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FUMARALDEHYDE MONODIMETHYL ACETAL : AN EASILY ACCESSIBLE AND VERSATILE INTERMEDIATE.

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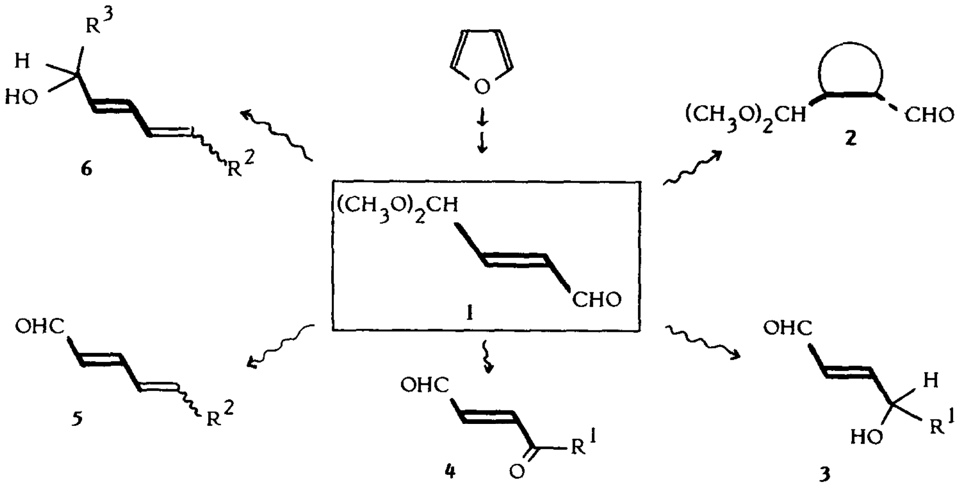
Summary - Fumaraldehyde monodimethylacetal **1** is both an easily accessible and versatile polyfunctionnal synthon ; the stereoselective preparation of various lipids from natural origin illustrates some of its synthetic possibilities.

Small and polyfunctional molecules are very useful building blocks for organic synthesis. As part of a program concerned with the use of compounds bearing masked aldehyde functions(1), we became interested in the possible applications of olefin **1**. Although known for a long time(2), this very attractive compound received only limited applications in synthesis(3), probably due to difficulties in its preparation. Recent improvements (cf. experimental section) allow now an easy synthesis of **1**, even on a large scale, in two steps from furan (61-65 % overall yield). The purpose of this Letter is :

1 - to show on simple examples the versatility of **1** (scheme 1) : dienophilic reactivity, preparation of polyfunctional olefinic or dienic derivatives,

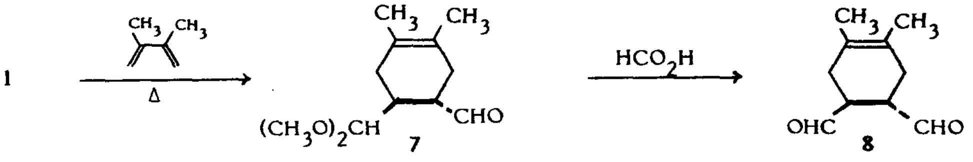
2 - to illustrate its potentialities by short stereoselective syntheses of various lipids of natural origin.

Scheme 1



I - 1 as a dienophile

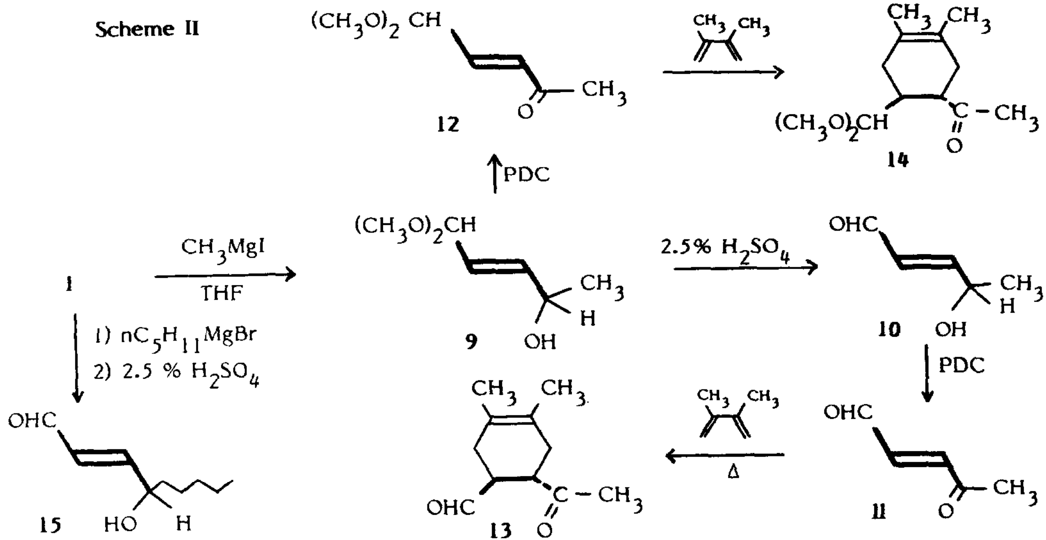
Olefin **1** reacts with dimethylbutadiene (9- fold excess) without solvent at reflux temperature to give the adduct 7 (77 % yield)(4). Both the free and the masked aldehyde functions of 7 can be used stepwise for further syntheses, for instance in Wittig type reactions(5). Formolysis (6) of 7 gives bisaldehyde **8** (72 % yield) ; the compound 1 thus behaves as a substitute for fumaraldehyde,which is both unstable and difficult to obtain in pure form(7) .



