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TOTAL SYNTHESIS OF UNSATURATED TRIHYDROXY C_{18} FATTY ACIDS

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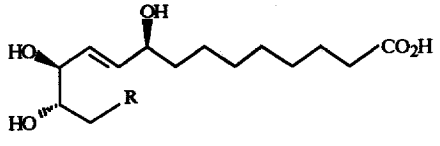
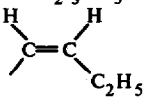
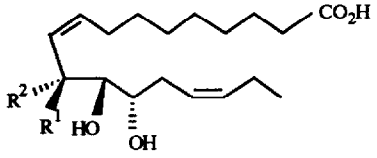
Abstract : The total synthesis, in chiral form, of unsaturated trihydroxy C_{18} fatty acids **13** and **14** as methyl esters, starting from natural tartaric acid via the key intermediate aldehyde **5** is reported.

Little is known about the biological importance of oxygenated fatty acids metabolites in vegetals. Then, it is interesting to point out that Kato and coworkers isolated from rice plants several oxygenated C_{18} fatty acids which can act as self-defense substances against rice blast disease [1]. Among these were the triols **1** to **4**.



1 : R = $-(CH_2)_3CH_3$

2 : R = 



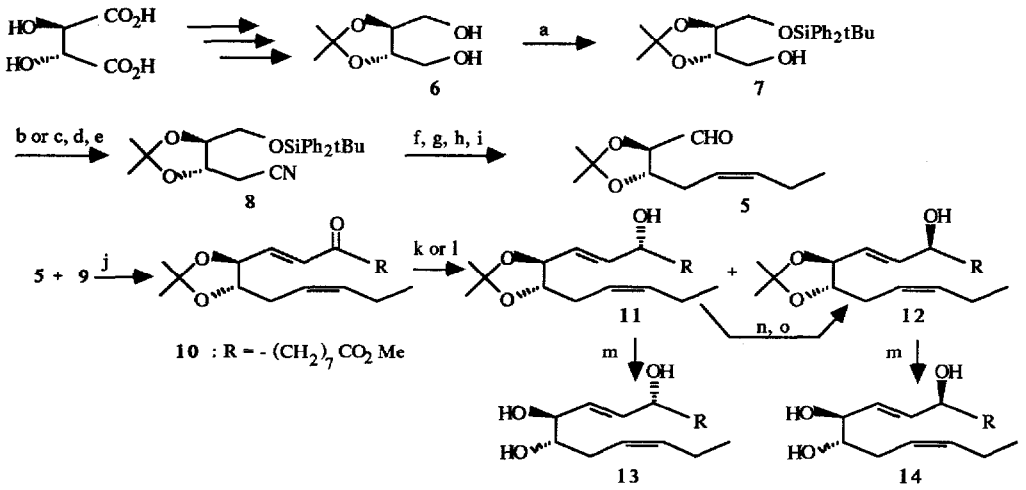
3 : R^1 = OH ; R^2 = H

4 : R^1 = H ; R^2 = OH

Due to the limited availability from natural sources, we were interested in designing a chiral synthesis which would allow the preparation of all these compounds via a key intermediate aldehyde **5**. During the course of our research, a chiral synthesis of **1** and **2** has appeared in the literature [2]. In this paper, we wish to report our own synthesis of **2** and its 9R diastereoisomer as methyl esters also starting from natural L-tartaric acid.

O-isopropylidene-L-threitol **6**, obtained by known procedures [3] was monoprotected as the silyl ether **7** [4]. One carbon homologation of the remaining alcohol function was performed by preparing the nitrile **8** via a mesylate or a tosylate and then an iodide. Elaboration of **8** to the key aldehyde **5** [$(\alpha)^{22}_D$ = + 7° (c = 1.45, $CHCl_3$)] was achieved by Dibal-H reduction of the nitrile, to the corresponding aldehyde, Wittig reaction with propylidenetriphenylphosphorane, silyl cleavage and oxidation of the primary alcohol.

Wittig condensation of **5** with methyl 10-(triphenylphosphoranylidene)-9-oxo-decanoate **9** [5] afforded the enone **10**. Luche reduction [6] afforded a 1:1 mixture of enols **11** and **12**. Using diisobutylaluminium 2,6-di-tertiobutyl-4-methylphenoxide[7], the ratio of **11** to **12** became ca. 4:1. These alcohols were separated by preparative TLC (SiO_2, 3 elutions with 2 % MeOH-CH_2Cl_2) ; the absolute 9R configuration of **11** was established by circular dichroism of the corresponding benzoate [8] (negative Cotton effect at 225 nm). **11** was also converted to its 9S diastereoisomer **12** by the Mitsunobu procedure [9] using benzoic acid followed by cleavage of the resulting benzoate with potassium carbonate in methanol. Acetonide cleavage by acidic methanol completed the sequence to afford the triols **13** from **11** and **14** from **12** respectively .



[a] t-BuPh$_2$SiCl, NaH, THF, 20°. [b] TsCl, Et$_3$N, CH$_2$Cl$_2$, 0°, 24 h, 77 %. [c] CH$_3$SO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$, - 10°, 0.75 h, 90 %. [d] NaI, acetone, (45°, 85 h with **8a** ; 50°, 80 h with **8b**, 70 %). [e] NaCN, DMF, 20°, 24 h. [f] Dibal-H, éther, - 50°, 2 h. [g] Ph$_3$P = CHC$_2$H$_5$, THF/HMPA (4 : 1), - 80 à 20°, 4 h. [h] n-Bu$_4$NF.3H$_2$O, THF, 45°, 2 h. [i] (COCl)$_2$, DMSO/CH$_2$Cl$_2$ (1 : 20) then Et$_3$N, - 60 à 0°. [j] **9**, CH$_3$CN, 80°, 2h. [k] CeCl$_3$/NaBH$_4$, MeOH, 20°, 15 mn, 85 %. [l] Dibal-H/BHT, PhCH$_3$, - 78 to 40°, 3h, 77 %. [m] HCl aq. 12M/MeOH (1 : 20), 0°C, 20 h, 89 % with **11**, 64 % with **12**. [n] Ph$_3$P, PhCO$_2$H, DEAD, THF, 20°, 3 h, 83 %. [o] K$_2$CO$_3$, MeOH, 20°, 24 h, 59 %.

The total syntheses of the other metabolites **3** and **4** via the key intermediate **5** are also under active investigation in our laboratory.

References and notes

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5 - The ylid **9** was prepared in four steps starting from azelaic acid monomethyl ester : conversion to the acid chloride by SOCl$_2$, direct obtention of methyl 10-chloro-9-oxo-decanoate by rapid addition to diazomethane, reaction with triphenylphosphine in refluxing chloroform to afford the corresponding ketophosphonium salt which was converted into the ylid **9** by simple treatment with aqueous sodium hydroxide until basic and subsequent extraction with chloroform.

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