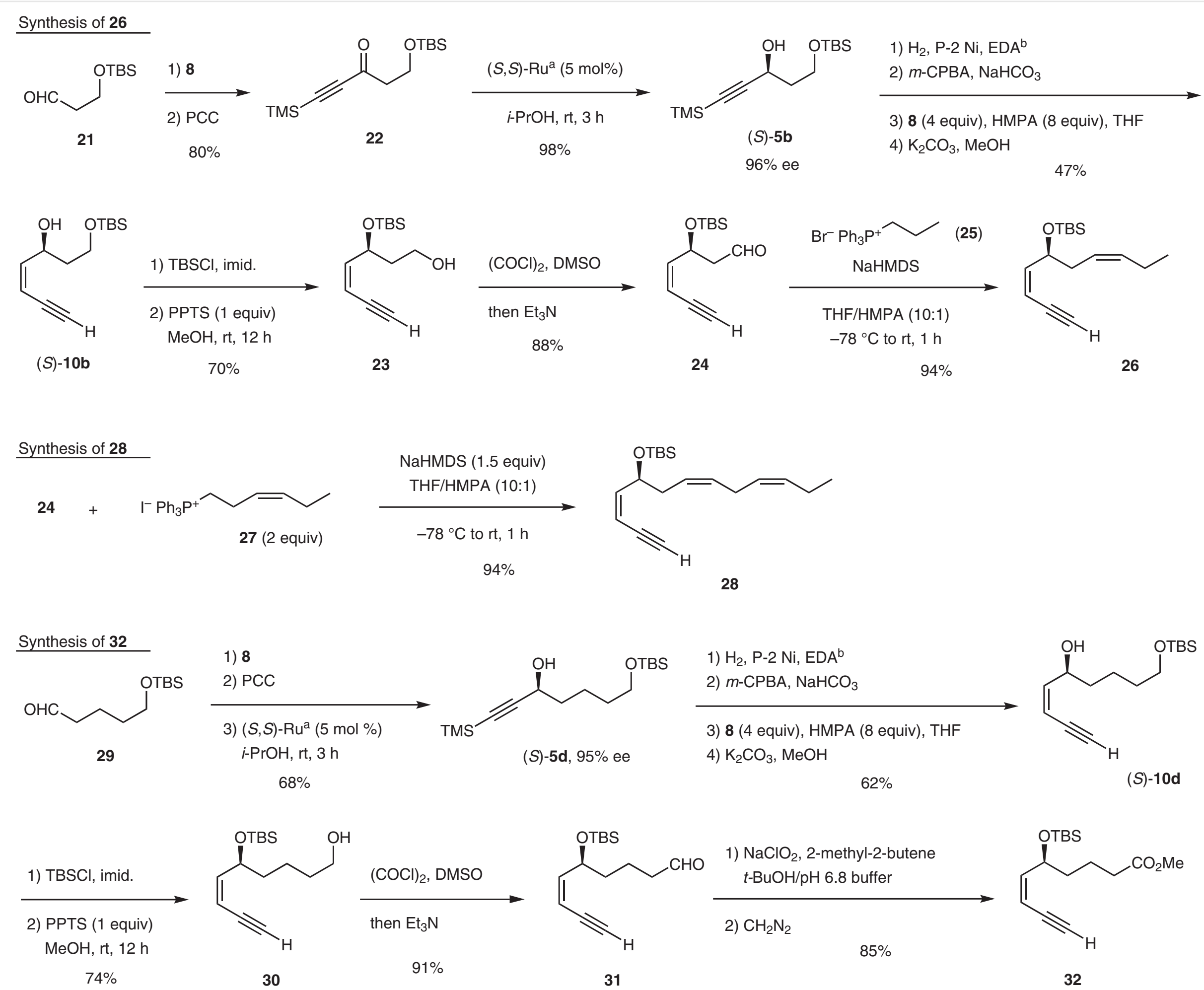


Scheme 5 Plausible transition states

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 K_2CO_3 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 B_4.[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 hydrogenation[13] 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 TBSCl 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 ($NaN(TMS)_2$). Since the elimination of the TBS-oxy group was expected, HMPA was added according to the previous results,[14] and the protectin D1 intermediate **26**[7b] was produced in 94% yield. Similarly, the Wittig reaction of **24** with **27**/NaHMDS afforded **28**, which is the synthetic fragment of maresin 1.[7a] The synthesis of **32**, the intermediate of RvE1[7c] and LTB_4,[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 transfonrmation 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 CH_2N_2 gave **32** in a good yield. The ^1H NMR and ^{13}C 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 1-heptyne and phenylacetylene completed in 1 h to afford *cis*-enynyl alcohols in good yields.[15] The TBS



Scheme 6 Synthesis of intermediates **26**, **28**, and **32**. [a] (*S,S*)-Ru: Ru[(*S,S*)-TsDPEN](p-cymene). [b] Ethylenediamine.

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 protectin D1, maresin 1, resolvin E1, and leukotriene B_4. Furthermore, the method would give compounds for the study of structure and activity relationship.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611809.

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(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 NH_4Cl solution to afford a mixture of **4a**, **9a**, and **10a** (total 93 mg). A mixture of the products and K_2CO_3 (95 mg, 0.687 mmol) in MeOH (1.6 mL) was stirred at rt for 1 h and diluted with saturated NH_4Cl 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; R_f = 0.50 (hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): 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, 0.8 Hz, 1 H), 4.61–4.68 (m, 1 H), 5.50 (ddd, *J* = 11.2 Hz, 2.2 Hz, 0.8 Hz, 1 H), 5.96 (ddd, *J* = 11.2 Hz, 8.4 Hz, 0.8 Hz, 1 H). ^{13}C–APT NMR (100 MHz, $CDCl_3$): 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 $C_{10}H_{16}O$ [M$^+$]: 152.1201; found: 152.1206.