Stereocontrolled Total Synthesis of (5*Z*,8*Z*,11*Z*,13*E*)(15*S*)-15-Hydroxyeicosa-5,8,11,13-tetraenoic Acid (15*S*-HETE) and Analogues

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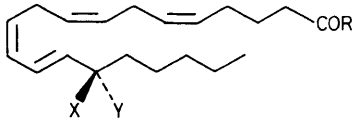
A novel and stereoselective synthesis of 15*S*-HETE and a number of analogues based on a Cu^{I}–Pd^{0} coupling reaction is described.

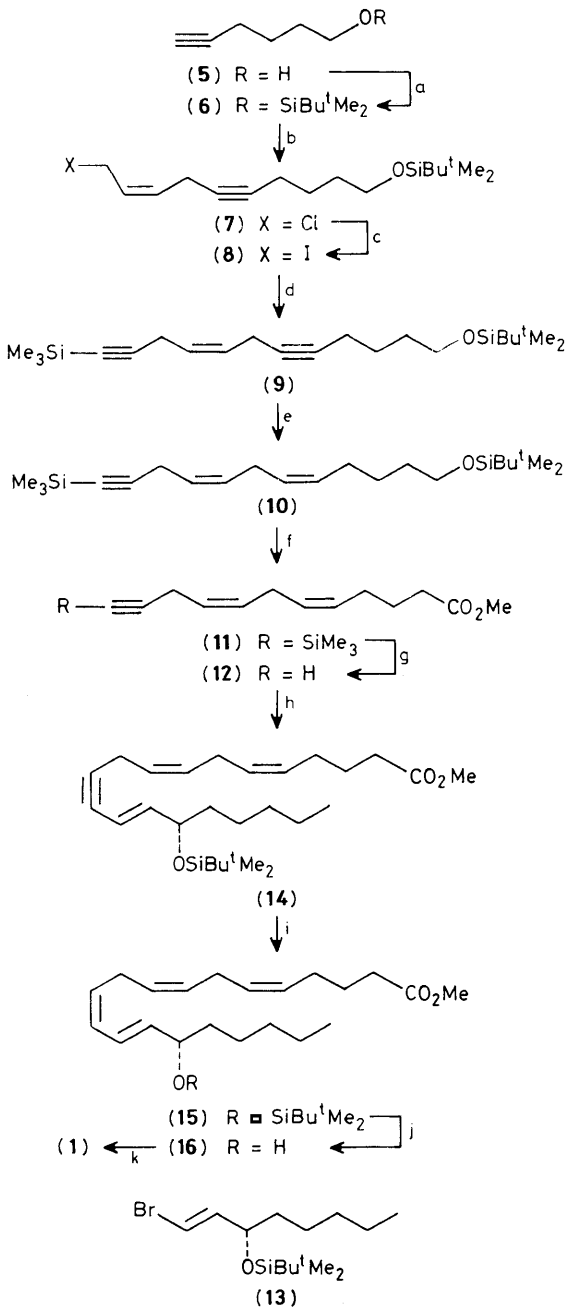
(5*Z*,8*Z*,11*Z*,13*E*)(15*S*)-15-Hydroxyeicosa-5,8,11,13-tetraenoic acid (15*S*-HETE) is an important enzymatic product of the oxidation of arachidonic acid (AA) by human leukocytes[1,2] and soybean lipoxygenase.[3,4] 15*S*-HETE has recently been shown to be a potent inhibitor of 5-lipoxygenase[5] and thus it, or analogues of it, may prove useful in the development of therapeutic approaches to allergic disorders such as asthma and anaphylaxis. In this communication, we report the first stereocontrolled total synthesis[6] of 15*S*-HETE (**1**). This enantioselective and flexible route is based on our recently proposed general strategy towards linear eicosanoids employing Cu^{I}–Pd^{0} coupling reactions[7] and was used to produce a number of analogues such as (**2**)—(**4**).

According to this strategy the *E*,*Z*-conjugated diene system of (**1**) is dissected retrosynthetically to unravel the two requisite building blocks, the terminal acetylene (**12**) and the vinyl bromide (**13**) (Scheme 1).† The construction of (**12**) and



(**1**) X = H, Y = R = OH
(**2**) X = R = OH, Y = H
(**3**) X = OH, Y = H, R = NHOH
(**4**) X = H, Y = OH, R = NHOH

† All new compounds gave satisfactory spectroscopic and analytical data.



