Formal Syntheses of Hepoxilin B_3, Trioxilin B_3 and Substances against Rice Blast Disease from D-Mannitol

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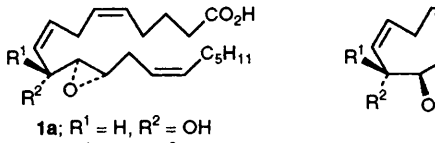
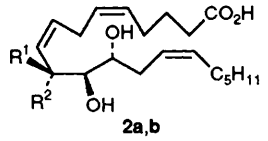
A pair of epimeric key intermediates for preparation of the title compounds are readily available from 1,2 : 3,4 : 5,6-tri-*O*-isopropylidene-D-mannitol *via* selective cleavage of acetonide and lactol-formation-induced epimerization.

Oxygenated metabolites of unsaturated fatty acids play various important roles in animals and plants.[1] Recently, we have completed the total syntheses of arachidonic acid metabolites derived from (12*S*)-12-hydroxyperoxyicosatetraenoic acid [12(*S*)-HPETE], such as hepoxilin B_3 **1a**, **1b**, trioxilin B_3 **2a**, **2b**[2,3] and several oxygenated C_{18} fatty acids **3a**, **3b**[4,5] which can act as self-defence substances against rice blast disease. Owing to the need for biological evaluation and the limited availability from natural sources, we were interested in designing efficient syntheses, which would allow the preparation of all these compounds starting from D-mannitol, by application of our newly developed one-pot procedure[6] for selective hydrolysis of terminal acetonide and subsequent oxidative cleavage of glycol.

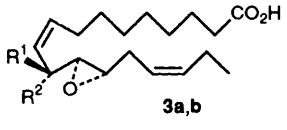
The known aldehyde **5**,[7] readily prepared from 1,2 : 3,4 : 5,6-tri-*O*-isopropylidene-D-mannitol **4** in an improved yield (58% + 31% recovered starting material) by exposure to periodic acid in diethyl ether,[6] was treated with prop-2-ynyl bromide in the presence of zinc dust[4] to give the *erythro* product **6** in 86% yield after chromatography, the ratio of *erythro* to *threo* isomer was *ca.* 12 : 1. Substitution of **6** with ethyl bromide (pentyl bromide) yielded compound **7a** (**7b**) in 87% (75%) yield. Partial hydrogenation of **7a** (**7b**) in the presence of Lindlar catalyst afforded **8a** (**8b**) in 93% (94%) yield. After silylation of free hydroxy group of **8a** (**8b**),



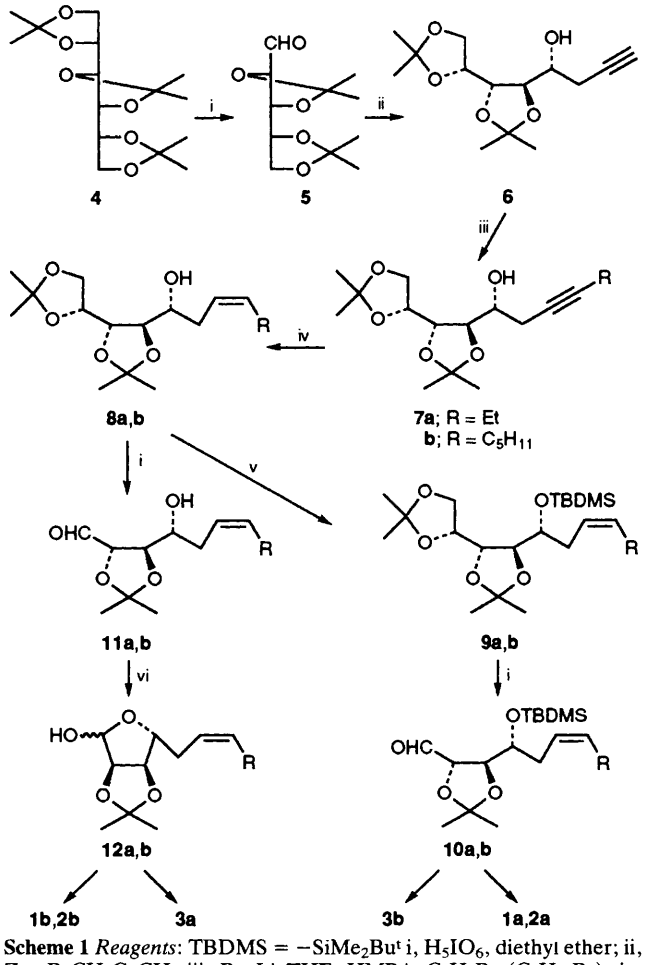
1a; R^1 = H, R^2 = OH
b; R^1 = OH, R^2 = H



2a,b



3a,b



Scheme 1 *Reagents*: TBDMS = $-SiMe_2Bu^t$ i, H_5IO_6, diethyl ether; ii, Zn, $BrCH_2C{\equiv}CH$; iii, Bu^nLi–THF, HMPA–C_2H_5Br ($C_5H_{11}Br$); iv, H_2, Pd–Pb–$CaCO_3$; v, TBDMSCl, imidazole; vi, K_2CO_3, MeOH

selective deacetonization and subsequent periodate cleavage using our one-pot reaction (H_5IO_6 in diethyl ether)[6] afforded aldehyde **10a** (**10b**) in 86% (85%) yield in two steps. **10a**, $[\alpha]_D^{20}$ −29.2 (*c* 0.54, $CHCl_3$); **10b**, $[\alpha]_D^{20}$ −29.6 (*c* 0.42, $CHCl_3$).

When the ethereal periodic acid[6] was used, the transformation of **8a** (**8b**) to **11a** (**11b**) *via* selective hydrolysis of terminal acetonide followed by glycol cleavage proceeded in one pot in 93% (89%) yield. Although the epimerization of acetonide of *erythro*-2,3-dihydroxy aldehyde to the more stable *threo*-2,3-dihydroxy acetonide is known,[8] the reversed transformation has not yet appeared in literature. It is clear that in the presence of γ-OH, the acetonide of *threo*-2,3-dihydroxy aldehyde could be transformed into the *cis*-fused five-membered ring lactol with C(2) epimerization. Thus, treatment of **11a** (**11b**) with 3 equiv. potassium carbonate in methanol at reflux temperature effected a smooth epimerization, providing the known lactol **12a** (**12b**)[3,5] in 84% (80%) yield.

The further reaction sequences of **10a**, **10b** and **12a**, **12b** to **1a**, **1b**, **2a**, **2b** and **3a**, **3b** have been established,[2–5] hence syntheses of aldehyde **10a** (**10b**) and lactol **12a** (**12b**) formally constitute the syntheses of **1a**, **1b**, **2a**, **2b**, **3a** and **3b**. These syntheses are more concise, efficient and have higher overall yields than those reported previously.[2–5]

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