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Total Synthesis of 11-R,12-R-Dihydroxyeicosatrienoic Acid, A Metabolite of the Cytochrome P-450 Epoxygenase Pathway

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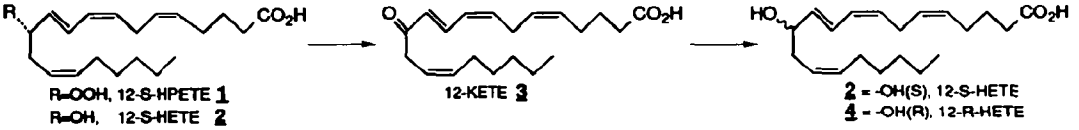
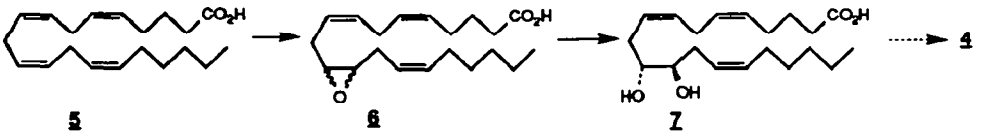
Abstract: The first total and enantioselective synthesis of 11-R,12-R-dihydroxy-5,8,14-eicosatrienoic acid **7** is reported. We have used the carbohydrate 2-deoxy-D-glucose as a masked 1,6-dialdehyde precursor **20** to perform the synthesis. The availability of this material will allow, among other things, the testing of the hypothesis that it can be a biochemical precursor to 12-R-HETE *in vivo*.

We are currently involved in the study of the metabolic transformation of the 12-lipoxygenase pathway and, in particular, the biochemical origins and transformation of 12-KETE and 12-R-HETE which are potent proinflammatory agents.[1,2,3] As a result of these and other studies,[4,5] the biochemical transformation shown in Scheme 1 is established.



Scheme 1

In the eye it has been shown that 12-R-HETE is a Na/K ATPase inhibitor, and a potent inhibitor of intraoccular pressure. Its origin in the eye, however, has been shown to be the result of a cytochrome P-450 oxidation of arachidonic acid.[6] Whereas the possibility exists that **4** is formed directly by the action of the enzyme,[7] another possible way to account for its formation is via the epoxygenase pathway as shown in Scheme 2.[7]