Scheme 1. *Reagents and conditions* (THF = tetrahydofuran; DMF = dimethylformamide): a, Bu^{t}Me$_2$SiCl (1.1 equiv.), imidazole (1.1 equiv.), DMF, 0 → 25 °C, 95%; b, EtMgBr (1.1 equiv., 0.5 M in THF), THF, 0 → 50 °C, then CuBr (0.04 equiv.), 0 → 25 °C, then 1,4-dichloro-2*Z*- butene (3.0 equiv.), 25 → 50 °C, 67%; c, NaI (3.0 equiv.), acetone, heat, 100%; d, Me$_3$SiC≡CH (5.0 equiv.), THF, then EtMgBr (4.8 equiv., 0.5 M in THF), −10 → 0 °C, then CuBr (0.04 equiv.), then (**8**) in THF, 0 → 60 °C, 87%; e, H_2, Lindlar catalyst (15% w/w), quinoline (1%), hexane, 25 °C, 83%; f, Jones reagent (2.0 equiv.), acetone, 0 °C, then CH_2N_2, Et_2O, 0 °C, 91%; g, KF · 2H_2O (2.0 equiv.), DMF, 25 °C, 98%; h, (**13**) Pd(PPh$_3$)$_4$ (0.06 equiv.), CuI (0.16 equiv.), Pr^{n}NH$_2$ (1.2 equiv.), benzene, 25 °C, 92%; i, H_2, Lindlar catalyst (20% w/w), quinoline (1%), hexane, 25 °C, 87%; j, HF · pyridine (excess), THF, 0 → 25 °C, 91%; k, LiOH (5.0 equiv.), THF–H_2O (1:1), 25 °C, 86%.

the complete synthesis of (**1**) are outlined in Scheme 1. Thus, the hydroxyacetylene (**5**) was converted into its silyl ether (**6**) and coupled to 1,4-dichloro-2*Z*-butene with the aid of EtMgBr and CuBr to afford the allylic chloride (**7**) in 67% yield. Conversion of the chloride (**7**) into the iodide (**8**) followed by coupling to trimethylsilylacetylene in the presence of EtMgBr and CuBr led to the diacetylene (**9**) in 87% yield. Selective hydrogenation of (**9**) with Lindlar catalyst and H_2 resulted in the formation of the acetylenic diene (**10**) in 83% yield which upon Jones oxidation and diazomethane treatment furnished directly the methylester (**11**) in 91% yield. Liberation of the terminal acetylene then led to the key intermediate (**12**) in 98% yield [^{1}H n.m.r. ($CDCl_3$; 250 MHz): δ 5.67 (m, 1H, olefinic), 5.42 (m, 3H, olefinic), 3.65 (s, 3H, CO_2Me), 2.92 (m, 2H, allylic–propynylic), 2.77 (m, 2H, bis-allylic), 2.30 (t, *J* 7.0 Hz, 2H, CH_2CO_2Me), 2.08 (m, 3H, allylic and acetylenic), and 1.69 (quintet, *J* 7.0 Hz, 2H, CH_2)]. Coupling of (**12**) with the previously synthesized[7] vinyl bromide (**13**) (enantiomeric excess ≥95%) in the presence of the CuI–Pd(PPh$_3$)$_4$ catalyst system led to the derivative (**14**) in 92% yield [^{1}H n.m.r. ($CDCl_3$; 250 MHz); δ 6.05 (dd, *J* 16.0 and 7.5 Hz, 1H, olefinic), 5.61 (m, 2H, olefinic), 5.40 (m, 3H, olefinic), 4.10 (m, 1H, CHO), 3.67 (s, 3H, CO_2Me), 3.02 (m, 2H, allylic–propynylic), 2.77 (m, 2H, bis-allylic), 2.30 (t, *J* 7.5 Hz, 2H, CH_2CO_2Me), 2.06 (m, 2H, allylic), 1.70 (quintet, *J* 7.0 Hz, 2H, CH_2), 1.5—1.18 (m, 8H, CH_2), 0.90 (s, 9H, Bu^t and t, *J* 7.0 Hz, 3H, Me), 0.06 and 0.04 (singlets, 3H each, $SiMe_2$)]. Reduction of (**14**) under Lindlar conditions then furnished (**15**) from which 15*S*-HETE (**1**) was generated.‡ Using the enantiomer of (**13**) (enantiomeric excess ≥95%),[7] and acetylene (**12**), 15*R*-HETE (**2**) can also be synthesized by this route in similar overall yield.

As part of our efforts to improve upon the 5-lipoxygenase inhibitory properties of (**1**), the hydroxamic acid[8] derivatives (**3**) and (**4**) were synthesized in *ca.* 50% overall yield from the silyl derivative (**15**) (Scheme 1) and its enantiomer respectively. This was achieved by (a) ester hydrolysis (5 equiv. of LiOH, H_2O–THF, 25 °C), (b) acid chloride formation [2.0 equiv. of $(COCl)_2$, 1.0 equiv. of DMF, benzene, 0→25 °C], and (c) reaction with hydroxylamine (3.0 equiv. of $NH_2OH \cdot HCl$, 3.0 equiv. of NaOAc, THF–H_2O, 0→ 25 °C). These and other derivatives of 15*S*- and 15*R*-HETE carrying other siderophores, such as ethylenediaminetetra-acetate and catechol groups at C-1, are currently being evaluated as potential inhibitors of 5-lipoxygenase.

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‡ Both 15*S*-HETE (**1**) and its methyl ester (**15**) exhibited identical spectral and chromatographic properties to authentic samples generated by the method of Baldwin *et al.*[3]