

RESEARCH NOTE

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Synthesis of aromatic lactone analogues of Lipoxin A4

Aya Ismael[†], Muhammad Zeeshan[†] and Jørn H. Hansen^{*†}

Abstract

Objective: Synthesis of novel aromatic Lipoxin A4 lactone analogues.

Results: Novel *para*-substituted aromatic lactone analogues of Lipoxin A4 have been synthesized in a convergent manner with six steps in the longest linear sequence in 12–13% yields, employing 2-deoxy-D-ribose as a chiral pool starting material and the classical *E*-selective Wittig olefination.

Keywords: Lipoxin analogues, Aromatics, Wittig olefination, Lactones

Introduction

Lipoxins (LXs) are naturally occurring oxygenated derivatives of arachidonic acid that are produced and act at sites of inflammation [1–6]. Lipoxin A4 (LXA4) and Lipoxin B4 (LXB4) were first reported by Serhan and Samuelsson in 1984 [7]. They are biosynthesized from arachidonic acid via lipoxygenases and both LXA4 and LXB4 are known to exhibit potent and selective anti-inflammatory activity. Even though LXs play a vital role in the resolution of inflammation, their use in therapeutics is compromised because of their rapid metabolism [8–11]. This instability dramatically reduces the potential of LXs to be used as pharmacological agents, thus providing the impetus for us and others to develop syntheses of more stable analogues.

In recent decades, significant progress has been made in the synthesis of lipoxin-analogues. In the first reported synthesis by Petasis et al., the triene core of LXA4 was replaced by a more stable benzene ring, which introduced metabolic stability while conserving crucial biological activity [12, 13]. A stereoselective synthesis of aromatic LXA4 and LXB4 was reported by O'Sullivan

et al. where they utilized a series of advanced reactions (Sharpless epoxidation, Pd-mediated Heck coupling and diastereoselective reductions) to achieve the desired stereochemistry. The resulting analogs exhibited increased phagocytotic activity compared to the native LXA4 [6]. A number of other synthetic strategies have also been reported [14–21]. In this paper, we describe a different and potentially more flexible approach to the synthesis of aromatic lipoxin analogues in their lactone forms using simple and available starting materials and the classical Wittig olefination to craft the central double bond. This research note reports on the performance of our synthetic approach to two novel lipoxin A4 analogues.

Main text

Results and discussion

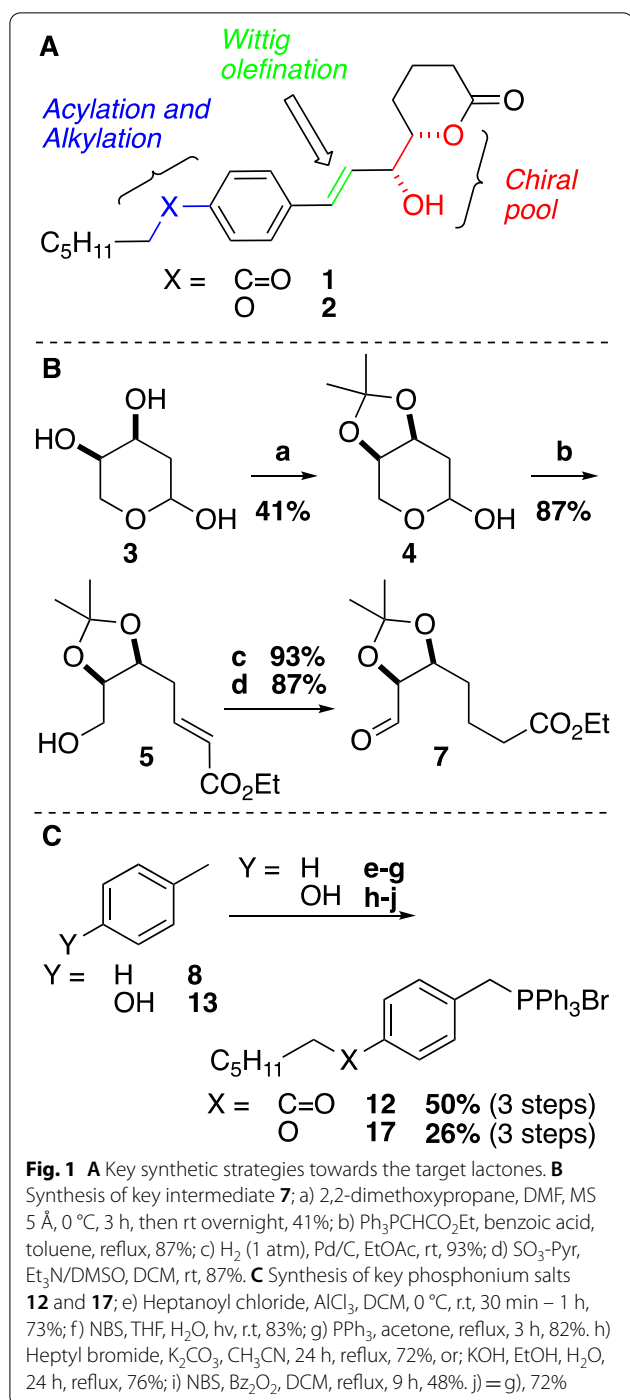
We envisioned a synthetic strategy as outlined in Fig. 1A in which the aliphatic side chain would be connected via Friedel-Craft acylation and phenolate alkylation to generate the ketone and ether analogues **1** and **2**, respectively. The chiral diol moiety can be harvested from the chiral pool via an enantiomerically pure, commercially available 2-deoxy-D-ribose. The central double bond could be crafted via an *E*-selective Wittig-olefination.

