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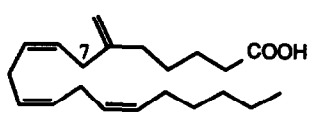
SYNTHESIS OF NEW 5 AND 6-EXOMETHYLENIC ARACHIDONIC ACID ANALOGS.

A. STOLLER, C. MIOSKOWSKI*
Université Louis Pasteur, Laboratoire de Chimie Bio-organique associé au CNRS,
Faculté de Pharmacie, 74 route du Rhin BP 24, F-67401 STRASBOURG

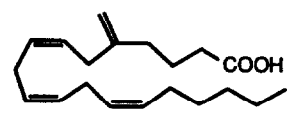
C. SEPULCHRE, F. BELLAMY*
Laboratoires Fournier, Centre de Recherches, 50 route de Dijon Daix,
F-21121 FONTAINE les DIJON

Summary: The synthesis of two new analogs of arachidonic acid bearing a 5 or a 6-exomethylenic function are reported .

The metabolism of arachidonic acid by diverse oxygenases leads to a wide variety of oxygenated compounds which form what is commonly known as the arachidonic acid cascade. Most of these metabolites are highly biologically active and are involved in important physiological and pathophysiological processes[1]. During the last decade much work has been devoted to the 5-lipoxygenase pathway leading to the leukotrienes which are implicated in respiratory diseases and inflammation processes[2]. We report herein the synthesis and the activity of two new arachidonic acid analogs[3] **1** and **2**, in which the 5-6 double bond has been replaced by an exomethylenic function.



1

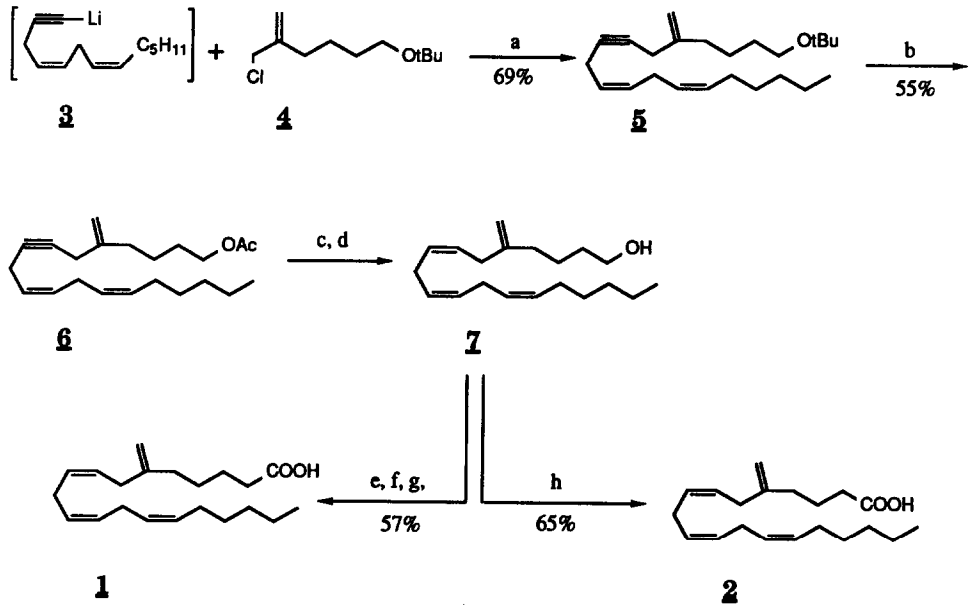


2

Scheme 1

The structures of both analogs retain four double bonds and four bis-allylic positions, in particular the one at position 7.

Coupling of the lithio dienyne **3** with the allylic chloride **4** in refluxing THF leads to compound **5** in 69% yield. Cleavage of the *t*-butyl ether function with acetic anhydride in ether in the presence of iron chloride[4] gives the correspondig acetate in 55% yield after chromatography on silicagel. Hydrolysis with lithium hydroxide in DME/H_2O leads to the alcohol **7** which is submitted to hydrogenation using Nickel P-2 at room temperature in ethanol. The nor-derivative **2** is then obtained in 65% yield by oxidation of **7** using pyridinium dichromate in DMF at room temperature[5]. On the other hand, mesylation of the alcohol **7** followed by cyanylation and hydrolysis under basic conditions gives the analog **1** in 57% yield after purification[5].

