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Synthesis of Rigidified Arachidonic Acid Analogues

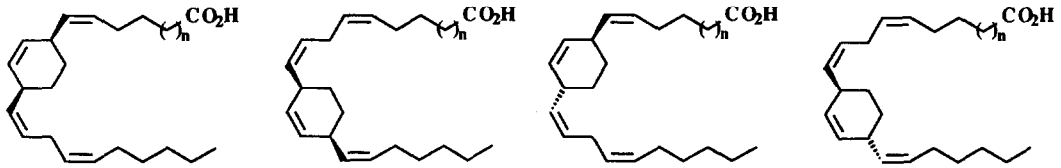
A. Stoller, C. Mioskowski*
Université Louis Pasteur, Laboratoire de Chimie Bio-organique associé au CNRS,
Faculté de Pharmacie, 74 route du Rhin BP 24, F-67401 Strasbourg

J. Millet, C. Sepulchre, F. Bellamy
Laboratoires Fournier, Centre de Recherches, 50 route de Dijon Daix,
F-21121 Fontaine-les-Dijon

Summary: *The synthesis of eight arachidonic acid analogues, rigidified by bridging the 7- and 10- or the 10- and 13- bis-allylic positions, is described.*

During the last decades, the metabolisation of arachidonic acid has been thoroughly studied [1]. This acid is converted by the 5-lipoxygenase through a multistep process into leukotriene A_4 and subsequently into all other leukotrienes [2]. These substances are mediators of important pathologies [3]. Recently, several rigidified analogues of eicosanoids have been reported [4], in particular arachidonic acid analogues presenting 5-lipoxygenase inhibitor activity [5].

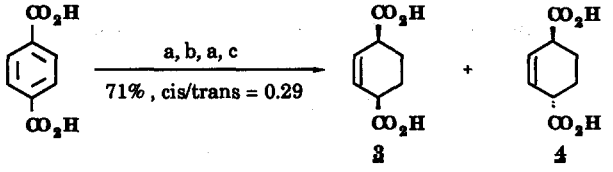
Although the stereochemistry of this process is well established [6], the mechanism is still uncertain and the conformation of the substrates as well. Several models have been proposed [7], the one of Hesp and Willard suggests a coplanarity of the 5-6 and 8-9 double bonds in order for the intermediate to have the same conformation as the product. Assuming that the abstraction of the *pro*-S-hydrogen at the 7- position and the *pro*-R-hydrogen at the 10-position is accomplished with the minimum energy requirements, we synthesized arachidonic acid analogues with rigidified conformations. The C-H bonds to be broken are weaker when their σ-orbital presents a maximum overlap with the π-orbitals of the two adjacent double bonds. By bridging two consecutive bis-allylic positions, including the 8-9 or the 11-12 double bonds into a cyclohexene ring, the bis-allylic C-H bonds on this ring are close to the desired geometry in the most stable conformation. In each case, the *cis*- and the *trans*-1,4-disubstituted cyclohex-2-enes, as well as the corresponding *nor*- analogues were obtained in racemic form and tested as inhibitors of the biosynthesis of leukotrienes (fig. 1).



7-10 , cis **1a**: n = 1 **1b**: n = 0 | 10-13 , cis **1c**: n = 1 **1d**: n = 0 | 7-10 , trans **2a**: n = 1 **2b**: n = 0 | 10-13 , trans **2c**: n = 1 **2d**: n = 0

Fig. 1

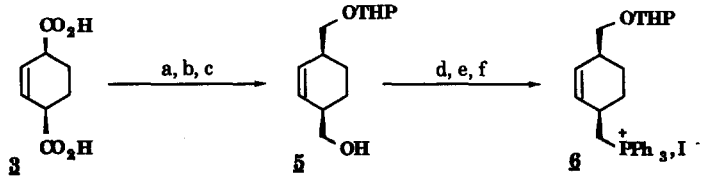
The *cis*- and the *trans*-1,4-disubstituted cyclohexene parts of our target molecules were prepared starting with terephthalic acid via *cis*- and *trans*-1,4-dicarboxylic cyclohex-2-ene acids (scheme 1). Therephthalic acid was submitted to reduction by sodium amalgam in carbonated water, followed by acid catalysed isomerization and a similar reduction step to yield the *cis*- and the *trans*- diacids (**3** and **4** resp.) which were separated by crystallization from water[8].



a: Na-Hg / CO_2 / H_2O/-5°C; b: H_3O^+/ 100°C; c: separation of the isomers by recrystallization.

