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Synthesis of 8-HEPE and 10-HDoHE in both (*R*)- and (*S*)-Forms via Wittig Reactions with COOH-Ylides

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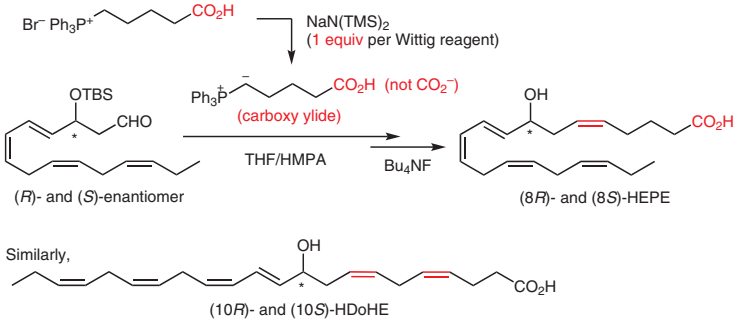

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Abstract Wittig reactions using carboxy (CO_2H) ylides derived from a carboxylic phosphonium salt and $NaN(TMS)_2$ (NaHMDS) in a 1:1 ratio were applied to the synthesis of 8-HEPE and 10-HDoHE, which are metabolites of eicosapentaenoic acid and docosahexaenoic acid, respectively. The attempted Wittig reaction of 3-(TBS-oxy)pentadeca-4*E*,6*Z*,9*Z*,12*Z*-tetraenal with the carboxy ylide (2 equiv) derived from $Br^- Ph_3P^+(CH_2)_4CO_2H$ and NaHMDS (1:1) competed with the elimination of the TBS-oxy group at C3 to give a mixture of the Wittig product and the elimination product in 45–50% and 30–40% yields, respectively. The elimination was suppressed completely by using three equiv of the carboxy ylides in THF/HMPA (7–8:1), and the subsequent desilylation gave 8-HEPE in (*R*)- and (*S*)-forms. Similarly, both enantiomers of 10-HDoHE were synthesized.

Key words lipoxygenase metabolite, 10-HDoHE, 8-HEPE, Wittig reaction, carboxy phosphonium salt

In the preceding paper, we reported that the one equiv of $NaN(TMS)_2$ (NaHMDS) is sufficient to generate ylides from carboxy (CO_2H) phosphonium salts of the form $[Ph_3PCH_2\text{-alk-}CO_2H]^+ X^-$ for use in Wittig reactions and that the carboxy ylides can be reacted to give *Z*-olefinic acids stereoselectively. To demonstrate the utility of these ylides in organic synthesis, we selected 8-HEPE (**1**) and 10-HDoHE (**2**) as specific synthetic targets (Figure 1). These compounds are metabolites of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in mammals[1] and marine creatures.[2] The former enhances adipogenesis and glucose uptake.[2a] In a previously reported synthesis of (8*R*)-HEPE, a protected hydroxymethyl group was used as a precursor to the carboxy moiety, and the (*R*)-chirality was derived from mannitol.[3] However, no access to the (*S*)-isomer was indicated. As for 10-HDoHE, no organic synthesis has been published, whereas biochemical oxidation of DHA by potato lipoxygenase produces (10*S*)-HDoHE in minute quantities.[4] However, racemic forms of 8-HEPE and 10-HDoHE are commercially available. Herein, we present syntheses of 8-HEPE (**1**) and 10-HDoHE (**2**) in both the (*R*)- and (*S*)-forms.

