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Reaction of 1-Trimethylsilyl-1,2-epoxy-3-alkanols with Alkynes and Application to the Synthesis of 18-HEPE

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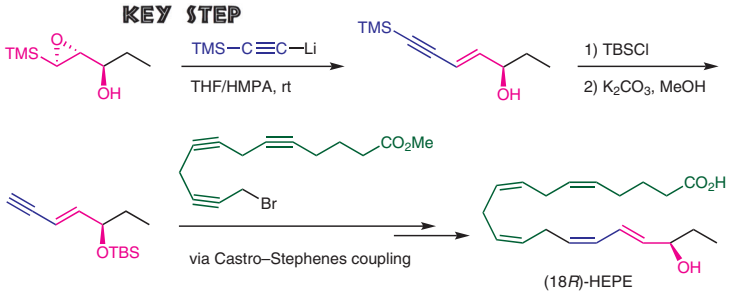

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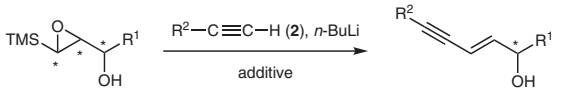
Abstract A reaction of epoxy alcohols (*anti* and/or *syn* isomers) derived from (*E*)-TMS-CH=CHCH(OH)R with TMS-C≡CLi in THF/HMPA stereoselectively afforded (*E*)-TMS-C≡C-CH=CHCH(OH)R. The (*E*) stereochemistry was independent of the *anti*/*syn* stereochemistry, but the *syn* isomers showed higher reactivity than the *anti* isomers. The reaction was applied to the synthesis of (18*R*)- and (18*S*)-HEPE.

Key words alkynes, epoxide ring opening, silicon, stereoselective synthesis, Castro–Stephens coupling, eicosapentaenoic acid

The epoxide ring opening of epoxysilane by nucleophiles at a carbon bearing a silyl group (known as the Hudrlik reaction), and the subsequent Peterson olefination, is a potentially useful combination that affords nucleophile-containing olefins in a stereoselective manner.[1] Alkyl, alkenyl, and aryl Grignard reagents/Cu catalysts, and organocopper reagents with or without $BF_3{\cdot}OEt_2$, have been intensively studied as reagents for that reaction.[2] As regards alkynyl species, the formation of enynes was reported only by Negishi, who used epoxysilanes derived from 1-TMS-1-alkenes (TMS: trimethylsilyl) and alkynyl lithiums.[2c] It is particularly noteworthy that this two-step conversion took place through a one-pot reaction. In contrast, the first step of the epoxide ring opening was reported using alkynylaluminum reagents.[3] Although the above-mentioned epoxysilanes were structurally simple substrates,[2c] we envisaged the combination of epoxy alcohol **1** with 1-alkynes **2** (R^1 = any alkyl; R^2 = TMS, alkyl, aryl, etc.) as delineated in Scheme 1. The resulting enynyl alcohols **3** would be intermediates for the synthesis of metabolites of unsaturated fatty acids. Previously, **3** (R^1 = TMS, H) and their derivatives have been synthesized by several methods, including the reduction of ynenones,[4] reduction of diynyl alcohols,[5] Sonogashira coupling,[6] Wittig reaction,[7] and others.[8] Herein, we report a study of this transformation and its application to the synthesis of 18-hydroxyeicosapentaenoic acid (18-HEPE) (**5**) in its *R* and *S* forms.[9]



Scheme 1 Present study

Biochemical oxidation of eicosapentaenoic acid (EPA) (**4**) catalyzed by aspirin-treated COX-2 and by cytochrome P450 produces 18-HEPE (**5**) in optically active forms (Figure 1).[10] Several biological properties, including anti-inflammatory activity, have been reported.[9b,10] Soybean lipoxygenase (sLOX) was used to convert 18-HEPE into RvE3.[9c]

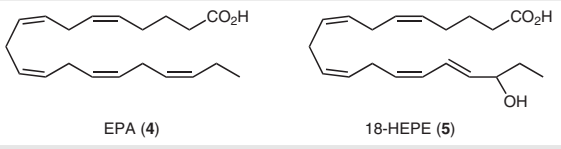
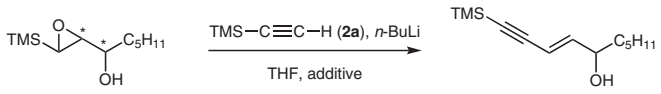


