Convergent Stereocontrolled Synthesis of 13-Hydroxy-9*Z*,11*E*-octadecadienoic Acid (13-HODE)

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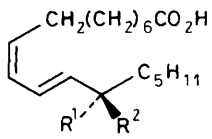
The readily available alkenes (**4**) and (**5**) were coupled using a palladium(II) catalyst to give the diene ester (**6**), a late-stage intermediate to 13-HODE.

(13*R*)-13-Hydroxy-9*Z*,11*E*-octadecadienoic acid (13*R*-HODE) (**1a**) has been isolated from the seed oil of *Coriaria Nepalensis*[1]; the enantiomer (13*S*-HODE) (**1b**), isolated from rice (*Oryza sative* L.), has been shown to act as a self-defence substance against rice-blast disease.[2] It has also been known for some time that coriolic acid (**1b**) is present in heart mitochondria[3] as well as in the sera of patients with familial Mediterranean fever.[4] Recently interest in 13-HODE (**1**) was heightened by the disclosure that this substance acts as a chemo-repellent which influences platelet/endothelial cell interactions[5] and may therefore play a very significant role in controlling thrombosis.

While several syntheses of 13-HODE have been described in the literature,[6] none is suitable for the synthesis of a wide range of analogues of the natural product. We report a short, highly flexible, convergent synthesis of 13-HODE in which C-1 of the natural product is introduced and maintained in the correct oxidation state.[7]

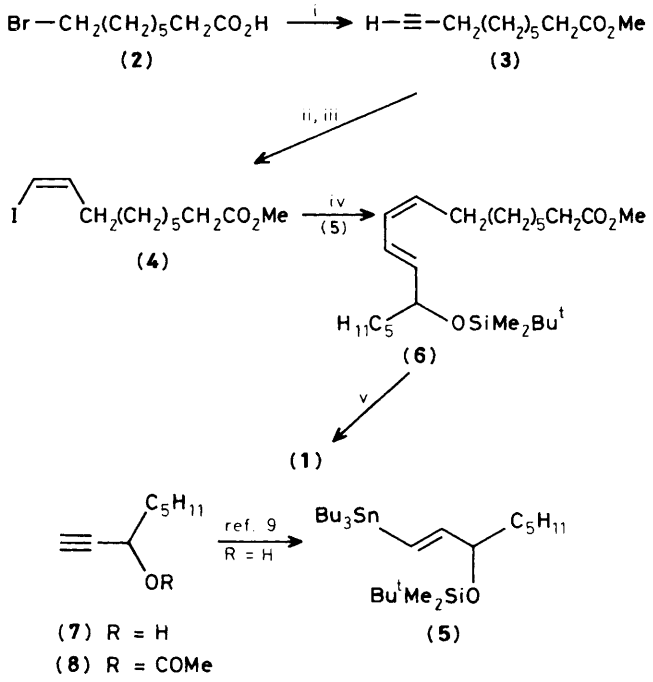
8-Bromo-octanoic acid (**2**) was converted into methyl dec-9-ynoate (**3**) (Scheme 1). Dehydroiodination of the alkyne followed by stereospecific reduction using diimide[8] gave the vinyl iodide (**4**). Coupling of this iodide with tributyl(3-t-butyldimethylsilyloxyoct-1-enyl)stannane (**5**) was achieved over four days in warm dimethylformamide using $Pd(PPh_3)_2Cl_2$ as catalyst to give the diene (**6**). Deprotection of compound (**6**) using tetrabutylammonium fluoride (TBAF) followed by potassium carbonate in aqueous methanol gave (±)-13-HODE.

The tin derivative (**5**) is prepared in two steps from the alkynol (**7**).[9] The new route to 13-HODE described above is particularly useful for the preparation of the enantiomers of (**1**) since the alkynol (**7**) is available in optically active form by a conventional resolution process, *i.e.* by preparation of the hemi-phthalate ester, formation of a salt with an optically active base, and crystallization.[10] We found that optically active oct-1-yn-3-ol can be obtained very simply by enan-



(**1**)

a; R^1 = H; R^2 = OH
b; R^1 = OH; R^2 = H



Scheme 1. *Reagents:* i, $LiC{\equiv}CH/(CH_2NH_2)_2$, NH_3, −33 °C, 10 h, then MeOH, H^+; ii, NaOMe then I_2; iii, $[{=}NCO_2K]_2$, HOAc in MeOH, Bu^nNH_2 then chromatography [33.5% from (**2**)]; iv, $Pd(PPh_3)_2Cl_2$, $HCONMe_2$, 60 °C under N_2, 4 days (60%); v, TBAF, then K_2CO_3, H_2O, MeOH.

tioselective hydrolysis of the acetate (**8**) using a cheap commercially available isolated enzyme. Thus stirring an aqueous suspension of the acetate (**8**) with *Mucor miehei* lipase gave (3*S*)-oct-1-yn-3-ol (80% enantiomeric excess) and recovered optically active acetate. Other lipases (*e.g. Candida cylindracea* lipase, porcine pancreatic lipase) were less useful. This work complements the studies of Griengl *et al.* who found that lyophilized yeast specifically hydrolysed the (*S*)-enantiomer of the acetate (**8**).[11] The availability of (3*S*)- and (3*R*)-octynol by these simple enzyme catalysed processes allows the ready synthesis of both enantiomers of 13-HODE for further biological evaluation.

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