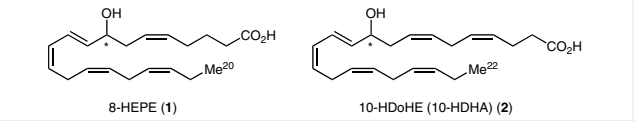
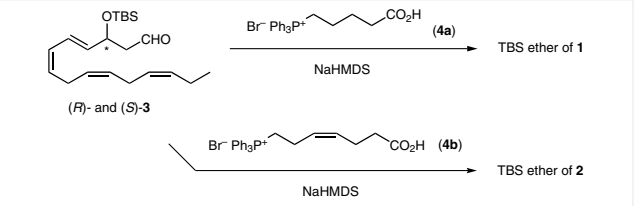


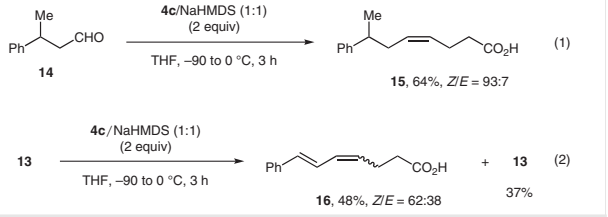
Figure 1 Two targets of the present study



Scheme 1 Synthesis of 8-HEPE and 10-HDoHE using **4a** and **4b**

Scheme 1 shows the key intermediate **3** in the (*R*)- and (*S*)-forms and the Wittig reactions with carboxy ylides derived from **4a** and **4b** with NaHMDS for the synthesis of the selected targets. Since competition between the Wittig reaction and the elimination of the β-siloxy group from aldehyde **3** was an issue, 3-alkoxy-3-phenylpropanals **5**–**8** were used in a preliminary study of the Wittig reactions with **4c**/NaHMDS to secure suitable reaction conditions (Table 1). The TBS derivative **6** afforded a mixture of olefin **10** and the elimination product **13** in an 80:20 ratio as expected, and the former was isolated in 56% yield with 95% *Z*-selectivity (Table 1, entry 4). TES- and TBDPS-oxy aldehydes **5** and **7** also underwent the elimination and produced **13** in 32% and 11% relative yields (Table 1, entries 1 and 6). The methoxy derivative **8** also afforded a mixture of olefin **12**

and byproduct **13** in a 79:21 ratio (Table 1, entry 7), whereas the α-ethoxyethyl ether gave a mixture of unidentified products. Similar *Z*-selectivity (93%) and reactivity were observed in the reaction of 3-phenylbutanal (**14**) to afford **15** in 64% yield (Scheme 2, eq. 1).



Scheme 2 Wittig reactions using aldehydes **14** and **13**

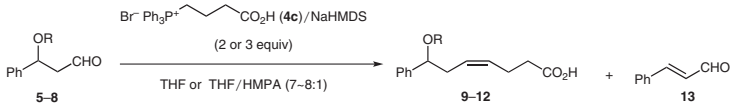
These results clearly indicated that the reactivity and selectivity were marginally influenced by the oxygen atom in the silyloxy substituent. Interestingly, the possible Wittig product of aldehyde **13** with **4c** was not detected by ^{1}H NMR spectroscopy (S/N ratio, >95:5),[5] indicating the lower reactivity of **13** than that of the silyloxy aldehydes. In fact, an independent reaction of **13** with **4c**/NaHMDS (1:1) under the same reaction conditions proceeded slowly to afford a mixture of diene **16** (*Z*/*E* = 62:38) and unreacted **13** in 48% and 37% yields, respectively (Scheme 2, eq. 2).

To identify reaction conditions that suppress the elimination, various were tested with TES-oxy aldehyde **5**, which underwent the elimination most easily among the silyloxy aldehydes (Table 1, entry 1, *cf.* entries 4 and 6). The use of HMPA as a co-solvent with THF was effective to some extent (Table 1, entry 2), and further elaboration using three equiv of the reagent in THF/HMPA afforded **9** exclusively in 75% yield (Table 1, entry 3). Similarly, TBS-oxy aldehyde **6** afforded **10** exclusively under the improved conditions (Table 1, entry 5, *cf.* entry 4).