Figure 1 EPA and 18-HEPE

An *anti*/*syn* mixture of **1a** in a ratio of 37:68 was subjected to an anion derived from TMS-acetylene **2a** and *n*-BuLi in THF at rt for 14 hours. However, the reaction was incomplete and the *anti* isomer of **1a** was recovered (Table 1, entry 1). Reactions attempted at higher temperatures of 40–45 °C (entry not shown) or in THF/DMPU (entry 2) resulted in the recovery of **1a** (anti), affording a mixture of **3a** and **1a** (*anti*) in ratios of 70:30 and 67:33. These results indicate that the *syn* isomer of **1a** was more reactive than the *anti* isomer; thus, the reaction conditions for conversion of the less reactive *anti* isomer were intensively ex-

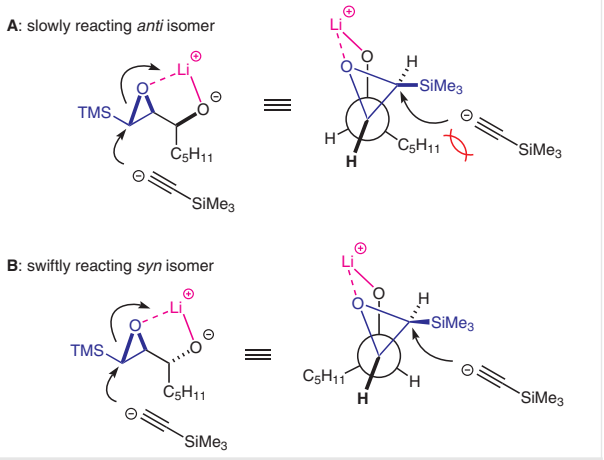
Table 1 Exploration of Reaction Conditions



1a (*anti* and/or *syn*) **3a**

Entry	*anti*/*syn*	**2a** (equiv)	*n*-BuLi (equiv)	Additive (equiv)	Temp. (°C)	Time (h)	Yield (%) of **3a**	**3a**/**1a** (*anti*)[a]
1	37:63	4.5	4	–	rt	14	48	64:36
2	37:63	4.5	4	DMPU (9)	rt	4	n.d.[b]	67:33
3	100:0	4.5	4	HMPA (9)	rt	5	n.d.[b]	40:60
4	100:0	9	8	HMPA (9)	rt	4	n.d.[b]	50:50
5	100:0	9	8	HMPA (18)	rt	3	60	91:9
6	0:100	4.5	4	–	rt	4	59	100:0
7	0:100	4.5	4	HMPA (9)	0	4	65	100:0

[a] Determined by ^{1}H NMR.
[b] Not determined.



Scheme 2 Plausible transition states **A** and **B** for the epoxide opening

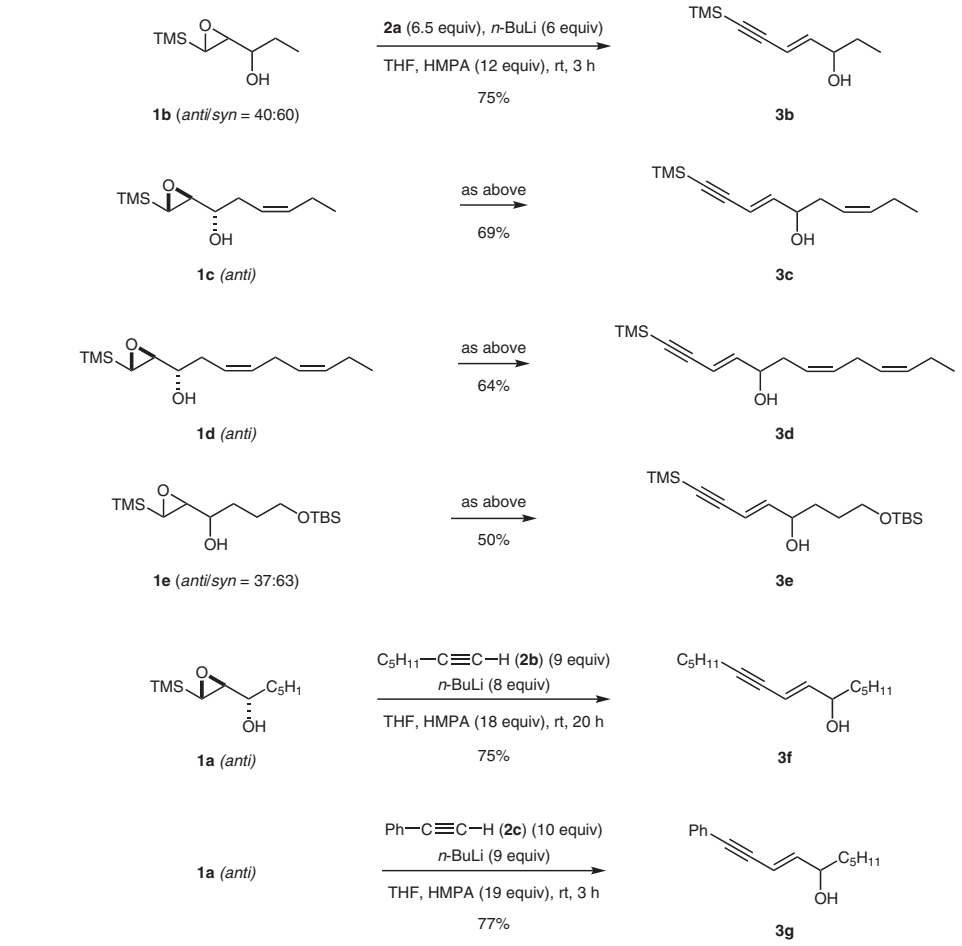
plored to find that the use of HMPA as a co-solvent with THF promoted the reaction. However, the reaction remained incomplete (entry 3). Increasing the quantity of the acetylide anion was partially effective (entry 4), and adding more HMPA drove the reaction to near completion, giving **3a** in 60% yield (entry 5).[11]