The chiral pool fragment is introduced from aldehyde **7** (Fig. 1B), set up for the key Wittig olefination, which was synthesized starting from commercial 2-deoxy-D-ribose

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(3). In a four-step procedure, protecting the diol moiety as a cyclic acetal via acid-catalysis, followed by a tandem ring-opening/Wittig olefination, Pd-catalyzed hydrogenation of the α , β -unsaturated double bond and a Parikh-Doering oxidation of the resulting alcohol, the aldehyde **7** was formed in overall 29% yield from **3**. The appropriate phosphonium salts for the key Wittig olefination (**12** and

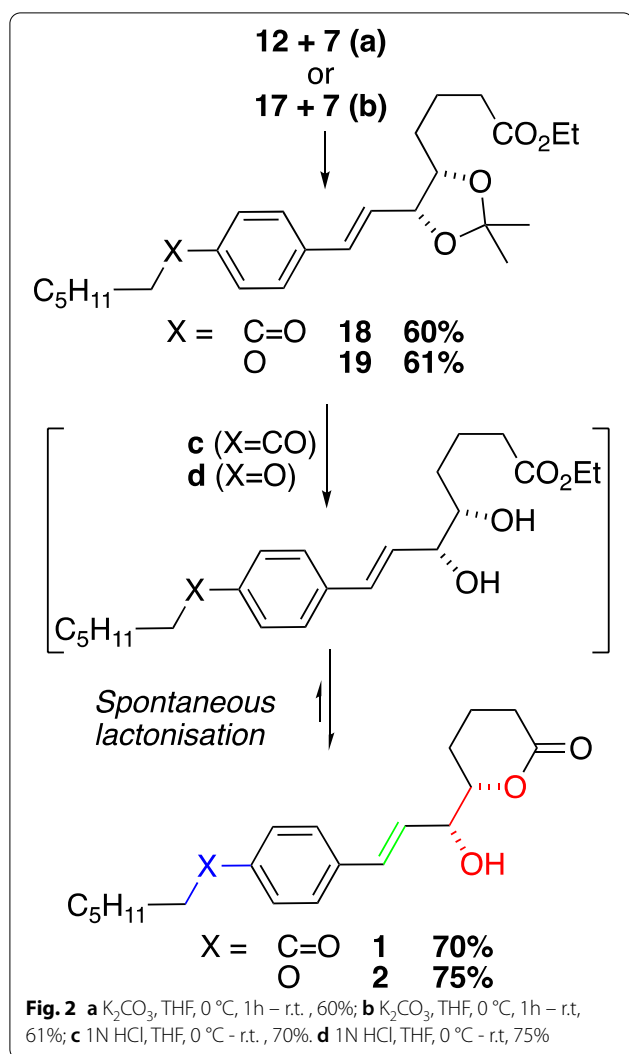
17) were generated from toluene (**8**) and *p*-cresol (**13**), respectively (Fig. 1C). **8** was subjected to Friedel-Craft acylation with heptanoyl chloride, followed by light-induced benzylic radical bromination and subsequent nucleophilic displacement with triphenylphosphine to generate ketone **12** in 50% yield over 3 steps. **13** was treated with hexyl bromide and base, followed by benzylic bromination with *N*-bromosuccinimide (NBS) and the final nucleophilic displacement with triphenylphosphine to form phosphonium salt **17** in overall 26% over 3 steps. The typical Wohl-Ziegler benzylic mono-bromination could not be achieved in the system with the electron-donating alkoxy-group. An acceptable conversion to the benzylic bromide was achieved with NBS and a catalytic amount of dibenzoyl peroxide in the presence of dichloromethane (48% yield). A number of reported conditions for phosphonium salt formation initially failed for the formation of **17** but, it was found that a relatively short reaction time (3 h in refluxing acetone) was crucial to achieve 72% yield in this step.

