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Synthesis of novel aromatic analogues of 12-HETE

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Abstract—New mono- and diaromatic analogues of the arachidonic acid metabolite 12-HETE have been prepared using versatile strategies. The easily accessible monoacetal of isophtalaldehyde **3** was developed as a key intermediate for these syntheses.

1. Introduction

Polyunsaturated fatty acid metabolites are very important mediators for the regulation of cell functions in mammals. Therefore, these eicosanoids play a critical role in human health and disease. Within the lipoxygenase family,[1] the 12-LO and its corresponding metabolite 12(*S*)-hydroxy-5(*Z*),-8(*Z*),-10(*E*),-14(*Z*)eicosatetraenoic acid appears very important: it has been involved in many pathologies including inflammation, cardiovascular problems, cancer and diabetes for instance.[2] Its enantiomer, the 12(*R*)-HETE, is present in psoriatic tissue and is more proinflammatory than the 12(*S*)-isomer.[3] Both enantiomers exhibit a good activity (in the micromolar range) in antagonizing TXA_2 induced platelet aggregation, even if the 12(*R*)-isomer is slightly more potent.[4]

Since 12-HETE is unstable like most of the polyunsaturated fatty acid metabolites, it is important to design more stable analogues. Such derivatives, which maintain part of the basic skeleton of 12-HETE, should be useful in establishing structure–activity relationships and designing selective biosynthesis inhibitors as well as agonists or antagonists of action.

A simple and classical way to stabilise such eicosanoids is to replace the *E*,*Z* diene by an aromatic ring in a cyclisation–aromatisation process:[5] applied to 12-HETE, this strategy leads to a first series of monocyclic

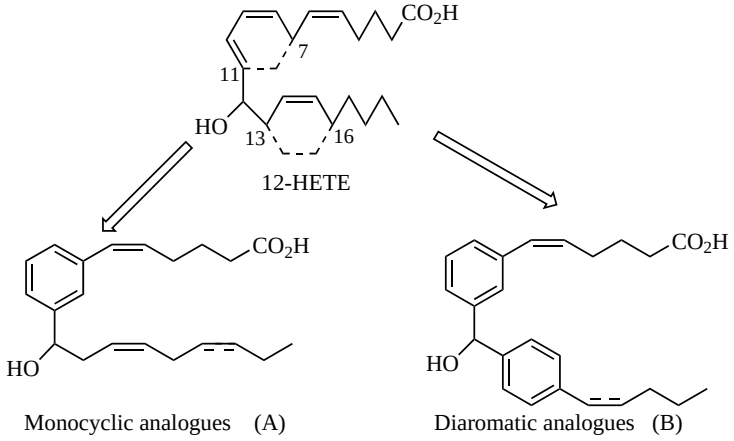

Figure 1.

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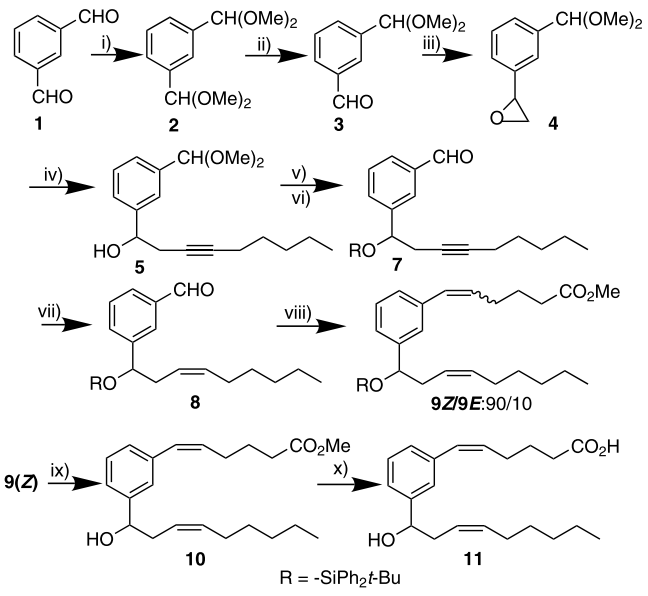
analogues (A) by junction of carbon 7 and 11. Starting from these analogues, a second aromatic ring can be introduced also between carbons 13 and 16 leading to a second family of diarylcarbinols analogues (B) (Fig. 1). As it has been well established that the nature of the fatty acid chain (ω-3 or ω-6 series) has strong effects on the biological properties of corresponding lipids, it appeared important to design a flexible synthetic strategy in order to obtain either the unsaturated or the saturated derivatives on this terminal alkyl chain.