The difference in reactivity of the *anti* and *syn* stereoisomers of **1a** is understood by assuming transition states **A** and **B** (Scheme 2), in which chelation of a lithium cation (Li^+) to the epoxy oxygen atom fixes the conformation and partially activates the epoxide C–O bond for the reaction. Between **A** and **B**, the epoxide ring opening of **A** is probably prevented by steric hindrance from the C_5H_{11} group, and addition of HMPA prompted the reaction by increasing the nucleophilicity of the anion. In accordance with this mechanism, the TBS ether of **1a** was slightly reactive under similar conditions, giving the corresponding enyne in 21% yield.

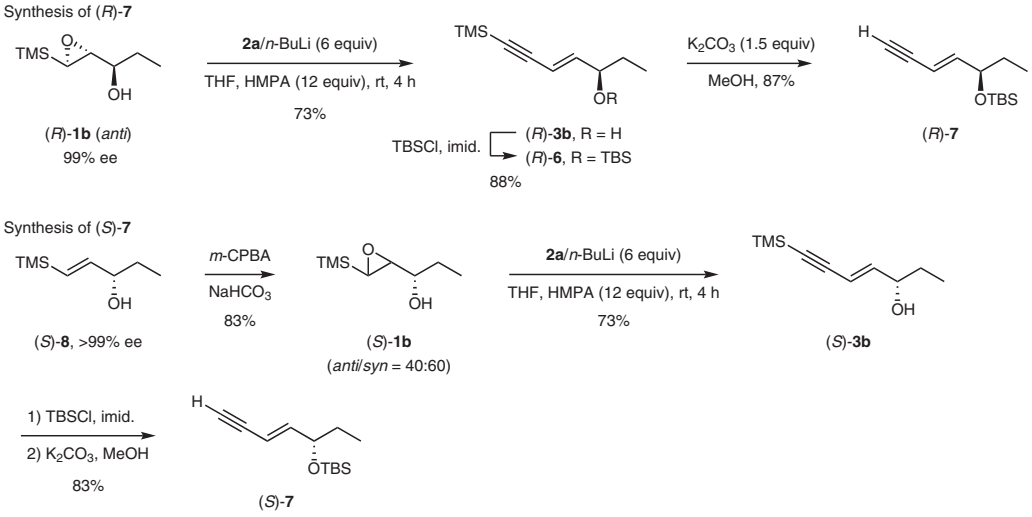
The conditions optimized above were applied to reactions of other epoxy alcohols with acetylenes as shown in Scheme 3. A stereoisomeric mixture of **1b** (*anti*/*syn* = 40:60) was converted into **3b** in 75% yield, with complete conversion of the less reactive *anti* isomer. Similarly, the pure *anti* isomers **1c** and **1d** afforded **3c** and **3d** in 69 and 64% yield, respectively. The latter result would be useful for planning a synthesis of metabolites possessing the same side chain, as described in the following paragraph. An *anti*/*syn* mixture of **1e** also afforded **3e** in 50% yield. Unlike TMS-acetylene **2a**, 1-heptyne (**2b**), selected as a representative 1-alkyne, was less reactive, affording **3f** in 75% yield after 20 hours, whereas phenylacetylene (**2c**) showed a similar reactivity to TMS-acetylene (**2a**).

