Epoxide ring opening of α,β-epoxysilanes with prop-2-ynyl sulfide dianion—synthesis of (11*R*,12*S*,5*Z*,7*E*,9*E*,14*Z*)-dihydroxyeicosa-5,7,9,14-tetraenoic acid

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A new methodology for synthesis of lipoxygenase metabolites possessing *vic*-diol substructures coupled with the conjugated alkene system is developed and successfully applied to the synthesis of (11*R*,12*S*,5*Z*,7*E*,9*E*,14*Z*)-dihydroxyeicosa-5,7,9,14-tetraenoic acid (DiHETE).

The biological importance of the lipoxygenase pathways of arachidonic acid metabolism has been repeatedly reviewed.[1] Since these metabolites are available only in minute quantities from biological sources, their total synthesis for further evaluation of their biological properties has attracted much interest.[2] The lipoxygenase metabolites are characterised by monool, *vic*-diol, or epoxide substructures coupled with a conjugated alkene system. So far, a number of syntheses of the monool and epoxide metabolites have been published. However, much less attention has been directed toward the *vic*-diol metabolites (Fig. 1).[3–5]

On the basis of Wicha's finding,[6,7a] we recently reported that reaction of the γ-trimethylsilyl epoxy alcohols **3** and the anions derived from **2**, in which the leaving group (Y) is attached at the α carbon, affords silyl ethers **4** (R^4 = $SiMe_3$) or free alcohols **4** (R^4 = H) after hydrolysis (Scheme 1).[8] Taking into account these results and the ready availability of optically active **3**[9] (>99% ee) in large quantities by the kinetic resolution of the corresponding racemic allylic alcohols using the Sharpless epoxidation,[10] we envisaged that, if *anti*,*trans* enyne **6** were prepared by reaction of the *anti* epoxy alcohol **3** and dianion derived from a prop-2-ynylic compound **5** (where L is a leaving group), hydroboration of **6** (R^3 = R^4 ≠ H) and subsequent palladium-catalysed coupling reaction[11] with *cis* iodide **7** would furnish DiHETE **1** stereoselectively (Scheme 2). We recently applied a similar palladium-catalysed coupling reaction to the highly stereoselective construction of leukotriene B_4 (LTB_4) and its derivatives.[2b,12] Herein we report the substantiation of our postulate, exemplified by the facile synthesis of (11*R*12*S*)-DiHETE **14**, a metabolite of the 12-lipoxygenase cascade of arachidonic acid.[4a,13]

Requisite *anti* γ-silyl epoxy alcohol **9** (>99% ee), the enantiomer of the intermediate for synthesis of LTB_4,[12a] was prepared by the kinetic resolution of racemic allylic alcohol dl-**8** in 43% yield based on dl-**8**.[9] Since we had no prior knowledge of the leaving group (L) of **5** and the requisite reaction conditions to afford the key intermediate **10** with *trans* alkene geometry, we examined reaction of **9** or the α-ethoxyethyl ether of **9** with the dianion derived from **5** [L = SPh, S(O)Ph] and BuLi. The reaction proceeded smoothly when **9** and 3 equiv. of **5** (L = SPh) were used in THF. However, after hydrolysis of the *vic*-diol monosilyl ethers under acidic conditions, the ratio of the desired enyne **10** and the *cis* isomer **15** incidentally produced was a disappointing 66 : 34 by ^{1}H NMR spectroscopy (Table 1, entry 1).

Other prop-2-ynyl sulfides were then tried (entries 2–4) and *tert*-butyl sulfide **5** (L = SBu^t) was finally found to show high stereoselectivity. Thus, **9** was added to a THF solution of the dianion of **5** (L = SBu^t) generated by using 2 equiv. of BuLi (1 h, −15 °C). The solution was stirred at −15 °C for 2 h and then at room temp. for 12 h to give the product which, upon treatment with dil HCl, furnished **10** and **15** in a ratio of 89 : 11 (entry 4). Both isomers were easily separated by column chromatography on silica gel [R_f values: **10**, 0.67; **15**, 0.57 (hexane–Et_2O = 2:5)] and **10** [$\alpha]_D^{23}$ +1.8 (*c* 0.56, $CHCl_3$)] was isolated in 70% yield. Addition of HMPA resulted in low stereoselection (entry 5).