II - 1 as a precursor of polyfunctional olefins

Scheme 2 gives, on simple models, indications about the reactivity of **1** : addition of methyl Grignard leads to alcohol **9** (75 % yield) which can be easily hydrolyzed to hydroxyaldehyde **10** (76 %). The oxidation of **10** with PDC and 3 Å mol. sieves(8) gives **11**(50%). The oxidation of **9** yields (67 %) ketoacetal **12**. It is interesting to note that these useful olefins have been prepared before only by indirect routes using isoxazoline methodology (9). These derivatives react with excess dimethylbutadiene without solvent at reflux to give adducts **13** (92 %) and **14** (92 %).

Scheme II



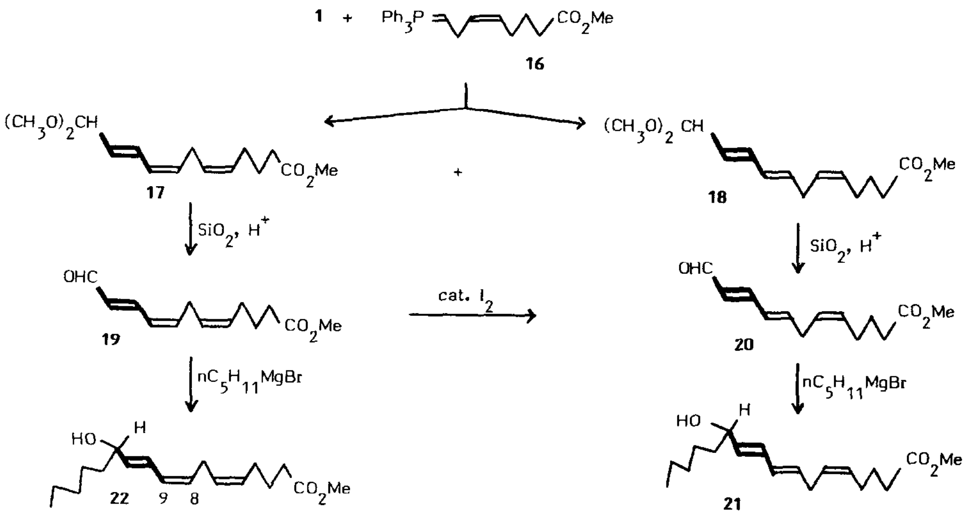
As an application of these results, we prepared from **1** in two steps (reaction with $nC_5H_{11}MgBr$ followed by hydrolysis of the acetal, 71 % overall yield) compound **15** which is a lipid metabolite with various potent biological properties (10).

Remark : Olefin **1** is also a very useful starting material for the preparation of functionnal 1,3 dienes and their corresponding organometallic complexes (11).

III - Synthesis of polyenes

Many natural products, especially in the field of lipids, have polyenic systems either conjugated with formyl groups (general type **5**) or linked to a chain with a secondary alcohol (ex. **6**). Olefin **1** can be useful in devising short and stereocontrolled syntheses of such compounds. The scheme III gives an example of such an approach.

Scheme III



Reaction of **1** with phosphorane **16**(12) gives (85 % overall yield) a 85/15 (NMR control) mixture of **17** and **18** which is directly hydrolyzed(13) (SiO_2, 5 % H_2SO_4, 80 % yield) to the mixture of **19** and **20**. These compounds have been separated by chromatography and their spectral characteristics are in excellent agreement with those obtained from natural products : the acid corresponding to **19** is a recently discovered metabolite from arachidonic acid which has significant biological activity in the activation of leucocytes(14). Its isomer **20** (also in the acid form) is a metabolite isolated from the algae Laurencia(15), and has antibiotic type properties Under iodine catalysis, it is possible to isomerize **19** into **20** (CH_2Cl_2, room temperature, 93% yield). The reaction of **20** with n-pentyl Grignard leads (50 % yield) to (±) HHT methyl ester **21**(16). Although it was known for a long time as a test molecule for the cyclooxygenase pathway, there was no simple and stereoselective synthesis of this compound(16). Under the same conditions, the aldehyde **19** gives (45 % yield) the Z isomer **22**, whose NMR data(17) are clearly different from those of **21**. To the best of our knowledge, the acid corresponding to **22** has not been characterized yet as a natural product.

In conclusion, olefin **1** appears as a very easily accessible and useful building block for organic synthesis. Further work is in progress towards the preparation of HETES and resolution of type **3** or **6** alcohols.

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Experimental - To a magnetically stirred solution of furan (88 g, 129 mmoles) in anhydrous methanol (640 ml) is added dropwise at -45°C under nitrogen a solution of bromine (68 ml, 1.02 eq.) in methanol (650 ml). At the end of the addition, the reaction mixture is stirred for two hours at -10° (ice-salt bath). Two hundred grams of powdered anhydrous Na_2CO_3 are then added portionwise over a period of about 30 min. and the reaction mixture is stirred for 18 hours at room temperature. After filtration of mineral salts and removal of the solvent, the bis dimethylacetal of fumaraldehyde is purified by vacuum distillation : Eb_{15} = 85-90°, yield : 165-175 g (72-77 %). The olefin 1 is obtained by reaction of this bisacetal with $HClO_4$ in ether or more selectively (85 % yield after distillation) using Amberlyst 15 as recently described(18) .

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