Synthesis of Resolvin D6 and the Silyl Ether of the Resolvin E2 Methyl Ester via trans-Enynyl Alcohols

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Abstract
Two trans-enynyl alcohol intermediates corresponding to the C1–C8 and C13–C22 parts of resolvin D6 (RvD6) were prepared through the Hudrlik–Peterson reaction of the TMS-substituted trans-epoxy alcohols with TMS-acetylide and subsequent TMS-desilylation. These intermediates were coupled with a 1,4-dihalo-2-butyne derivative under copper catalysis, and the resulting acetylene was reduced with Zn(Cu/Ag) to afford the TBS ether of RvD6 methyl ester. Desilylation with TBAF yielded the trans-lactone of RvD6, which was hydrolyzed to RvD6. The total yield of RvD6 was 1.9% in 19 steps from (3-trimethylsilyl)propargyl alcohol. The TBS ether of RvE2 methyl ester was also synthesized.

Key words resolvin D6, resolvin E2, stereoselective synthesis, epoxide ring opening, semi-hydrogenation, zinc, enynes

Hydroxy metabolites of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), including resolvins, show anti-inflammatory and pro-resolution activities.1 Because they are available only in minute quantities by enzymatic conversion and/or in limited quantities from commercial sources, organic syntheses have been developed.2 However, synthesis of several resolvins, especially newly isolated resolvins, remains undeveloped, and thus fundamental biological investigations such as the structure and activity relationships are unexplored. The E,Z-dienyl alcohol unit is found in several metabolites and has been constructed by several methods. Resolvins D6 and E2 (abbreviated as RvD6 and RvE2, respectively) each possess two such units3,4 which are connected through the butenyl bridge (Figure 1). A few organic syntheses of these metabolites have been developed.5,6 However, yields in the synthesis of RvD6 were not fully reported,7 and RvD6 is not commercially available.

To improve the availability of RvD6, the synthesis of RvD6 was started and the established method was then applied to the synthesis of RvE2.

Recently we reported7 the Hudrlik–Peterson reaction of the TMS-substituted trans-epoxy alcohols 1 with TMS-acetylide 2 followed by TMS-desilylation to afford trans-enynyl alcohols 3 (Scheme 1). These transformations were used as the key steps for the syntheses of 18-HEPE7 and an intermediate of resolvin D1.8 As the next target we chose RvD6, envisaging that the central part would be synthesized by connecting two intermediates, 5 and 6, to 1,4-dihalo-2-butynyl derivative 49 by the copper-catalyzed couplings followed by semi-hydrogenation as delineated in Scheme 2. Herein, we report a synthesis of RvD6 along this strategy and its application to the formal synthesis of RvE2.
rac-11 with t-BuO₂H and Ti(O-i-Pr)_4/L-(+)-DIPT (Scheme 3). As reported earlier, the Hudrlik–Peterson reaction of 8 by using the racemate corresponding to 8, proceeded well to afford trans-enynyl alcohol 9, which was then subjected to TMS desilylation to afford alcohol 10 in 78% yield from 8. Then, TBS protection afforded the C13–C22 intermediate 6 in 89% yield.

Allylic alcohol 11 was converted to ent-8 by the Sharpless asymmetric epoxidation with use of D-(–)-DIPT. The increased enantiopurity (>99% ee) was the result of the kinetic resolution between 11 and ent-11 at a ratio of 99.5:0.5. The Mitsunobu inversion afforded syn-epoxy alcohol 12 in 85% yield. The Hudrlik–Peterson reaction of 12 with acetylide 2 at room temperature was complete within four hours to afford 10 in 78% yield.

Next, the above strategy, including the Sharpless asymmetric epoxidation followed by the Hudrlik–Peterson reaction, was applied to the synthesis of the C1–C8 intermediate 5. The reaction of the anti-epoxy alcohol anti-13, a product of the Sharpless asymmetric epoxidation, followed by the removal of TMS in 14, gave 15 in only 34% yield (Scheme 4). In contrast, the yield of 15 from syn-13 was 59%. In consideration of these yields and the two additional steps for the Mitsunobu inversion of anti-13 to syn-13 in 83% yield, a syn-rich mixture of syn- and anti-epoxy alcohols 13 was synthesized by a different method for the Hudrlik–Peterson reaction (Scheme 5).
The Weinreb amide 16 synthesized from γ-butyrolactone11 was converted to acetylene ketone 17, which was reduced by using the Noyori catalyst12 to propargylic alcohol 18 with 98% ee as determined by chiral HPLC analysis. Red-Al reduction of 18 gave a mixture of 19 and diol 20 in 59% and 41% yield, respectively. After separation by routine chromatography, epoxidation of 19 with m-CPBA gave a mixture of syn and anti isomers of 13 in a 3:2 ratio, and the Hudrlik–Peterson reaction with TMS-acetylide 2 followed by TMS-desilylation gave 15 in 42% yield. Protection of 15 with TBSCI followed by regioselective deprotection of the bis-TBS ether afforded 21 in 55% yield. Finally, two-step oxidation of 21 to the acid followed by esterification gave 5 in 51% yield.

