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A versatile asymmetric synthesis of highly enantiomerically enriched 12(*S*)-HETE via a combination of enzymatic and chemical processes

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Abstract—This paper describes a versatile asymmetric synthesis of highly enantiomerically enriched 12(*S*)-HETE via enzymatic kinetic resolution of the key allylic alcohol synthon and the facile introduction of three alkyne units which were concomitantly converted to three alkenes units.

Arachidonic acid is metabolized through the 12-lipoxygenase (12-LOX) and the cytochrome P-450 pathways to produce 12(*S*)-hydroxyeicosatetraenoic acid (12(*S*)-HETE, **1a**) and 12(*R*)-hydroxyeicosatetraenoic acid (12(*R*)-HETE, **1b**), respectively. These two endogenous substances have recently been discovered to be implicated in a number of important biological activities such as hypertension, thrombosis, metastasis of tumor cell, angiogenesis, and inflammation.[1] In particular, it has recently been reported by us that both the capsaicin-activated channel of sensory neurons and the cloned capsaicin receptor (VR1) are activated by the eicosanoids including these metabolites.[2] Accordingly, the necessity of the extended studies on VR1 activation by HETEs prompted us to synthesize a substantial amount of HETEs and a variety of their structural analogues including stereoisomer (Fig. 1).

The synthetic approaches toward 12-HETE have been continuously studied since the first synthesis of 12-HETE has been reported in 1978 by Corey group.[3] In particular, the enantioselective synthesis of 12-HETE has recently been intensively investigated by a number of research groups. However, we wished to develop a concise and divergent synthetic route to both (*R*)- and (*S*)-12-HETE because most of the reported syntheses have employed the limited synthetic precursors such as carbohydrates or glycidol as a chiral source.[4] We report herein a novel and efficient asymmetric synthesis of (*S*)- and (*R*)-12-HETE via combination of enzymatic and chemical processes.

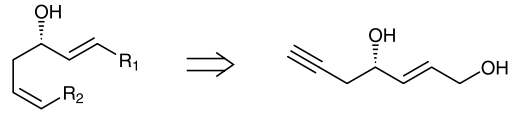

Figure 1. The key structure of 12-LOX metabolites and its corresponding chiral synthon.

Our synthetic strategy (Scheme 1) envisions (1) the prompt access to both (*S*)- and (*R*)-allylic alcohol synthons in a highly optically pure form utilizing enzymatic kinetic resolution, (2) the facile introduction of three alkyne units as a perfect *cis*-olefin precursors, (3) the single step generation of the requisite three *cis*-olefins by P-2 nickel catalyzed reduction.

Our synthesis (Scheme 2) commenced with the preparation of the optically pure allylic alcohol (*S*)-**5** as the initial key intermediate. Monosilylation[5] of the readily available *cis*-1,4-butenediol followed by Swern oxidation[6] afforded the *trans*-olefinic aldehyde **7**. Treatment of the aldehyde **7** with propargylaluminium sesquibromide provided the allylic alcohol **5** as a racemic mixture.[7] At this stage, we looked for an enzymatic kinetic resolution of **5** for the optically active (*S*)-**5** because the enzymatic process turn out to be superior to the chemical process in terms of high enan-

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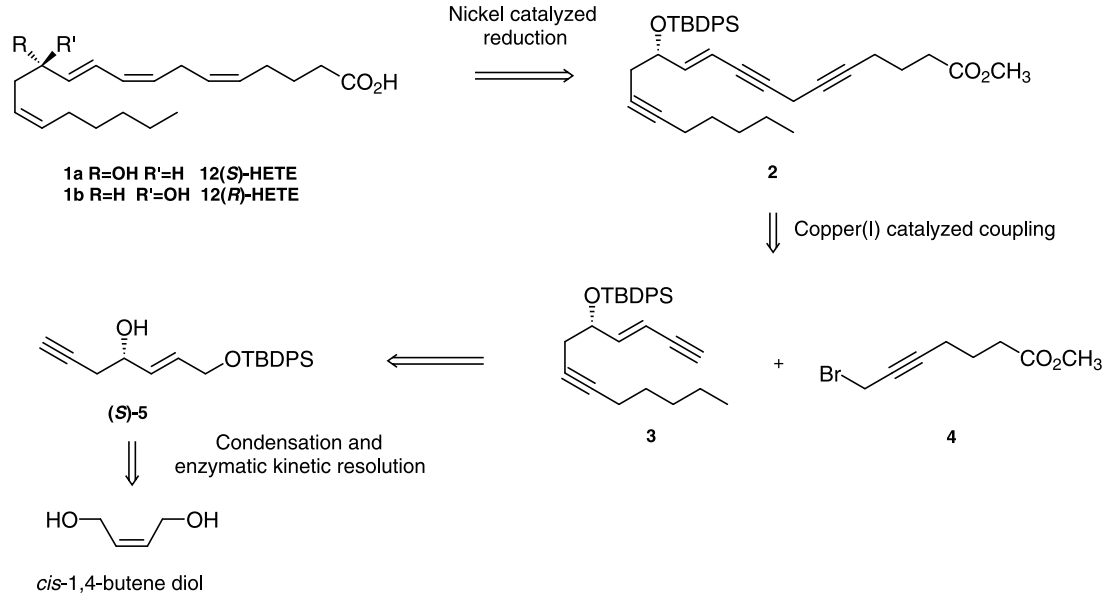
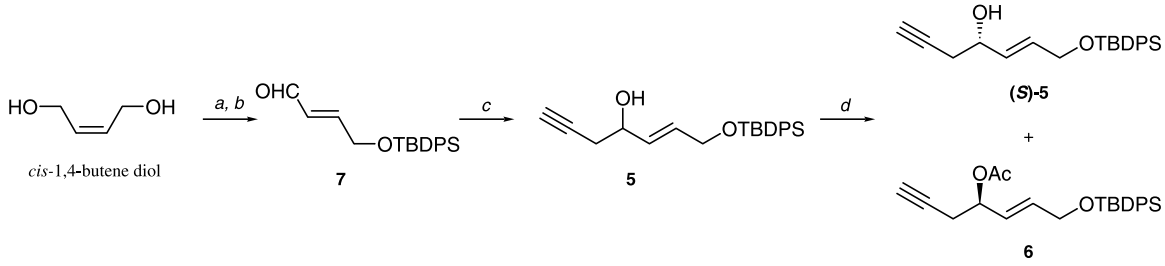