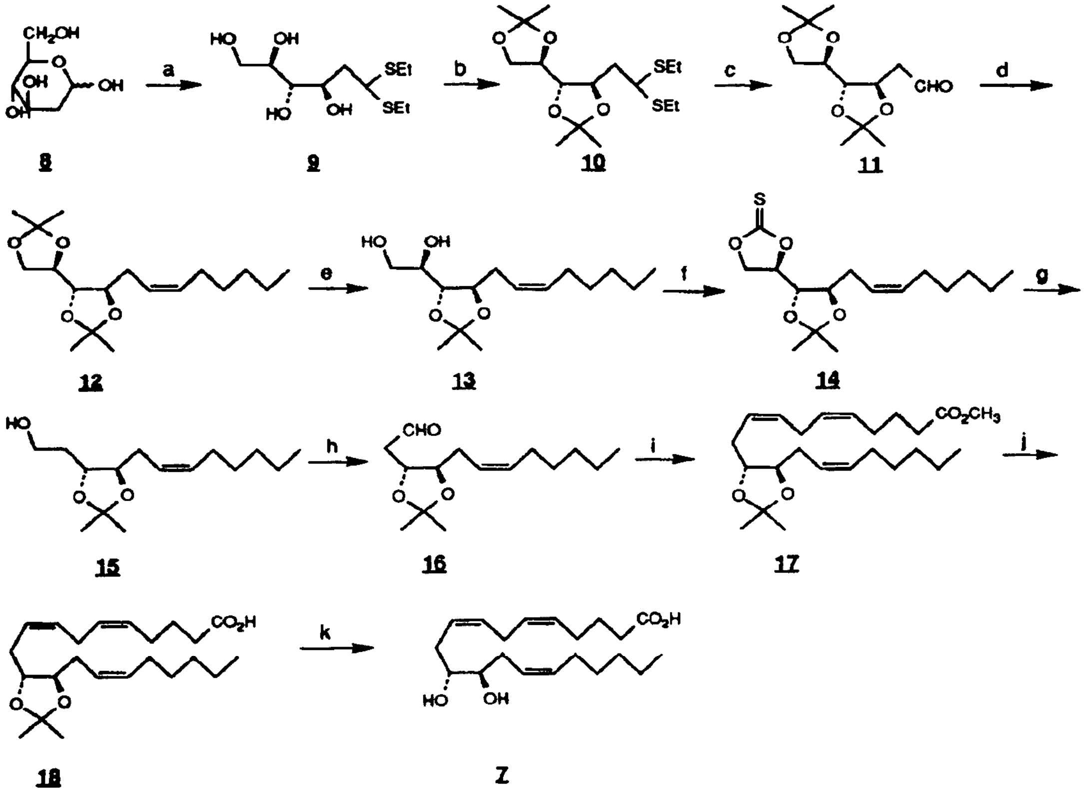


Scheme 2

The transformation of **5** to **6** is well documented.[8,9] Recent studies have shown that the 11,12-epoxides **6** can be transformed to 11,12-diols by the action of an epoxide hydrolase.[9,10] Chemical hydrolysis has also been performed and the resulting diols identified.[11] In addition, it has been shown that the 11,12-diols as a mixture are biologically active and play a role in the control of fluid and electrolyte balance in the kidney.[9] The biological activity of the individual stereoisomers has not been tested because of the their inaccessibility. We decided to perform the synthesis of diol **7** in order to evaluate its biological activity and to check its

biochemical transformation. In particular we were interested to check the hypothesis that 7 can be transformed *in vivo* by a dehydrase reaction to yield 12-R-HETE 4. The stereochemistry of the 12-OH in 7 is the same as in 4. We report here on the first total synthesis of 7 starting from commercial 2-deoxy-D-glucose, Scheme 3.

Treatment of 2-deoxy-D-glucose 8 with ethanethiol in the presence of concentrated hydrochloric acid gave the tetrahydroxy dithioacetal 9 in 95% yield.[12] Reaction of the tetraol 9 with 2,2-dimethoxypropane in the presence of a catalytic amount of PTSA generated the diacetonide dithioacetal 10 in 85% yield. Deprotection of the dithioacetal 10 with NCS and $AgNO_3$ afforded diacetonide aldehyde 11 in 90% yield. Wittig reaction of 11 with hexyl triphenylphosphonium bromide gave 12 in 80% yield. The selective hydrolysis of the diacetonide 12 with 0.8% H_2SO_4 in methanol afforded monoacetonide diol 13 in 90% yield based on



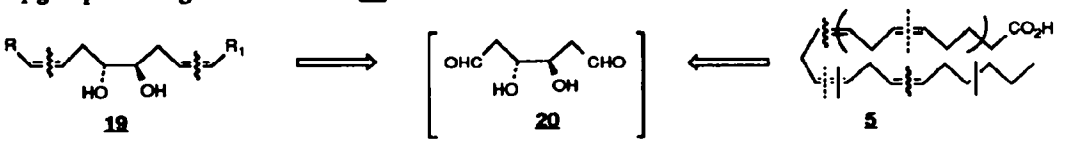
a) EtSH, HCl, 1hr. b) $(CH_3)_2C(OCH_3)_2$, PTSA, CH_3CN, room temperature, 30min. c) 4.0 eq NCS, 5.0 eq $AgNO_3$, CH_3CN/H_2O (80:20), 0°C, 5min. d) 2.0 eq hexyl triphenylphosphonium bromide, 1.5 eq BuLi, THF/HMPA (90:10), -78°C, 45min, then 11, -78°C to room temperature. e) 0.8% H_2SO_4, MeOH, room temperature, 6hr. f) 1.1 eq 1,1'-thiocarbonyl diimidazole, CH_2ClCH_2Cl, room temperature, 48hr. g) 6 eq Bu_3SnH, AIBN, toluene, reflux, 6hr. h) 2 eq $(COCl)_2$, 4eq DMSO, CH_2Cl_2, -78°C, 10min, then 15, -78°C 5min, 5 eq NEt_3, -78°C, 15min, then to room temperature. i) 1.5 eq ((3Z)-7-methoxycarbonyl-3-heptenyl)-triphenylphosphonium iodide, IPh_3P–CO_2CH_3, 1.2 eq KOBu-*t*, 0°C, 40min, 16, -78°C to room temperature. j) 15 eq LiOH/THF, room temperature, 24hr. k) 2.0M HCl/THF (2:3), room temperature, 24hr.