The purpose of this paper is to report short and versatile syntheses of these derivatives.[6]

2. Synthesis of the monoaromatic analogues

The first key intermediate in these series was the monoacetal of isophtalaldehyde **3** (Scheme 1). It was best obtained by selective monodeprotection of the bisdimethyl acetal **2** (79% overall yield from **1** on a 40 mmol scale).[7,8] To introduce the lipid chain corresponding to the C_{12}–C_{20} part of 12-HETE, the best solution proved to be the opening of the easily accessible[9] styryl epoxide **4** by a propargylic nucleophile. Starting from **5**, a classical protection–deprotection strategy gave aldehyde **7**. The hydrogenation using Lindlar's catalyst led to key intermediate **8** (77% overall yield from **3**). Starting from **8**, a Wittig reaction led to a (9/1) mixture of **9*Z*** ($J_{HH}=11.6$ Hz) and **9*E*** ($J_{HH}=16.0$ Hz) separated by chromatography.



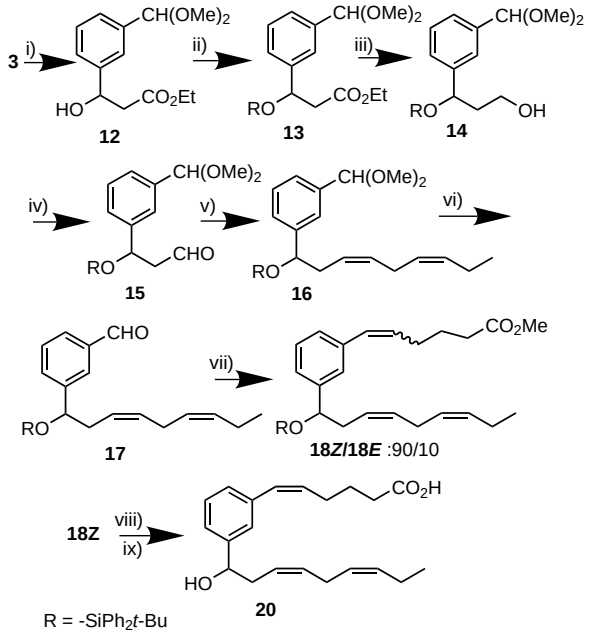
Scheme 1. *Reagents and conditions*: (i) $HC(OMe)_3$ (4 equiv.), NH_4NO_3 (cat.), MeOH (reflux, 2 h), 90%; (ii) SiO_2, 1% H_2SO_4, CH_2Cl_2 (rt, 45 min), 88%; (iii) Me_3S^+, $MeSO_4^-$ (2.2 equiv.), NaOH, CH_2Cl_2 (rt, 4 h), 85%; (iv) $H_{11}C_5C{\equiv}CLi$ (2 equiv.), HMPA/THF (from 0°C to rt, 7 h), 97%; (v) imidazole (2.5 equiv.), *t*-$BuPh_2SiCl$ (1.2 equiv.), DMF (rt, 24 h), 97%; (vi) SiO_2, 2.5% H_2SO_4, CH_2Cl_2 (rt, 1.5 h), quantitative; (vii) H_2–Lindlar's catalyst, pyridine, *n*-hexane (rt, 80 min), 97%; (viii) $Ph_3P^+(CH_2)_4CO_2HBr^-$ (1.5 equiv.), LiHMDS (3 equiv.), HMPA/THF (–80°C, 1.5 h), then Na_2CO_3, Me_2SO_4 (rt, 12 h), 87%; (ix) *n*-$Bu_4N^+F^-$ (1.3 equiv.), THF (from 0°C to rt, 15 h), 91%; (x) LiOH, THF/H_2O (rt, 15 h), acetic acid 87%.

After deprotection and saponification, the first analogue **11** was obtained in 10 steps and 42% overall yield from **1**.