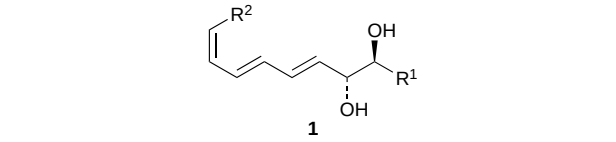
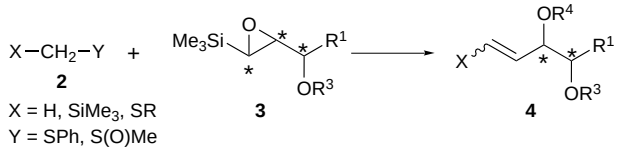
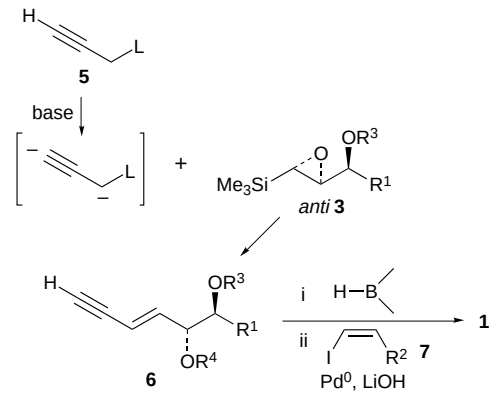


Fig. 1 General structure of the *vic*-diol metabolites



Scheme 1



Scheme 2

Table 1 Reaction of **9** and the dianion generated from **5** and BuLi[a]

Entry	Sulfide **5** L	Solvent	Ratio[b] **10** : **15**	Yield (%)[c]
1	SPh	THF	66 : 34	82
2	SC_6H_4-*p*-OMe	THF	75 : 25	—[d]
3	SBu	THF	52 : 48	74
4	SBu^t	THF	89 : 11	79
5	SBu^t	THF–HMPA[e]	60 : 40	65

[a] Dianion of **5** was generated by using BuLi (2 equiv.) at −15 °C for 1 h. Reaction was carried out at −15 °C to room temp. for 4–14 h and the crude monosilyl ethers were treated with aqueous HCl in MeOH. [b] Determined by ^{1}H NMR spectroscopy. [c] Combined yields of **10** and **15** after chromatography on silica gel. [d] Not determined. [e] THF–HMPA = 3 : 1.

