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Synthesis of a rigidified fatty acid derivative containing a highly strained 1,3-bis methylenecyclopentane moiety.

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Summary: *The synthesis of a new rigidified fatty acid derivative bearing a highly strained 1,3-bis methylenecyclopentane moiety is described using Julia's olefination reaction.*

Only very few molecules containing 1,3-bis methylenecyclopentane moieties have been reported in the literature. Moreover all of them are symmetrically substituted(1). We became interested in such planar, rigid and highly strained structures during the course of our studies directed toward the metabolisation of fatty acid derivatives by 5-lipoxygenase. Recently we described the synthesis of several arachidonic acid analogs, rigidified by including the 5-6 or the 8-9 double bonds into cyclohexene rings(2). Herein we report our preliminary results concerning the synthesis of the analog **1b**, which will be extended to the synthesis of the arachidonic acid analog **1a**. The rigidification obtained by the dissymetrically substituted 1,3-bis methylenecyclopentane framework, locates carbon atoms 4 to 10 in a plane bissecting the angle formed by the two allylic C-H bonds at carbon 7. In this blocked conformation, both *pro-R* and *pro-S* hydrogens are equivalent and the corresponding σ C_7-H bonds orbitals cannot overlap any longer efficaciously with either one of the 5,6 or 8,9-π orbitals (figure 1).

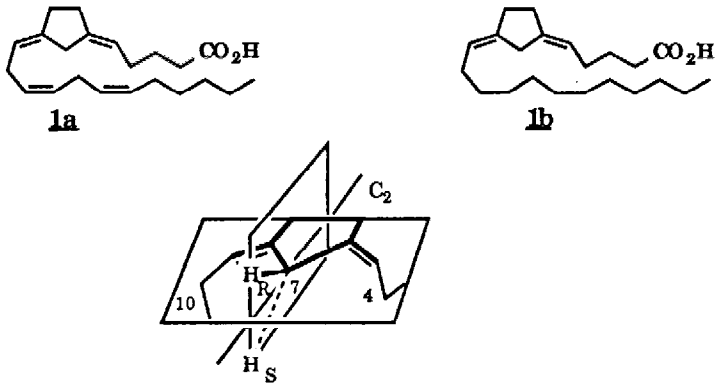
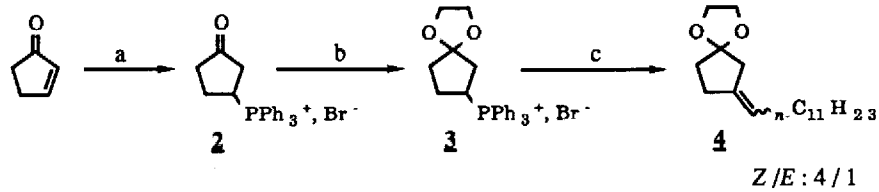


Figure 1

The procedures described in the litterature for the synthesis of 1,3-bis methylenecyclopentanic structures being unsuitable for the synthesis of **1b**, we envisaged a new approach starting from 2-cyclopentenone.

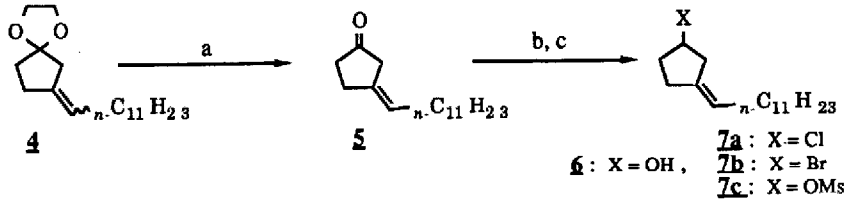
Treatment of 2-cyclopentenone with 1 equivalent of triphenylphosphine hydrobromide[3], led to the phosphonium salt **2**, which could not be converted directly to the corresponding ylide[4]. The carbonyl group of **2** had to be protected as a dioxolane to afford, after treatment with n-butyllithium and dodecyl aldehyde, a mixture of (E) and (Z)-olefins **4**. We observed an unexpected high (Z) selectivity (Z/E : 4/1), in spite of the remote position of the bulky ketalic group respective to the double bond. The two isomers were separated by careful column chromatography over kieselgel and the stereochemistry of the double bond could be assigned unambigously by NOE experiments (scheme 1).



a: PPh_3,HBr / CH_2Cl_2 , 20°C (89%); b: ethylene glycol, H^+, benzene, Δ (93%);
c: i) *n*-BuLi / THF; ii) *n*-$C_{11}H_{23}$-CHO (68%).

Scheme 1

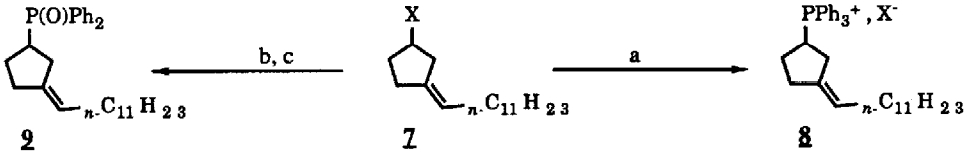
Hydrolysis of the dioxolane group of **4** , to the ketone **5** , could be achieved without migration of the double bond under Conia's conditions [5] (scheme 2).



a: H_2SO_4 10% / SiO_2 / CH_2Cl_2 (89%); b: $NaBH_4$ / EtOH, 0°C (81%); c: $SOCl_2$/ HMPA, 20°C (67% of **7a**), or CBr_4 / PPh_3 / Et_2O (61% of **7b**), or MsCl / Et_3N / CH_2Cl_2, 0°C (89% of **7c**).