The above products **3a–d** could be converted into metabolites of fatty acids: for example, **3a** to 15-HETE, and 8,15-dihydroxyl-ARA; **3b** to resolvins E1, E2, 18-hydroxy-EPA (18-HEPE), and 20-hydroxy-DHA; **3c** to resolvins D4, D5, and 17-hydroxy-DHA; and **3d** to 12-hydroxy-EPA, and 14-hydroxy-DHA. Among these targets, (18*R*)- and (18*S*)-HEPE [(*R*)- and (*S*)-**5**] were chosen for the present investigation, and the results are described below.

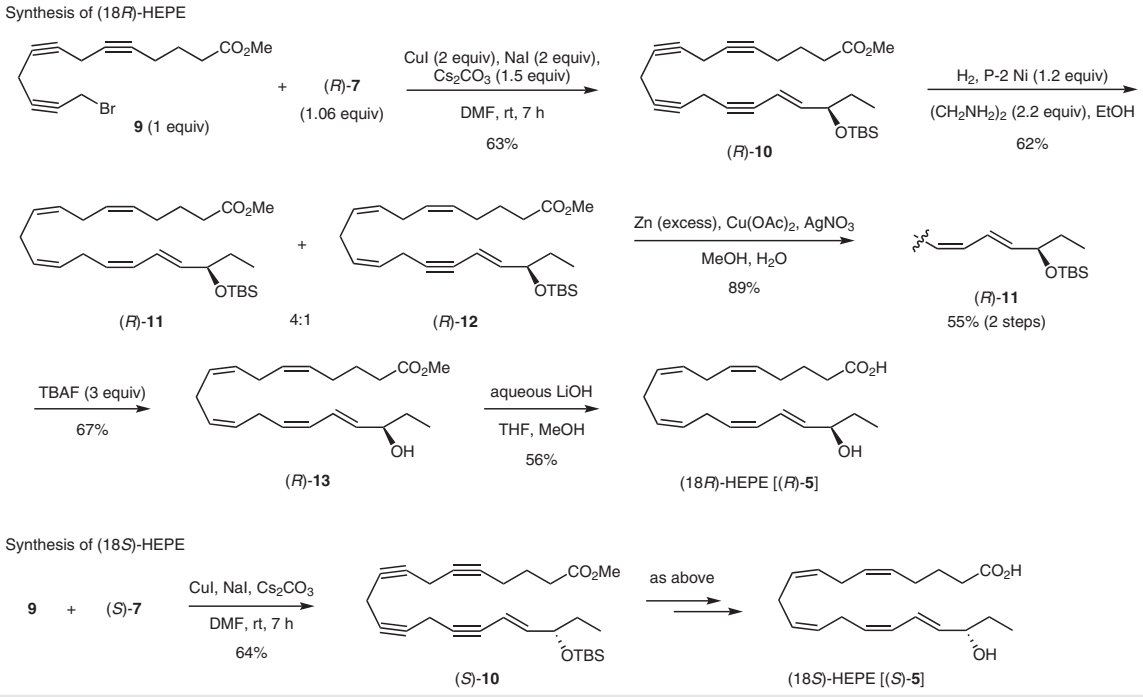
Epoxy alcohol (*R*)-**1b** (anti) with 99% ee and allylic alcohol (*S*)-**8** with >99% ee, shown in Scheme 4, were obtained by Sharpless asymmetric epoxidation of racemic (*E*)-1-(trimethylsilyl)pent-1-en-3-ol (see the Supporting Information).[12] As with the synthesis of racemic **3b** (*anti*/*syn*) from **1b** (Scheme 3), (*R*)-**1b** (*anti*) was converted into enyne (*R*)-**3b** in 73% yield with >99% ee as determined by the derived MTPA ester. The enyne was transformed into (*R*)-**7** in 88% yield by protection with TBSCl, followed by protodesilylation of the resulting (*R*)-**6** with K_2CO_3 in MeOH. In the synthesis of (*S*)-**7**, epoxidation of (*S*)-**8** with *m*-CPBA afforded epoxy alcohol (*S*)-**1b** as a 40:60 mixture of *anti*/*syn* isomers. Without separation, the mixture was converted



Scheme 3 Further examples of the enyne synthesis



Scheme 4 Synthesis of enantiomeric enynes (*R*)- and (*S*)-**8**



Scheme 5 Synthesis of 18*R*- and 18*S*-HEPE

into the (*S*)-enantiomer of enyne (*S*)-**7**. Previously, (*S*)-**7** or its (*R*)-isomers and derivatives have been synthesized through asymmetric reduction,[4a] optical resolution,[4b] and biosynthesis[8d] using a fungus, and the presented methods will be complementary to these methods.