The above method using carboxy ylides was applied to the construction of the Δ^5 olefin group of 8-HEPE (**1**), and the Δ^4 and Δ^7 olefin groups of 10-HDoHE (**2**). Synthesis of the common aldehydes (*R*)- and (*S*)-**3** commenced with conversion of β-propiolactone (**17**) to amide **18**, which upon reaction with TMS-acetylene/*n*-BuLi afforded ketone **19** in 87% yield (Scheme 3). The asymmetric transfer hydrogenation[6] gave (*R*)-**20** with 97% ee as determined by chiral HPLC. Subsequently, Red-Al reduction followed by TBS protection of the resulting diol afforded (*R*)-**21** in 67% yield. Transformation of (*R*)-**21** to aldehyde (*R*)-**23** was conducted in three steps consisting of the epoxidation, the epoxide ring opening with Et_2AlCN,[7] and DIBAL reduction. The Wittig olefination with phosphonium salt **24**[8] under the standard conditions for alkyl ylides afforded (*R*)-**25** with high *Z*-stereoselectivity, and the TBS group on the primary carbon was removed with PPTS in EtOH (46% over two steps). Finally, Swern oxidation of the resulting alcohol (*R*)-**26** afforded (*R*)-**3** in 67% yield. In a similar manner, alcohol (*S*)-**20** was derived from ketone **19** and converted into (*S*)-**3** (Scheme 3).

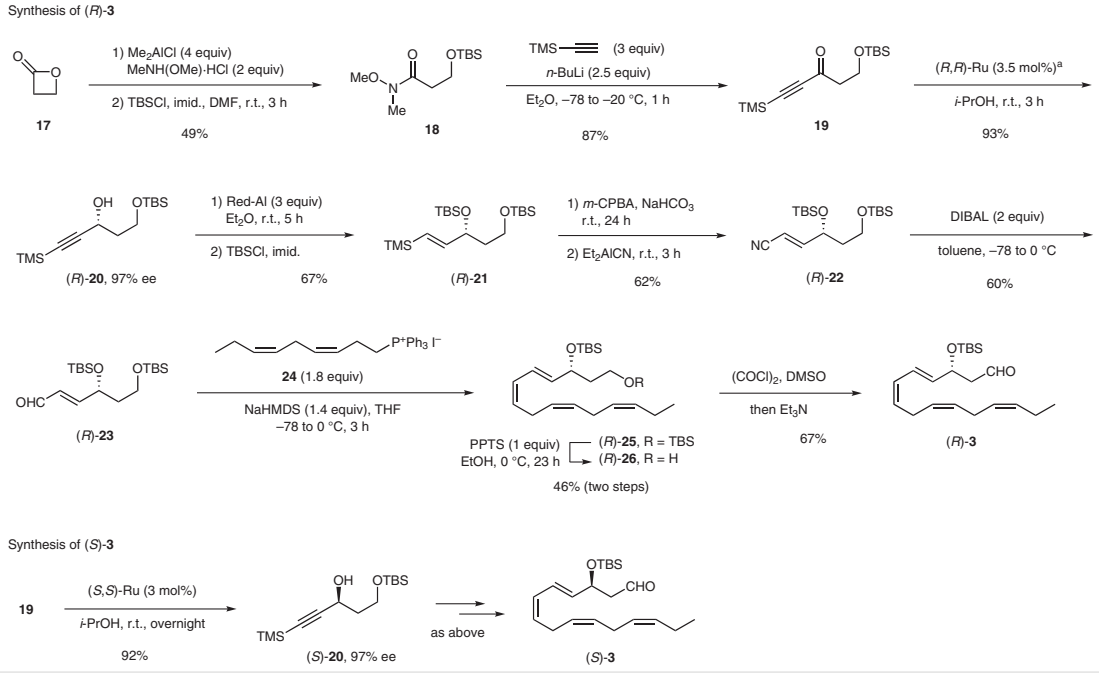
The Wittig reaction of (*R*)-**3** with the carboxy ylide derived from **4a**/NaHMDS (1:1) in THF/HMPA (7:1) according to the procedure in Table 1, entry 5 afforded (*R*)-**27** as the sole product in 84% yield (Scheme 4), whereas the ylide in THF under the conditions in Table 1, entry 4 gave a mixture of (*R*)-**27** and the unsaturated aldehyde **28** in 45–50% and 30–40% yields, respectively, as observed over several runs. Finally, desilylation of (*R*)-**27** with TBAF afforded (8*R*)-HEPE