Scheme 1

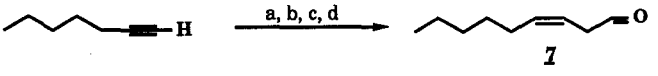
Compounds **3** and **4** were treated separately to obtain the *cis*- and the *trans*- compounds (**1** and **2** resp.). Alcohol **5** was obtained from **3** by esterification, subsequent reduction with LAH and monoprotection of the resulting diol. Alcohol **5** was then converted into the corresponding phosphonium salt **6** in a three-step sequence (scheme 2).



a: CH_2N_2 (90%); b: LAH / Et_2O (93%); c: DHP / DME / cat. H^+(43%);
d: MsCl / Et_3N / CH_2Cl_2 (94%); e: NaI / acetone / Δ (85%); f: PPh_3 / Δ (65%).

Scheme 2

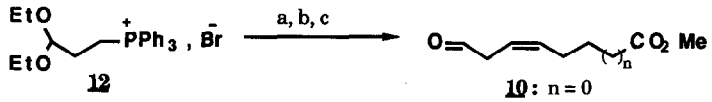
For the preparation of (Z)-non-3-enal **7** (scheme 3), heptyne was treated with ethyl grignard followed by ethylene oxide. The resulting acetylenic alcohol was reduced by catalytic hydrogenation and oxidized using Sarett's reagent [9].



a: EtMgBr; b: ethylene oxide (63%); c: H_2 / Pd / $BaSO_4$ / Py / MeOH (99%); d: $CrO_3(Py)_2$ (50%).

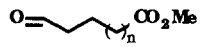
Scheme 3

The two unsaturated aldehyde-esters **10** and **11** were prepared from the corresponding aldehyde-esters **8** and **9** by a three-carbon homologation reaction using the Wittig reagent **12** [10], followed by hydrolysis of the acetalic intermediate (scheme 4).



10: n = 0
11: n = 1

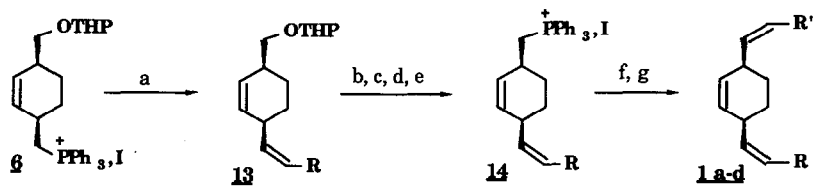
a: n-BuLi / THF; b: 8 or 9 (55%); c: TFA / H_2O / CH_2Cl_2 (93%)



8 : n = 0
9 : n = 1

Scheme 4

The *cis*- analogues bridged between the 7- and the 10- positions (scheme 5), were obtained by a first Wittig reaction of the ylide derived from phosphonium salt 6 and the unsaturated aldehyde 7. The resulting protected alcohol was then converted into the phosphonium salt 14 and used in a second set of Wittig reactions with the aldehydes 9 and 8 to lead to the normal length and to the *nor*- analogues (1a and 1b respectively).



a:i) n-BuLi / THF; ii) RCHO (30%); b: MeOH / PPTS / Δ (72%); c: MsCl / Et_3N / CH_2Cl_2 (95%); d: NaI / acetone / Δ (95%); e: PPh_3 / CH_3CN / Δ (75%); f: i) n-BuLi / THF; ii) R'CHO (20-40%); g: LiOH / DME / H_2O (80-90%).

Scheme 5

The 10-13 bridged *cis*-analogues 1c and 1d were synthesized in a similar way using n-hexanal in the first Wittig reaction and the two unsaturated aldehyde-esters 11 and 10 for the second coupling.

The four trans-analogues 2a-d were obtained separately from the *trans*-diacid 4 using similar reaction sequences.

All these compounds (fig. 1) have been tested on human polymorphonuclear cells:
In the 7-10 bridged series, compound 2b presented the highest inhibition activity of the biosynthesis of leukotriene B_4 (72% inhib. at 5.10^{-6}M) and 5-HETE (81% inhib. at 5.10^{-6}M).

In the 10-13 bridged series, the most potent compound proved to be 1d with 81% inhib. at 10^{-5}M for leukotriene B_4 and 81% inhib. at 10^{-5}M for 5-HETE .

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