Scheme 1. Retrosynthetic analysis of 12(*S*)-HETE.

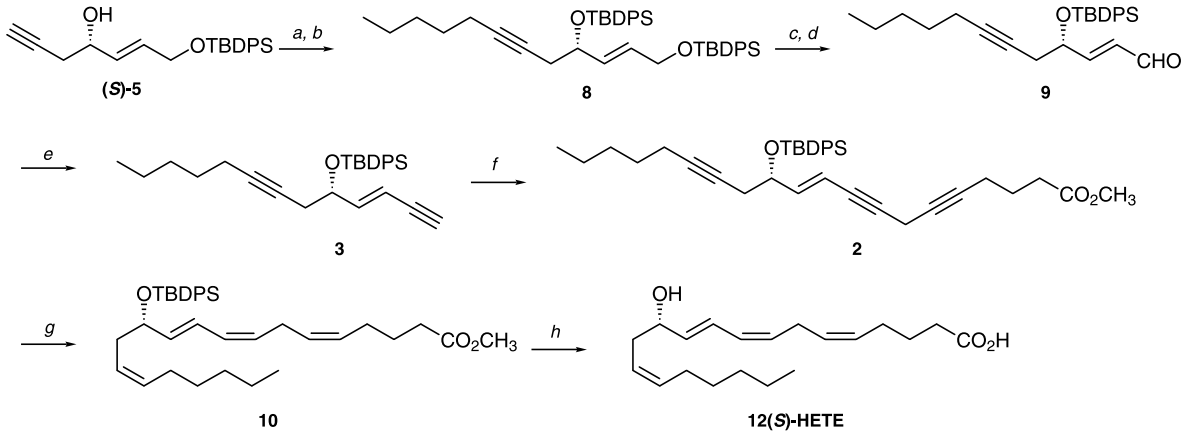


Scheme 2. *Reagents and conditions*: (a) TBDPSCl, $(i\text{Pr})_2\text{NEt}$, CH_2Cl_2, rt; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (c) Al, $HgCl_2$, $CH{\equiv}CCH_2Br$, THF, −78°C, 80% for three steps; (d) Amano AK (80 mg/mmol), vinyl acetate (0.55 equiv.), *t*-BuOMe, 20°C.

tioselectivity and stereochemical diversity of the products. Moreover, this procedure is capable of providing both enantiomers in highly optically pure form through a single step operation. The kinetic resolution of the racemic alcohol **5** was carried out in *t*-BuOMe at 20°C using *P. fluorescens* lipase (Amano AK) as a biocatalyst and vinyl acetate as an acyl donor.[8] As we anticipated, the enzyme-catalyzed kinetic resolution afforded the considerably high enantiomeric excesses (>99.5%) for both (*S*)-**5** and **6** as well as the high chemical yields (>49%) in short reaction time (4.5 h).[9] It is noticeable that the multi-gram quantities of the optically pure allylic alcohol (*S*)-**5** and (*R*)-**5** could be procured by this sequence.

The carbon chain elongation of (*S*)-**5** followed by the introduction of additional two alkyne units for the intermediate **2** were quite straightforward. Protection of the alcohol (*S*)-**5** with TBDPSCl and then alkylation of the terminal alkyne with bromopentane gave the bissilyl ether **8** in 90% yield for two steps. Selective TBDPS deprotection of **8** by HF–pyridine treatment[10] and TPAP oxidation[11] of the resulting alcohol afforded the α,β-unsaturated aldehyde **9**. Introduction of the second alkyne unit to **9** was executed by a facile conversion of aldehyde to alkyne according to Corey–Fuchs protocol.[12] For the introduction of the third alkyne unit, the enyne **3** was coupled with the known propargylic bromide **4**[13] in the presence of copper to give triyne **2** in 90% yield.[14,15] Finally, the requisite three *cis*-alkene units of 12(*S*)-HETE was successfully elaborated by the concomitant reduction of three alkynes of **2** to three *cis*-alkenes. Initial attempts for the conversion of the triyne **2** to the tetraene **10** under a variety of reduction conditions did not provide the successful result. In most cases, complete reduction of three alkynes to alkanes or partial reduction of only one or two alkynes was observed.[16] However, partial hydrogenation of three alkynes of **2** in the presence of P-2 nickel catalyst afforded the desired tetraene **10**.[17] The perfectly selective partial reduction of all three alkynes to alkenes was quite effective under these conditions. The synthesis of 12(*S*)-HETE was completed by the known two step sequence (Scheme 3).[4]