Table 1 Wittig Reactions of β-Alkoxyaldehydes with **4c**[a]



Entry	R	Aldehyde	Solvent	Product	Yield (%)	*Z*/*E*[b]	Product /**13**
1	TES	**5**	THF	**9**	56	92:8	68:32
2	TES	**5**	THF/HMPA[c]	**9**	ND[d]	ND[d]	77:23
3[e]	TES	**5**	THF/HMPA[c]	**9**	75	92:8	>95:5[f]
4	TBS	**6**	THF	**10**	56	95:5	80:20
5[e]	TBS	**6**	THF/HMPA[c]	**10**	70	94:6	>95:5[f]
6	TBDPS	**7**	THF	**11**	56	92:8	89:11
7	Me	**8**	THF	**12**	61	93:7	79:21

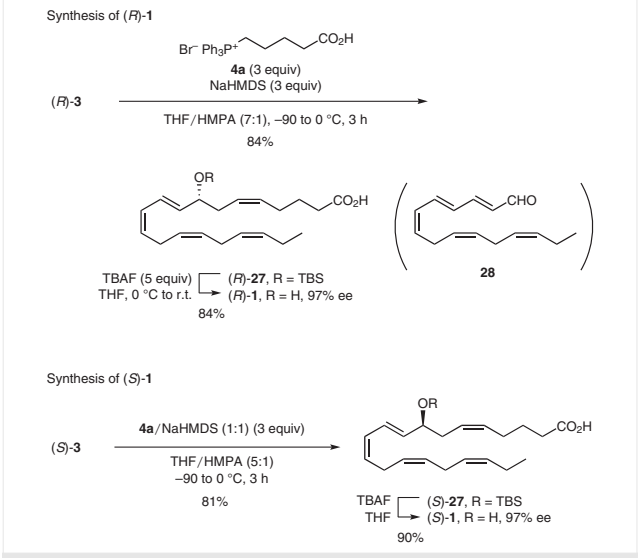
[a] Carried out with the ylide derived from **4c** (2 equiv) and NaHMDS (2 equiv) at –90 to 0 °C for 3 h unless otherwise noted.
[b] Ratios of peak heights in the ^{13}C NMR spectrum.
[c] 7–8:1.
[d] Not determined.
[e] Three equiv of **4c**/NaHMDS (1:1).
[f] S/N ratio of ^{1}H NMR spectrum = ca. 95:5. The aldehyde proton of **13** was not seen in the ^{1}H NMR spectrum.



Scheme 3 Synthesis of the key aldehyde. [a] RuCl[(*R*,*R*)-TsDPEN](*p*-cymene).

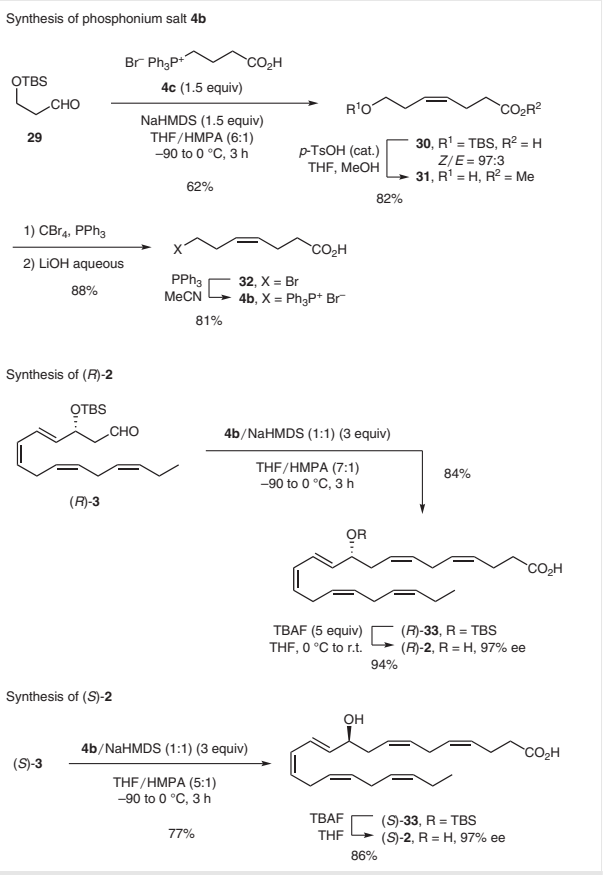
((*R*)-**1**) in 84% yield. The ^{1}H NMR spectral data of the product were consistent with the reported data.[2d] The ^{13}C-APT NMR and UV spectra further supported the structure. The ^{1}H NMR spectrum of the derived methyl ester (with CH_2N_2) was consistent with the reported data.[2c] The high chemical purity of (*R*)-**1** was confirmed by these NMR spectra. Enantiomeric purity of (*R*)-**1** was 97% ee as determined by chiral HPLC of the derived methyl ester (CH_2N_2), and the ee indicated that no isomerization occurred during synthesis.[9] In a similar manner, aldehyde (*S*)-**3** was converted into (8*S*)-HEPE ((*S*)-**1**) (97% ee) in 73% yield over two steps.