Scheme 2

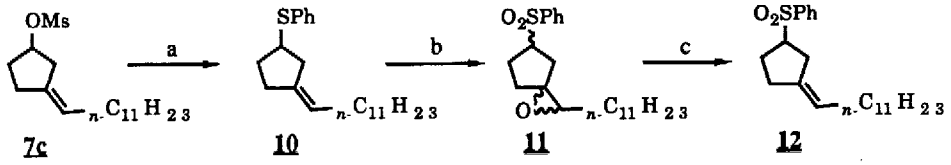
Several attempts to introduce the second double bond by standard olefination methods failed, probably due to the high strain present in the 1,3-bis methylenecyclopentane structure. Reduction of the carbonyl group by sodium borohydride afforded alcohol **6** which was converted into a leaving group (**7a**[6],**7b**[7], **7c**) (scheme 2). Phosphonium salts **8** could be obtained from these three derivatives (scheme 3), but all attempts to perform the Wittig olefination with methyl 4-formylbutyrate remained unsuccessful. As the diethyl and dimethylphosphonates could not be obtained, neither from **7a**, nor from **7b**, we synthesized the corresponding phosphine oxide. Treatment of **7c** with lithium diphenylphosphide followed by oxidation with hydrogen peroxide gave **9** in 61% yield. Unfortunately the attempted olefination reactions under various conditions gave only very poor yields (< 5%).



a: PPh_3 / CH_3CN / 80°C (60-90%); b: PPh_2Li excess / THF, 20°C; c: H_2O_2 / THF, 20°C (61%).

Scheme 3

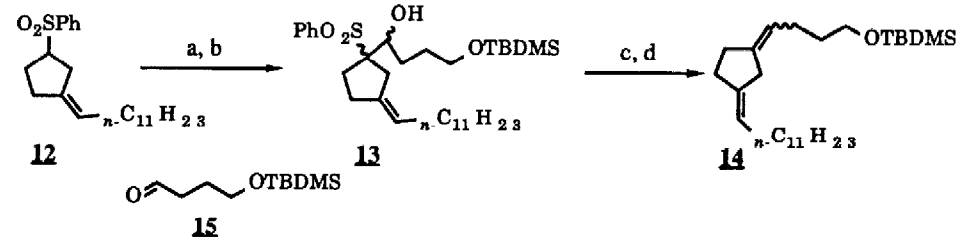
Finally, as Wittig-type olefination reactions gave no satisfactory results, we turned our attention to Julia's reaction[8] (scheme 4 and 5). Mesylate **7c** was treated with lithium thiophenoxide to generate the thioether **10**. Sulfone **12** was then obtained in 52% yield from sulfide **10** in a two-step process. Oxidation of the sulfide with *m*-CPBA afforded the epoxy-sulfone **11**, which was refluxed with potassium selenocyanate[9] in aqueous methanol, thus regenerating the double bond with retention of configuration.



a: 2.5 equiv. PhSLi / THF, 20°C (69%); b: *m*-CPBA / CH_2Cl_2 / 20°C (79%);
c: KSeCN / MeOH / H_2O, reflux (66%).

Scheme 4

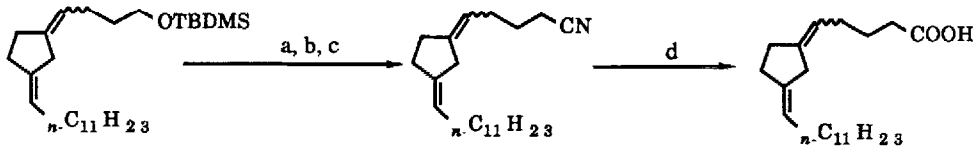
Sulfone **12**, after treatment with LDA followed by addition of the aldehyde **15**[10], gave the β-hydroxysulfone **13** (scheme 5). Conversion of the free hydroxyl group to the mesylate, and subsequent reduction with sodium amalgam in a methanol-THF mixture, afforded the olefin **14** as mixture of (E) and (Z) isomers (50/50) in 58% overall yield.



a: LDA / THF, -78°C; b: aldehyde **15**, -78°C; c: MsCl / Et_3N / CH_2Cl_2, 0°C;
d: Na-Hg / MeOH - H_2O, 20°C (58% overall).

Scheme 5

Fluoride deprotection of the hydroxyl group followed by treatment with mesyl chloride and subsequent nucleophilic displacement of the mesylate by cyanide ion in DMSO afforded the nitrile **16** which was hydrolyzed to the target acid **1b**.



14 **16** **1b**

a: TBAF / THF / 20°C (99%); b: MsCl / Et_3N / CH_2Cl_2, 0°C (99%);
c: 10 equiv NaCN / DMSO, 50°C (71%); d: NaOH / EtOH / H_2O, 100°C (85%).

Scheme 6

Compound **1b** is the first fatty acid analogue rigidified by a 1,3-bis methylenecyclopentane moiety. The introduction of the second double bond could only be achieved using Julia's olefination reaction which is a very powerful method for the elaboration of highly strained structures. The separation of the isomers as well as the preparation of the arachidonic acid analog **1a** are underway in our laboratory.

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