In summary, a versatile and concise synthetic route to 12(*S*)-HETE has been developed. The key part of this synthesis involves the enzymatic preparation of enantiomerically pure allylic alcohols as a useful chiral synthon for the synthesis of both 12(*S*) and 12(*R*)-HETE as well as the related eicosanoids. In addition, the facile and concomitant conversion of three alkynes



Scheme 3. *Reagents and conditions*: (a) TBDPSCl, imidazole, DMF, rt, 91%; (b) *n*-BuLi, $Br(CH_2)_4CH_3$, THF, HMPA, 0°C→rt, 82%; (c) HF–pyridine, THF/pyridine (2/1), 20°C, 80%; (d) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 89%; (e) i. CBr_4, PPh_3, CH_2Cl_2, ii. *n*-BuLi, THF, 0°C, 77%; (f) **4**, *n*-Bu_4NBr, CuI, K_2CO_3, DMF, −20°C→rt, 90%; (g) $NaBH_4$, $Ni(OAc)_2{\cdot}4H_2O$, H_2, $H_2NCH_2CH_2NH_2$, EtOH, rt, 69%; (h) Ref. 4.

to three alkenes using P-2 nickel catalyst is also involved. This unique synthetic procedure which is capable of providing both 12(*S*) and 12(*R*)-HETE in an efficient and versatile way offers a useful synthetic route to the biologically important eicosanoids.

Acknowledgements

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8. A mixture of (±)-**5** (1.52 g, 4.17 mmol), Amano AK (333 mg) and vinyl acetate (0.21 mL, 2.29 mmol) in *t*-BuOMe (20 mL) was stirred at 20°C for 4.5 h. The lipase was filtrated off and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (15% EtOAc/hexane) to give 758 mg (49.8%) of (*S*)-**5** and 840 mg (49.5%) of **6**. The enantiomeric excesses of the products were determined by chiral HPLC analysis (Chiralcel OD, *i*-PrOH:*n*-hexane = 99.5:0.5, 0.5 mL/min) after transformation of the remaining enantiomer (*S*)-**5** into the corresponding acetate. (*S*)-**5**; $[\alpha]_D^{20}$ +20° (*c* 0.96, acetone).
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15. Spectral data for **2**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67–7.73 (m, 4H), 7.34–7.44 (m, 6H), 6.31 (dd, 1H, J=15.0, 11.0 Hz), 5.93 (t, 1H, J=11.0 Hz), 5.76 (dd, 1H, J=15.0, 6.1 Hz), 5.28–5.41 (m, 5H), 4.33 (m, 1H), 3.67 (s, 3H), 2.79 (t, 2H, J=7.6 Hz), 2.29–2.33 (m, 4H), 2.06–2.11 (m, 4H), 1.67–1.17 (m, 2H), 1.26–1.31 (m, 6H), 1.08 (s, 9H), 0.89 (t, 3H, J=7.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) 144.2, 135.8, 133.8, 133.3, 129.7, 127.6, 109.1, 82.8, 78.6, 77.2, 75.6, 74.6, 72.1, 51.5, 32.8, 31.0, 28.5, 28.1, 26.9, 23.8, 22.6, 22.2, 19.3, 18.7, 18.2, 13.9, 10.4; $[\alpha]_D^{26}$ −25.8° (*c* 0.5, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{37}H_{46}O_3Si$ 566.3216, found 566.3214.

16. The conversion of single alkyne to *cis*-alkene by employing activated zinc for the synthesis of 12(*R*)- and 12 (*S*)-HETE has been reported: Chemin, D.; Gueugnot, S.; Linstrumelle, G. *Tetrahedron* **1992**, *48*, 4369–4378.
17. Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226–2230. To a suspension of $Ni(OAc)_2 \cdot 4H_2O$ (36 mg, 0.04 mmol) in anhydrous EtOH (1 mL) at 0°C was added $NaBH_4$ (8 mg, 0.21 mmol) under Ar. The reaction mixture was stirred for 20 min and ethylene diamine (30 μL) and **2** (20 mg, 0.04 mmol) were added. After exchange of the Ar for H_2, the reaction mixture was stirred at room temperature for an additional 15 min, and filtrated through a Celite pad. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (5% EtOAc/hexane) to give 14 mg (69%) of **10**. Repeated purification of the fractions contaminated with small amount of the isomeric products provided the higher yield (80∼85%). The tetraene **10** was identical in all aspects to the reported intermediate.