In the synthesis of (10*R*)-HDoHE ((*R*)-**2**), two intermediates **30** and (*R*)-**33** were prepared by the carboxy ylide Wittig reaction, as delineated in Scheme 5. Although the elimination of the TBS-oxy group from aldehyde **29** was possible, a small-scale Wittig reaction of **29** (ca. 100 mg) with two equiv of **4c** (ca. 400 mg)/NaHMDS (1:1) in THF/HMPA produced **30** in 64% yield. Since the yield was similar to that (70%) for the Wittig reaction of aldehyde **6** with **4c**/NaHMDS in Table 1, entry 5, we concluded that the elimination to produce CH_2=CHCHO was negligible. The reaction could be performed with an increased quantity (11 g) and a reduced equivalency (1.5 equiv) of **4c** to give **30** in 62% with 97% *Z*-selectivity, as presented in Scheme 5 (the first step). Then, **30** was converted in four steps into the carboxy phosphonium salt **4b**. Subsequently, the Wittig reaction of (*R*)-**3** with the carboxy ylide derived from **4b** afforded (*R*)-**33** stereoselectively in 84% yield. Finally, desilylation with TBAF furnished (10*R*)-HDoHE ((*R*)-**2**) with 97% ee (according to



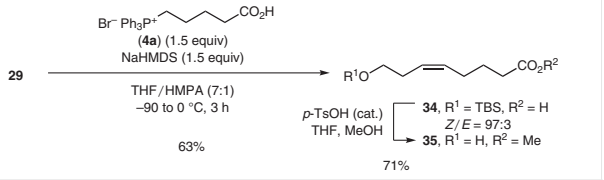
Scheme 4 Synthesis of (8*R*)- and (8*S*)-HEPE

chiral HPLC analysis of the methyl ester) in good yield. The ^{1}H NMR and ^{13}C-APT NMR spectra, UV spectrum, and HRMS data were consistent with the structure. Furthermore, the ^{1}H NMR spectrum of the derived methyl ester (CH_2N_2) was consistent with the reported data.[2b] Synthesis of (10*S*)-HDoHE ((*S*)-**2**) from (*S*)-**3** was also completed (Scheme 5).



Scheme 5 Synthesis of (10*R*)- and (10*S*)-HDoHE (**2**)

The reasonable yield of **30** obtained using 1.5 equiv of **4c** prompted us to study a similar reaction of **29** with phosphonium salt **4a**, which is one carbon longer than **4c**. As delineated in Scheme 6, olefinic acid **34** with 97% *Z*-selectivity was obtained in 63% yield using 1.5 equiv of the reagent. Exposure of **34** to acidic MeOH gave hydroxy methyl ester **35**, which has been used as a component in the synthesis of fatty acid metabolites.[10,11]



Scheme 6 Preparation of **35** for the synthesis of fatty acid metabolites

In summary, the Wittig reactions of aldehydes possessing a silyloxy group at the β-position with carboxy (CO_2H) ylides proceeded smoothly without the elimination of the silyloxy group by using a carboxy ylide (3 equiv) in THF/HMPA (7–8:1).[12] The method was successfully applied for the synthesis of both enantiomers of 8-HEPE and 10-HDoHE. This method would be applicable for the synthesis of structurally similar metabolites such as monohydroxy-ARA, -EPA, and -DHA, and their dihydroxy derivatives that include maresin 1, protectin D1, and resolvin D5, which are anti-inflammatory and pro-resolving mediators.[11]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611976.