Scheme 3

recovered starting material.[13] Diol **13** was reacted with 1,1'-thiocarbonyl diimidazole to give monoacetonide thionocarbonate **14** in 91% yield. Reduction of **14** with tributyltin hydride in the presence of AIBN produced monoacetonide alcohol **15** in 82% yield. Oxidation of **15** with oxalyl chloride, DMSO and triethylamine gave aldehyde **16** in 79% yield. Coupling of aldehyde **16** with ((3Z)-7-methoxycarbonyl-3-heptenyl)-triphenylphosphonium iodide[3] gave the protected diol methyl ester **17** in 65% yield. Saponification of **17** gave **18** in 97% yield. Deprotection of **18** with 2M hydrochloric acid gave the 11,12-dihydroxyeicosatrienoic acid **7** in 96% yield.[14]

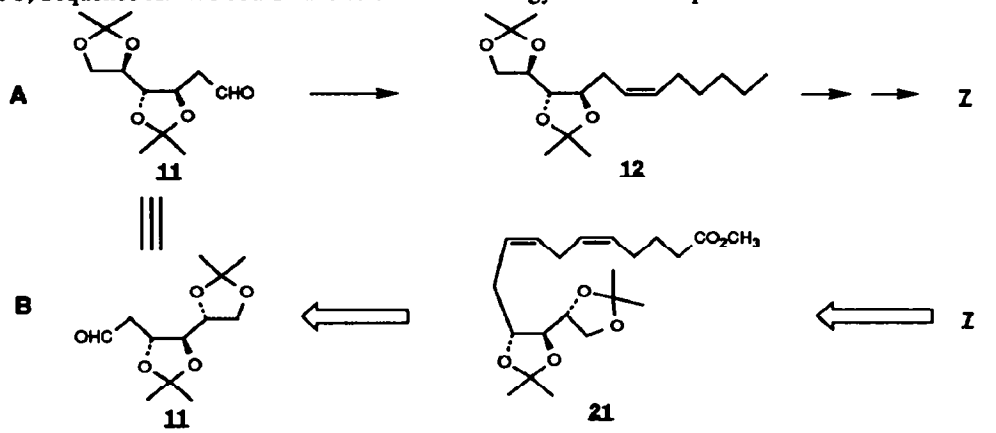
We have recently used quite extensively the thionocarbonate group such as in **14** in order to generate a secondary radical.[15] This group, originally pioneered by Barton *et al.*,[16] has received very little attention and has the advantage over the widely used methylthioxanthate derivative in that it saves two steps in the synthesis: protection and deprotection of the primary alcohol. In addition we have found that this group is more rugged and less sensitive than the thioxanthate to basic and acidic conditions.

The selection of the starting carbohydrate **8** and the synthetic design shown in Scheme 3 is predicated on our desire that the synthetic route selected be of general use. If need be, an easy access to other dihydroxy compounds such as the 5,6-, 7,8-and 14,15-dihydroxyeicosatrienoic acid could be attained by change of R and R_1 groups in the generic structure **19**.



Scheme 4

In the particular case in hand, the synthon **11** is a masked 1,6-dialdehyde **20**. The two -OH groups in **20** being *trans*, an axis of symmetry exists. In other words, the two ends of the synthon are equivalent, and one can start the synthesis from either end and obtain the same stereochemistry at C11 and C12. For example, in the synthesis shown in Scheme 3 we have used the C1 aldehyde to introduce the bottom side chain in **7** Scheme 5, Sequence A. We could have selected the strategy shown in Sequence B.



Scheme 5

The dual strategy, as illustrated in Scheme 5 for compound **7**, will allow the use of synthon **11** to perform the synthesis of various metabolites of 11,12-dihydroxyeicosatrienoic acid either from the C1-end of the molecule (Strategy A) or from the ω-end of the molecule (Strategy B). Such metabolites, for example 11,12,19- and 11,12,20-trihydroxy-5,8-14-eicosatrienoic acid, and 11,12-dihydroxy-19-oxo-5,8,14-eicosatrienoic acid, have been identified in biological milieu and can be made synthetically by using Strategy B which will permit the use of a synthon such as **21** to make all these metabolites.

ACKNOWLEDGMENTS

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12. All compounds described in Scheme 3 have satisfactory spectroscopic data.
13. The reaction is stopped at about 35% conversion in which case the only products are the diol **13** and the starting *bis* acetonide **12** which are easily separated by chromatography. On prolonged exposure to acid an increasing amount of tetranol is formed.
14. ^{1}HNMR(360MHz, $CDCl_3$) δ **7**, 0.90(t, J=7.0Hz, 3H), 1.20-1.40(m, 6H), 1.70(m, 2H), 2.05(m, 2H), 2.15(q, J=6.9Hz, 2H), 2.30-2.45(m, 6H), 2.82(m, 2H), 3.60(m, 2H), 4.02(b, 2H), 5.35-5.55(m, 6H).
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