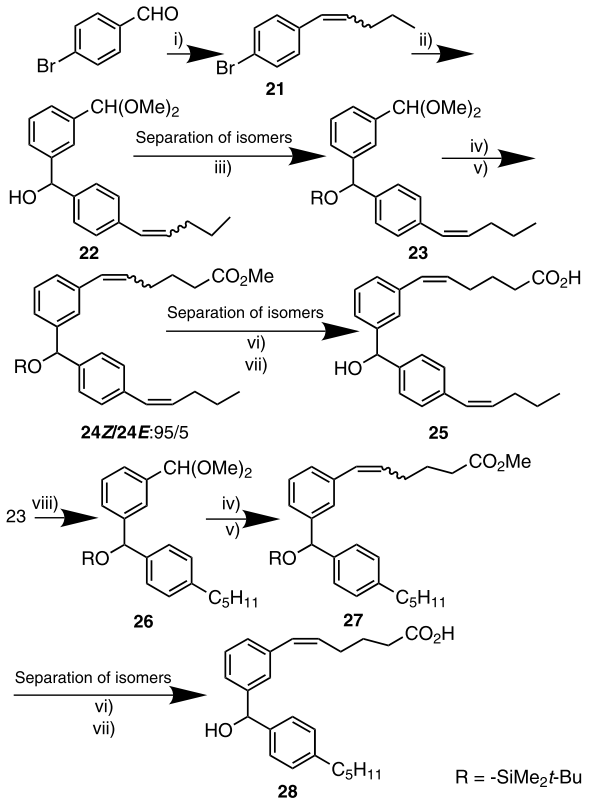
The second target molecule **20** was similar to the previous one, except for the supplementary terminal double bond designed to mimic the chain of the ω-3 fatty acids. Towards this goal, a two carbon homologation was first performed starting from **3** and using lithioacetate addition to give **12** in 79% yield (Scheme 2). The protection of the secondary alcohol, followed by reduction of the ester led to **14**. Oxidation of the latter derivative led to the sensitive aldehyde **15**, which was used directly in the next Wittig reaction to give **16**, isolated in 28% overall yield from **3**. After deprotection to aldehyde **17**, a sequence of reactions similar to the previous one led to the target molecule **20** (20% overall yield from **3**).

3. Synthesis of the diarylcarbinol analogues

For the preparation of these derivatives, the *p*-bromophenyl pent-1-ene **21** was selected as a building block for the terminal part of the molecule, corresponding to C_{13}–C_{20} of 12-HETE (Scheme 3). It was prepared



Scheme 2. *Reagents and conditions*: (i) LDA, AcOEt (1.8 equiv.), THF (–80°C, 30 min), 79%; (ii) imidazole (2.5 equiv.), *t*-$BuPh_2SiCl$ (1.2 equiv.), DMF (rt, 24 h), 91%; (iii) DIBAL-H (1.2 equiv.), Et_2O (–60°C, 1.5 h), 50%; (iv) Swern oxidation; (v) $Ph_3P^+CH_2CH_2CH{=}CHCH_2CH_3I^-$ (3 equiv.), *n*-BuLi (3 equiv.), HMPA/THF (–80°C, 4 h), 78%; (vi) SiO_2, 2.5% H_2SO_4, CH_2Cl_2 (rt, 1.5 h), quantitative; (vii) $Ph_3P^+(CH_2)_4CO_2HBr^-$ (1.5 equiv.), LiHMDS (3 equiv.), HMPA/THF (–80°C, 1.5 h), then Na_2CO_3, Me_2SO_4 (rt, 12 h), 80%; (viii) *n*-$Bu_4N^+F^-$ (1.3 equiv.), THF (from 0°C to rt, 15 h), 96%; (ix) LiOH, THF/H_2O (rt, 15 h), acetic acid, 93%.



Scheme 3. *Reagents and conditions*: (i) $Ph_3P^+(CH_2)_3CH_3Br^-$, *n*-BuLi, HMPA/THF (–80°C, 1.5 h), 82%; (ii) *sec*-BuLi (1.16 equiv.), THF (–80°C), then **3**, 97%; (iii) imidazole (2.5 equiv.), *t*-$BuMe_2SiCl$ (1.2 equiv.), DMF (rt, 15 h), 92%; (iv) SiO_2, H_2SO_4 2.5%, CH_2Cl_2 (rt, 1.5 h), quantitative; (v) $Ph_3P^+(CH_2)_4CO_2HBr^-$ (1.5 equiv.), LiHMDS (3 equiv.), HMPA/THF (–80°C, 1.5 h), then Na_2CO_3, Me_2SO_4 (rt, 12 h), 98% for **23**, 84% for **26**; (vi) *n*-$Bu_4N^+F^-$ (1.3 equiv.), THF (0°C to rt, 15 h), 91%; (vii) LiOH, THF/H_2O (rt, 15 h), acetic acid, 93%; (viii) H_2–Pd/C, AcOEt (rt, 30 min), 92%.

as a (9/1) mixture by a Wittig reaction on *p*-bromobenzaldehyde.