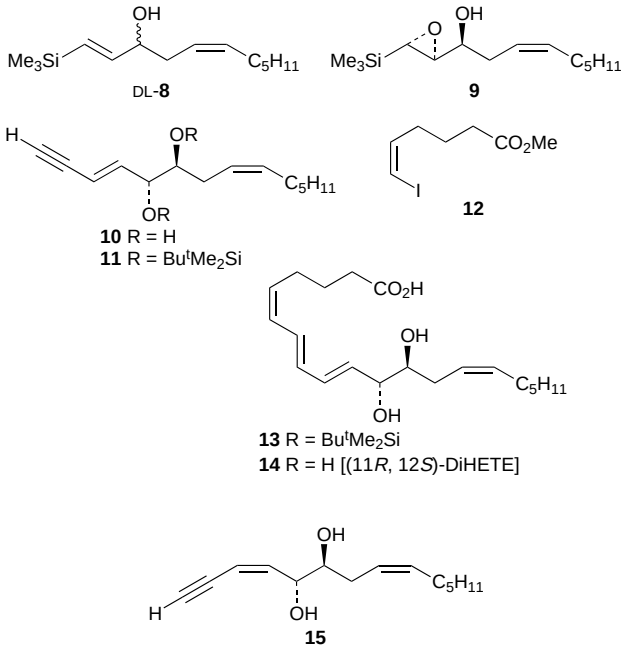


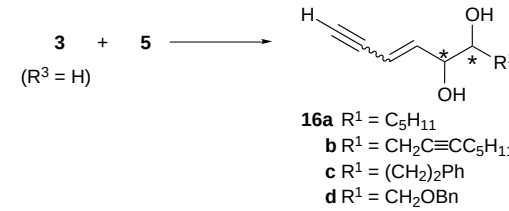
Table 2 Reaction of **3** (R^3 = H) and the dianion derived from **5**[a]

Entry	Stereochem. of **3**	R^1	L of **5**	Product[b]	*trans* : *cis*	Yield (%)[c]
1	*anti*	C_5H_{11}	SBu^t	**16a**	83 : 17	80
2	*anti*	C_5H_{11}	SPh	**16a**	73 : 27	84
3	*syn*	C_5H_{11}	SBu^t	**16a**	94 : 6	81
4	*syn*	C_5H_{11}	SPh	**16a**	87 : 13	84
5	*anti*	$CH_2C{\equiv}CC_5H_{11}$	SBu^t	**16b**	84 : 16	79
6	*anti*	$(CH_2)_2Ph$	SBu^t	**16c**	90 : 10	92
7	*anti*	CH_2OBn	SBu^t	**16d**	89 : 11	71

[a] See footnote *a* to Table 1. [b] In all cases, *trans* and *cis* isomers were separated by chromatography and characterized by ^{1}H NMR. [c] Combined yields of *trans* and *cis* enynes **16** after chromatography.

To complete the synthesis, the hydroxy groups of **10** were protected [Bu^{t}Me$_2$SiCl, imidazole, DMF, 45 °C] to afford the disilyl ether **11** {$[\alpha]_D^{25}$ −2.8 (*c* 1.06, $CHCl_3$)} in 85% yield. Hydroboration of **11** with disiamylborane (1.5 equiv., 0 °C, THF) and subsequent coupling with the iodide **12** (2.3 equiv.) in the presence of $Pd(PPh_3)_4$ (0.1 equiv.) and excess of aqueous LiOH at 35 °C furnished 11,12-DiHETE disilyl ether **13** in 96% yield. Finally, desilylation of **13** with Bu_4NF afforded in 90% yield (11*R*,12*S*)-DiHETE **14** (^{1}H NMR,[4a,13a] UV[4c]), whose chemical purity was > 95% by RP-HPLC.

In the above paragraphs, we described the synthesis of 11,12-DiHETE **14**, in which the key intermediate **10** was synthesized from **9** and the *tert*-butyl sulfide **5** (L = SBu^t) (Table 1, entry 4). By using the general strategy proposed in Scheme 2, synthesis of other DiHETEs **1** and their analogues as well as metabolites possessing the DiHETE substructure such as lipoxins should be possible. Thus, stereoselectivity of the key reaction was briefly examined by using various *anti* and/or *syn* γ-silyl epoxy alcohols **3** (R^3 = H) and prop-2-ynylic sulfides **5** (L = SBu^t, SPh) (Scheme 3) under the reaction conditions described above. Results are summarised in Table 2. With synthetically useful stereoselectivities and good yields were produced *trans* enynes **16a**–**d** in all cases when *tert*-butyl sulfide **5** (L = SBu^t) was used (entries 1 *vs.* 2, 3 *vs.* 4, 5–7). In every case, the major *trans* enyne and the minor *cis* isomer were



Scheme 3

separated easily by chromatography. Interestingly, higher *trans* selectivity was observed in the case of *syn* **3** (R^1 = C_5H_{11}, R^3 = H) (entries 1 and 3). It is also noteworthy that the sense of the *trans* alkenes afforded as the major product in our system was *opposite* to that reported by Wicha *et al*.[7]

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