The Castro–Stephens coupling[13] of (*R*)-**7** (1.06 equiv) with propargylic bromide **9**[14] (1.0 equiv) using CuI (2 equiv), NaI (2 equiv), and Cs_2CO_3 (1.5 equiv) in DMF at rt for seven hours gave (*R*)-**10** in 63% yield (Scheme 5).[15] Semi-hydrogenation of (*R*)-**10** under hydrogen by using P-2 nickel and ethylene diamine (EDA) gave a mixture of (*R*)-**11** and (*R*)-**12** in a ratio of 4:1. Without separation, the mixture was treated with freshly prepared Zn(Cu/Ag) to afford (*R*)-**11** in 55% yield from (*S*)-**10**, which gave alcohol (*R*)-**13** in 67% yield upon desilylation. Finally, hydrolysis produced (18*R*)-HEPE [(*R*)-**5**] in 56% yield. The ^1H and ^{13}C NMR spectra were consistent with those reported by Inoue.[9c] Similarly, the coupling of **9** and (*R*)-**7** afforded (*S*)-**10**, which was converted to (18*S*)-HEPE [(*S*)-**5**].

In summary, the transformation of 1-trimethylsilyl-1,2-epoxy-3-alkanols with 1-alkynes to the corresponding enynyl alcohols was studied. The *anti* and *syn* stereoisomers had different reactivity; less reactive *anti* isomers underwent the reaction using excess alkynes in THF/HMPA. The reaction was applied to the synthesis of (18*R*)- and (18*S*)-HEPE.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610194.

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(11) To an ice-cold solution of **2a** (0.40 mL, 2.89 mmol) and *n*-BuLi (1.55 M in hexane, 1.60 mL, 2.48 mmol) in THF (0.1 mL) were added HMPA (0.95 mL, 5.44 mmol) and a solution of **1a** (anti) (65 mg, 0.30 mmol) in THF (0.2 mL). After being stirred at rt for 3 h, the solution was diluted with saturated NH_4Cl. The mixture was extracted with EtOAc and the crude product was purified by chromatography on silica gel (hexane/EtOAc) to afford enyne *rac*-**3a** (41 mg, 60%). Liquid, R_f = 0.43 (hexane/EtOAc 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.19 (s, 9 H), 0.88 (t, *J* = 6.9 Hz, 3 H), 1.20–1.66 (m, 9 H), 4.08–4.22 (m, 1 H), 5.72 (dd, *J* = 15.9 Hz, 1.5 Hz, 1 H), 6.20 (dd, *J* = 15.9, 6.3 Hz, 1 H) ppm. ^{13}C–APT NMR (75 MHz, $CDCl_3$): δ = –0.05 (+), 14.1 (+), 22.6 (–), 25.0 (–), 31.8 (–), 36.9 (–), 72.3 (+), 95.1 (–), 103.2 (–), 109.8 (+), 147.0 (+) ppm. HRMS (FAB$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{24}OSiNa$: 247.1494; found: 247.1490.

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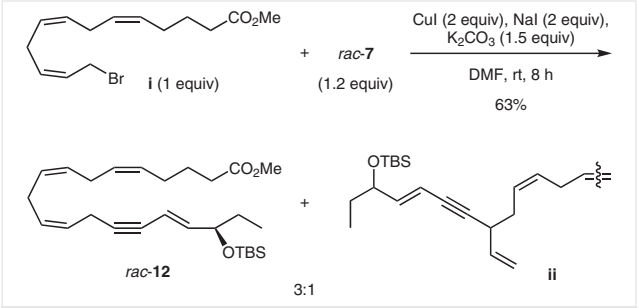
(15) Castro–Stephens coupling of *rac*-**7** (1.2 equiv) with *Z*-allylic bromide **i** (1 equiv) using CuI (2 equiv), NaI (2 equiv), and K_2CO_3 (1.5 equiv) at rt in DMF gave a mixture of *rac*-**12** and the regioisomer **ii** in a 3:1 ratio (^1H NMR), which were hardly separated by chromatography on silica gel (Scheme 6). The mixture was converted into 18-HEPE and the regioisomer by a sequence of reactions: 1) TBAF; 2) Zn (Cu/Ag); 3) LiOH; an attempted separation at each step was hardly successful.



Scheme 6 An unsuccessful result