After metallation of **21** with *sec*-BuLi and addition to **3**, the alcohol **22** was isolated (80% yield). After separation by chromatography, the *Z* isomer was protected as the silyl ether **23**. The latter derivative was used directly for the preparation of the target molecules **25** and **28** following the previously described strategy. Deprotection of the aldehyde followed by the Wittig reaction led to a 95/5 mixture of **24***Z* and **24***E*. After separation by chromatography, desilylation and saponification, the desired acid **25** was obtained in six steps and 74% overall yield from **3**. To prepare the next target molecule, the intermediate **26** was first obtained by hydrogenation of **23**; then the same series of reactions led to **28** in seven steps and 68% overall yield from **3**.[10]

In conclusion, we have reported a short and efficient synthesis of novel 12-HETE analogues. Such derivatives will be used in order to establish structure–activity relationships in these series and to design compounds with better agonists/antagonists properties.[11]

References

1. For a recent review on lipoxygenases, see: Brash, A. R. *J. Biol. Chem.* **1999**, *34*, 23679–23682 and references cited therein.
2. Han, X.; Corey, E. J. *Org. Lett.* **2000**, *2*, 2543–2544 and references cited therein.
3. Woolard, P. M. *Biochem. Biophys. Res. Commun.* **1986**, *136*, 169.
4. Lagarde, M.; Boutillon, M. M.; Guichardant, M.; Lellouche, J. P.; Beaucourt, J. P.; Vanhove, A.; Gree, R. *Biochem. Pharmacol.* **1989**, *38*, 1863–1864.
5. For a recent example (L-6310333), see: Johnson, T. E.; Holloway, M. K.; Vogel, R.; Rutledge, S. J.; Perkins, J. P.; Rodan, G. A.; Schmidt, A. *J. Steroid Biochem. Mol. Biol.* **1997**, *63*, 1–8.
6. Gree, R.; Hachem, A. M.; Gree, D.; Le Floc'h, Y.; Rolland, Y.; Simonet, S.; Verbeuren, T. Eur. Pat. Appl. EP 650, 953; *Chem. Abstr.* **1995**, *123*, 83092.
7. The use of wet silica gel for the deprotection of acetals has been first reported in: Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63–65.
8. Experimental procedure for the preparation of **3**: (a) bisacetal **2**. A mixture of isophtalaldehyde (25 g, 186 mmol), $HC(OMe)_3$ (78 g, 4 equiv.), NH_4NO_3 (0.6 g) in anhydrous MeOH (250 mL) was heated under reflux for 2 h. After evaporation of methanol under reduced pressure, the crude product was dissolved in ether and the solution was filtered. After evaporation of the solvent, the crude bisacetal **2** was purified by distillation (yield 38 g, 90%; bp 118°C/3 mm). ^{1}H NMR (90 MHz, $CDCl_3$, δ): 7.6–7.35 (m, 4H, arom.); 5.40 (s, 2H, C<u>H</u>$(OMe)_2$); 3.32 (s, 12H, CH(O<u>Me</u>)$_2$); (b) monoacetal **3**. To a slurry of SiO_2 (40 g) in CH_2Cl_2 (140 mL) are added 15 drops of an aqueous H_2SO_4 solution (1% weight). After stirring a few minutes to homogenize, the bisacetal **2** (10 g, 44 mmol) was added. The reaction mixture was stirred for 45 min at rt. After filtration and removal of the solvent under reduced pressure, the monoacetal **3** was purified by chromatography on silica gel using as eluent a 20:80 mixture of ether and low boiling (<60°C) petroleum ether containing 1% Et_3N (yield 7 g, 88%); TLC R_f=0.24 (E:PE=20:80). IR (NaCl, film; ν cm^{-1}): 1707 (C=O); 1600–1575 (C=C arom.). ^{1}H NMR (90 MHz, $CDCl_3$, δ): 10.04 (s, 1H, C<u>H</u>O); 8.17–7.22 (m, 4H, arom.); 5.47 (s, 1H, C<u>H</u>$(OMe)_2$); 3.35 (s, 6H, CH(O<u>Me</u>)$_2$); ^{13}C NMR (22.5 MHz, $CDCl_3$, δ): 191.5 (<u>C</u>HO); 139.2; 136.1; 132.3; 129.0; 128.5; 127.8 (C arom.); 101.7 (<u>C</u>H$(OMe)_2$); 52.1 (CH(O<u>Me</u>)$_2$).
9. For the preparation and use of trimethylsulfonium methylsulfate, see: Mosset, P.; Gree, R. *Synth. Commun.* **1985**, *15*, 749–757.
10. All new compounds have spectral and analytical data in agreement with the indicate structures.
11. For instance, preliminary data indicate that **11** is equipotent to 12-HETE as inhibitor of platelet aggregation induced by collagen with a $IC_{50}=2\pm0.1$ μM.