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(5) Signal-to-noise (S/N) ratios of ^{1}H NMR and ^{13}C NMR spectra are ca. 95% and ca. 97%, respectively.

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(9) Since the observed specific rotation of (*R*)-**1** ($[\alpha]_D^{21}$ +6 (*c* 1.58, $CHCl_3$)) was inconsistent with the reported data for 86% ee[11] ($[\alpha]_D^{24}$ +33.4 (*c* 2.1, $CHCl_3$)), the reported ^{1}H NMR analysis of the MTPA ester derived from the methyl ester of (*R*)-**1** was applied to our sample to determine ca. 96.6% ee of (*R*)-**1** (δ = 6.50–6.62 (m) and 6.60–6.69 (dd) ppm). Since accurate calculation was prevented by the slight overlap of the signals, the methyl ester was subjected to chiral HPLC analysis to establish 96.9% ee. In addition, the Δδ values between the (*S*)- and (*R*)-MTPA esters of the methyl ester indicated the (*R*)-chirality. The results are presented in the ESI.

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(12) To an ice-cold suspension of **4a** (374 mg, 0.844 mmol, 3 equiv) in THF (2.4 mL) and HMPA (0.5 mL) was added NaHMDS (1.0 M in THF, 0.843 mL, 0.843 mmol, 3 equiv). The resulting reddish-orange mixture was stirred at 0 °C for 1 h and cooled to –90 °C. A solution of aldehyde (*R*)-**3** (98 mg, 0.281 mmol, 1 equiv) in THF (0.7 mL) and HMPA (0.1 mL) was added to the mixture dropwise. After 1 h, the mixture was warmed to 0 °C over 2 h before addition of saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel to give olefin (*R*)-**27** (102 mg, 84%) as the sole product: liquid; R_f = 0.21 (hexane/EtOAc, 4:1); $[\alpha]_D^{20}$ –21 (*c* 0.86, $CHCl_3$). IR (neat): 1710, 1255, 836, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.90 (s, 9 H), 0.97 (t, *J* = 7.5 Hz, 3 H), 1.69 (quint., *J* = 7.5 Hz, 2 H), 2.08 (quint., *J* = 7.5 Hz, 2 H), 2.09 (q, *J* = 7.5 Hz, 2 H), 2.25 (t, *J* = 6.0 Hz, 1 H), 2.22–2.31 (m, 2 H), 2.81 (t, *J* = 6.0 Hz, 2 H), 2.95 (t, *J* = 6.0 Hz, 2 H), 4.20 (q, *J* = 6.0 Hz, 1 H), 5.25–5.51 (m, 7 H), 5.66 (dd, *J* = 15.0, 6.0 Hz, 1 H), 5.98 (t, *J* = 11.1 Hz, 1 H), 6.48 (dd, *J* = 15.0, 11.1 Hz, 1 H), 10.2–11.2 (br s, 1 H) ppm. ^{13}C-APT NMR (75 MHz, $CDCl_3$): δ = –4.7 (+), –4.4 (+), 14.3 (+), 18.3 (–), 20.6 (–), 24.5 (–), 25.6 (–), 25.9 (+), 26.1 (–), 26.7 (–), 33.5 (–), 36.4 (–), 73.0 (+), 124.4 (+), 126.8 (+), 127.0 (+), 127.6 (+), 128.2 (+), 128.9 (+), 129.5 (+), 130.2 (+), 132.1 (+), 136.7 (+), 180.3 (+) ppm. HRMS (FAB$^+$): *m/z* calcd for $C_{26}H_{43}O_3Si$ [(M – H)$^+$]: 431.2981; found: 431.2990.