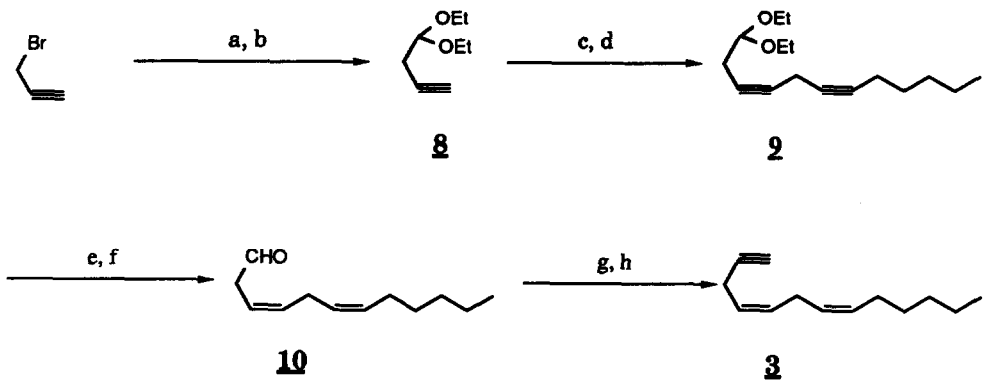


3 **4** **5** **6** **7** **1** **2**

a: THF, rflx; b: Ac_2O, $FeCl_3$, Et_2O, RT, 3h; c: LiOH, DME, H_2O, RT; d: H_2, Ni P-2, 1 atm., RT; e: MsCl, Et_3N, CH_2Cl_2; f: NaCN, DMSO; g: NaOH, EtOH, 80°C; h: PDC, DMF, RT.

Scheme 2

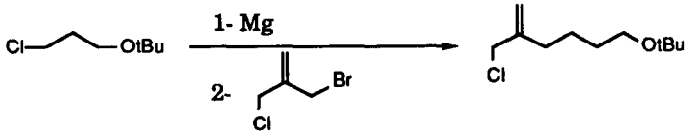
Intermediate **3** is obtained in 40% overall yield starting with the propargylic bromide **11**[6] via the acetylenic acetal **8** obtained by reacting the organoaluminium derivative with diethoxy phenoxy orthoester. Treatment with the ethyl Grignard reagent in THF and subsequent reaction with the propargylic bromide **11** leads to the diethoxy diynal **9** after chromatography on silicagel. Partial hydrogenation of the two triple bonds, in the presence of Nickel P-2, deprotection of the aldehyde and conversion to the corresponding acetylenic fonction gives **3** as shown in scheme 3.



a: Al, Et_2O; b: $HC(OEt)_2(OPh)$; c: EtMgBr, THF; d: **11** = $BrCH_2C{=}C(CH_2)_4CH_3$;
e: H_2, Ni P-2, 1atm., RT; f: TFA, CH_2Cl_2, H_2O, 0°C; g: CBr_4, PPh_3, CH_2Cl_2; h: BuLi, THF.

Scheme 3

Intermediate **4** is formed in 67% yield by reacting the Grignard derivative of chloropropanol protected as the *t*-butyl ether with the 2-bromomethyl allyl chloride chloride[7],in THF.



Scheme 4

The two arachidonic acid analogs **1** and **2**, at 10^{-5}M, strongly inhibit the formation of LTB_4 (91% and 67%) and 5-HETE (84% and 67%) in human PMN but they do not display any activity when tested at 10^{-6}M. It is interesting to note that analog **1** is slightly more active than the nor analog **2**.

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5- Satisfactory spectral data were obtained for all new componds. **1**: ($CDCl_3$ / 200Mz): 5.55-5.25 (m, 6H); 4.82 (s, 1H); 4.78 (s, 1H); 2.95-2.70 (m, 6H); 2.38 (t, J= 7.5 Hz, 2H); 2.20-1.80 (m, 4H); 1.75-1.15 (m, 10H); 0.89 (t, J= 7Hz, 3H) **2**: ($CDCl_3$ / 200Mz): 5.55-5.25 (m, 6H); 4.82 (s, 1H); 4.78 (s, 1H); 2.95-2.65 (m, 6H); 2.37 (t, J= 8 Hz, 2H); 2.22-1.92 (m, 4H); 1.92-1.72 (m, 2H); 1.57-1.12 (m, 6H); 0.89 (t, J= 7Hz, 3H)

6- Octynol is prepared by reacting the Grignard derivative of 1-heptyne with paraformaldehyde in ether.(Bp_{14}= 96-97°C). Treatment with phosphotribromide in ether in the presence of pyridine gives **11** in 68% yield after distillation (Bp_{15}: 90-92°C)

7- The 2-bromomethyl allyl chloride **13** is obtained by bromination of 2-methyl allyl chloride with NBS in CCl_4 at room temperature in the presence of benzoyl peroxide.[8] (Bp_{90}= 67-72°C).

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