The last stage of the synthesis of RvD6 is delineated in Scheme 6, in which both intermediates 6 and 5 were joined to 4 by copper-catalyzed coupling to construct the entire structure of RvD6. The coupling of 6 with 4 was followed by bromination of alcohol 22 to afford 23 in 73% yield. The second coupling reaction, carried out between acetylene 5 and bromide 23, produced acetylene 7, which was chemically unstable to some extent. We envisaged a Zn(Cu/Ag)-assist-
ed reduction\textsuperscript{13} of the conjugated acetylene followed by a reduction of the nonconjugated acetylene using P-2 Ni\textsuperscript{14} under H\textsubscript{2} because Zn(Cu/Ag) was reported not to reduce the nonconjugated acetylene.\textsuperscript{13} However, we observed that an isolated acetylene in an intermediate for the synthesis of RvE2 could be reduced by using a large excess of Zn(Cu/Ag).\textsuperscript{13} According to this protocol, reduction of 7 was conducted with a large excess of Zn(Cu/Ag) (about 1600 equiv) to produce 24 in 62\% yield from 5. Fortunately, removal of Zn(Cu/Ag) by filtration through Celite was not an operational problem. Desilylation of 24 was carried out with TBAF. However, dihydroxy ester of RvD6 and/or RvD6 was not isolated. Instead, hydroxy lactone 25 was obtained in 53\% yield. Finally, hydrolysis with LiOH afforded RvD6 in 79\% yield.

The \textsuperscript{1}H and \textsuperscript{13}C NMR spectral data in CD\textsubscript{3}CN were identical to those reported previously.\textsuperscript{5} In addition, the \textsuperscript{1}H and \textsuperscript{13}C–APT NMR spectra in CD\textsubscript{3}OD and UV spectra with \textsuperscript{\varphi} were consistent with the structure of RvD6.

In a similar manner, 36, the literature precursor to RvE2,\textsuperscript{6c} was synthesized as summarized in Scheme 7. The starting propargylic alcohol 26 with 98\% ee was synthesized from the corresponding ketone and converted to a diastereomeric mixture of epoxy alcohol 27, which upon the Hudrlick–Peterson reaction followed by TMS-desilylation produced 28 in 55\% yield (two steps). The functional groups of 28 were then manipulated to afford 31 in five steps via 29 and 30. Enyne 32 was the previous product of the Hudrlick–Peterson reaction,\textsuperscript{7} and was coupled with 4 to produce 33, which was then converted to bromide 34. The coupling of 31 with 34 proceeded well, and the semi-hydrogenation of the resulting acetylene 35 by using a large excess\textsuperscript{15} of Zn(Cu/Ag) afforded 36 in 63\% yield. There was no contamination with over-reduced products. The \textsuperscript{1}H and \textsuperscript{13}C NMR spectra of 36 were in good agreement with the reported values.\textsuperscript{6c}

In summary, we have applied the Hudrlick–Peterson reaction to the synthesis of RvD6.\textsuperscript{16} The semi-hydrogenation of three triple bonds including one isolated triple bond was achieved by using a large excess of Zn(Cu/Ag), thereby simplifying the synthesis. A total yield of RvD6 in the longest linear sequence through 11, 6, and 23 was 1.9\% in 19 steps from (3-trimethylsilyl)propargyl alcohol. The same procedure was then successfully applied for the synthesis of the bis-TBS ether of the RvE2 methyl ester. The procedure pro-
vided in the Supporting Information will be useful for reproducing the synthesis.

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Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611826.

References and Notes

(4) (a) Tjonahen, E.; Oh, S. F.; Siegelman, J.; Elangovan, S.; Percarpio, A.; Spur, B. W. Prog. Lipid Res. 2016, 63, 353. (b) Serhan, C. N.; Petasis, N. A.
(15) Reduction of 35 to 36 at 30 °C or 40 °C for 24 h is summarized in the Supporting Information (page S2).
(16) Synthesis of [(E)-1-[(tert-Butyldimethylsilyl)oxy]oct-5-en-7-yn-4-ol (15)
To a solution of tris(trimethylsilyl)acetYLENE (0.43 ml, 3.05 mmol) in THF (0.3 ml) was added dropwise n-BuLi (1.70 ml, 2.67 mmol, 1.57 M in hexane) at –78 °C. After 15 min of stirring at rt, HMPlA (0.69 ml, 3.97 mmol) and a solution of epoxy alcohol 13 (100 mg, 0.331 mmol) in THF (0.15 ml) were added. The solution was stirred at rt for 5 h and then diluted with saturated NH4Cl. The product was extracted with EtOAc and passed through a short column of silica gel for the next reaction. A mixture of the above enyne and K2CO3 (212 mg, 1.53 mmol) in MeOH (1 ml) was stirred at rt for 2 h and then diluted with saturated NH4Cl. The product was extracted with EtOAc and purified by chromatography on silica gel to give alcohol 15 (34 mg, 42% over two steps); colorless oil; Rf = 0.37 (hexane/EtOAc, 4:1); [α]D20 = 22 (c 1.1, CHCl3). 1H NMR (400 MHz, CDCl3): δ = 0.07 (s, 6 H), 0.90 (s, 9 H), 1.53–1.80 (m, 4 H), 2.87 (d, J = 2.1 Hz, 1 H), 3.25 (d, J = 4.0 Hz, 1 H), 3.66 (t, J = 5.2 Hz, 2 H), 4.16–4.25 (m, 1 H), 5.74 (dt, J = 16.0 Hz, 2.1 Hz, 1 H), 6.25 (dd, J = 16.0 Hz, 5.4 Hz, 1 H). 13C–APT NMR (75 MHz, CDCl3): δ = 5.4 (s), 18.4 (s), 26.0 (s), 34.6 (s), 63.5 (s), 71.3 (s), 77.6 (s). HRMS–FAB+: m/z [M + H]+ calcd for C16H22O5Si: 255.1780; found: 255.1782.