The phosphonium salts **12** and **17** were treated with base and the resulting ylides coupled with aldehyde **7** in Wittig olefinations to yield the desired products **18** and **19** in 60% and 61% yields respectively (Fig. 2). We were unable to extract the *E/Z*-ratios from the Wittig olefination steps from the raw data but minor peaks appear in spectra of purified materials. The final removal of the acetal group from both **18** and **19** under acidic conditions gave 70% and 75% yields of the target lactones **1** and **2**, respectively. The unprotected diol esters were not detected directly but are likely intermediates in the formation of the lactones via spontaneous cyclization.

In summary, we have successfully synthesized two novel *trans*-substituted aromatic lactone analogues of Lipoxin A4 in a convergent manner with six steps in the longest linear sequence using simple transformations and affordable reagents in overall 12–13% yield.

Methods

All reagents and solvents were purchased from commercial sources. The progress of the reactions were monitored by thin-layer chromatography (TLC) using Merck pre-coated silica gel plates (60 F₂₅₄). The TLC plates were visualized using either ultraviolet light or by immersion in a solution of phosphomolybdic acid, followed by heating. For preparative purification, flash column chromatography was carried out using silica gel from Merck (Silica gel 60, 0.040–0.063 mm). The intermediates and products were characterized by NMR on a 400 MHz Bruker Avance III HD. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak (CDCl₃: δ_H 7.26 and δ_C 77.16; methanol-*d*₄: δ_H 3.31 and δ_C 49.00, deuterium oxide: δ_H 4.79 and δ_C 49.00; DMSO-*d*₆: δ_H 2.51 and



δ_{C} 39.52). The raw data was analysed with MestReNova (Version 10.0.2–15,465). High-resolution mass spectra were obtained on a Thermo electron LTQ Orbitrap XL spectrometer, which was operated in electrospray ionization mass spectrometry (ESI) mode. The data was analyzed with Thermo Scientific Xcalibur software. Infrared spectra were recorded on a Varian 700e FT-IR spectrometer and bands are reported in wavenumbers (cm^{-1}).

Detailed synthetic procedures and analytical data can be found in Additional file 1.

Limitations

The initial protection of the chiral pool sugar **3** is difficult to achieve in high yields and is a weak point in this synthetic strategy. Moreover, the benzylic radical bromination of electron-rich aromatics is a clear limitation of the synthesis of the phosphonium salts. Alternative strategies

for this could be considered, e.g. direct chloromethylation. A third limitation appears to be that isomers generated in the key Wittig olefination step are difficult to separate.

Abbreviations

LXs: Lipoxins; LXA4: Lipoxin A4; LXB4: Lipoxin B4; DMF: Dimethyl formamide; MS: Molecular sieves; rt: Room temperature; DMSO: Dimethyl sulfoxide; DCM: Dichloromethane; NBS: N-Bromosuccinimide; THF: Tetrahydrofuran; Bz: Benzoyl; TLC: Thin-Layer Chromatography; NMR: Nuclear Magnetic Resonance; FT-IR: Fourier Transform-Infrared Spectroscopy.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13104-022-05917-4>.

Additional file 1. Experimental procedures, equipment, spectroscopic and analytical data for compounds presented in the manuscript.

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Authors' contributions

AI and MZ contributed equally to this manuscript. AI and MZ conducted experiments, analyzed data and contributed to manuscript. JHH designed research, supervised experiments, analyzed data and contributed to manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Spectroscopic data for all intermediates and final products can be found in a separate additional file and is also available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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