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Total synthesis of aspirin-triggered 15-*epi*-lipoxin A_4

Ana R. Rodríguez and Bernd W. Spur*

Department of Cell Biology, University of Medicine and Dentistry of New Jersey, SOM, Stratford, NJ 08084, USA

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Abstract—The total synthesis of aspirin-triggered 15-*epi*-LXA_4 has been achieved using a chiral pool strategy for the C1–C12 fragment starting from 2-deoxy-D-ribose. Sharpless catalytic AE generated the C15 chiral center with >98% ee. The stereospecific (*Z*)-reduction of the conjugated trienyne to the tetraene was achieved with Zn(Cu/Ag) in aq. CH_3OH at rt.

In 1984, Samuelsson and Serhan isolated a new class of arachidonic acid metabolites. These compounds, produced by cell–cell interaction, were named lipoxin A and B.[1] Their structures have been established by total syntheses.[2–8] The lipoxins showed potent biological activities distinct from other eicosanoids.[9–13] Lipoxin A_4 was identified in the bronchoalveolar lavage fluid of humans with different lung diseases.[14] We could demonstrate that inhaled lipoxin A_4 blocked the bronchoconstriction of leukotrienes in asthmatic subjects.[15] More recently Serhan et al. discovered that aspirin triggers a switch in the biosynthesis of lipoxins and initiates the formation of 15-*epi*-lipoxin A_4 (**1**), that is biologically more active than LXA_4 as an anti-inflammatory agent. Subsequent studies showed that **1** was twice as active as dexamethasone in animal models.[16,17] Due to their minute quantities from natural sources and in order to explore their full potential as a new lead structure for anti-inflammatory drugs, it is necessary to obtain sufficient quantities by chemical synthesis. We have previously reported the total synthesis of LXA_4 and LXB_4.[18] In this communication we describe the total synthesis of aspirin-triggered 15-*epi*-lipoxin A_4 (**1**). As shown in the retrosynthetic analysis (Fig. 1) 2-deoxy-D-ribose (**4**) and 2-(*E*)-octen-1-ol (**5**) were the required starting materials.

The key fragment A (**2**) was obtained from 2-deoxy-D-ribose (**4**) in seven steps as outlined in Scheme 1. Compound **4** was transformed to its isopropylidene derivative **6** with 2-methoxypropene and cat. PPTS in EtOAc. Wittig reaction of **6** with methyl (triphenylphosphoranylidene)acetate in THF at reflux-followed by catalytic hydrogenation with Rh (5 wt.% on alumina) in MeOAc afforded **7** in 65% overall yield.[19] Swern oxidation of **7** with SO_3·Py/DMSO in CH_2Cl_2 at 0°C gave the aldehyde **8** in 86% yield after chromatography.[20] Wittig reaction of **8** with [2(*E*)-5-

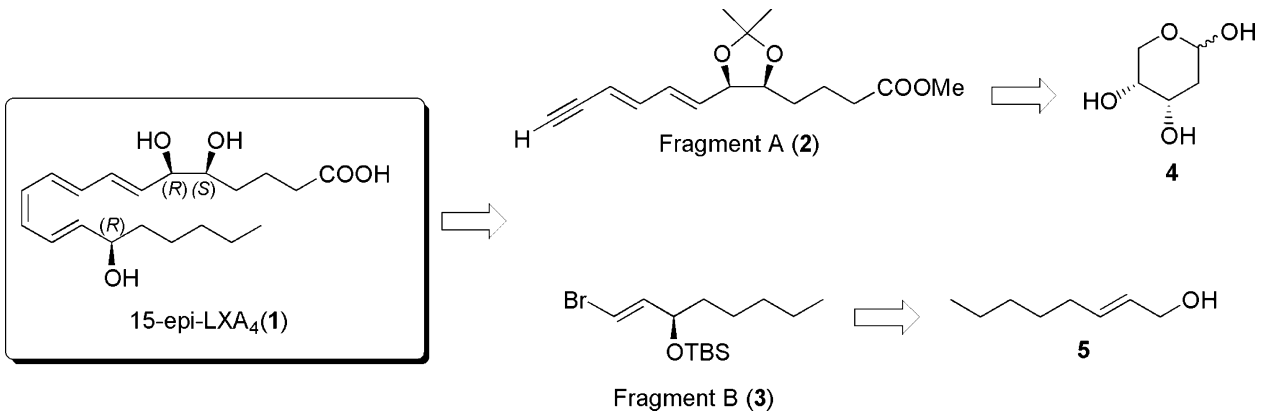

Figure 1.

Keywords: palladium catalyst; eicosanoids; Katsuki–Sharpless reaction; reduction.

* Corresponding author. Tel.: +1-856-566-7016; fax: +1-856-566-619; e-mail: spurbw@umdnj.edu

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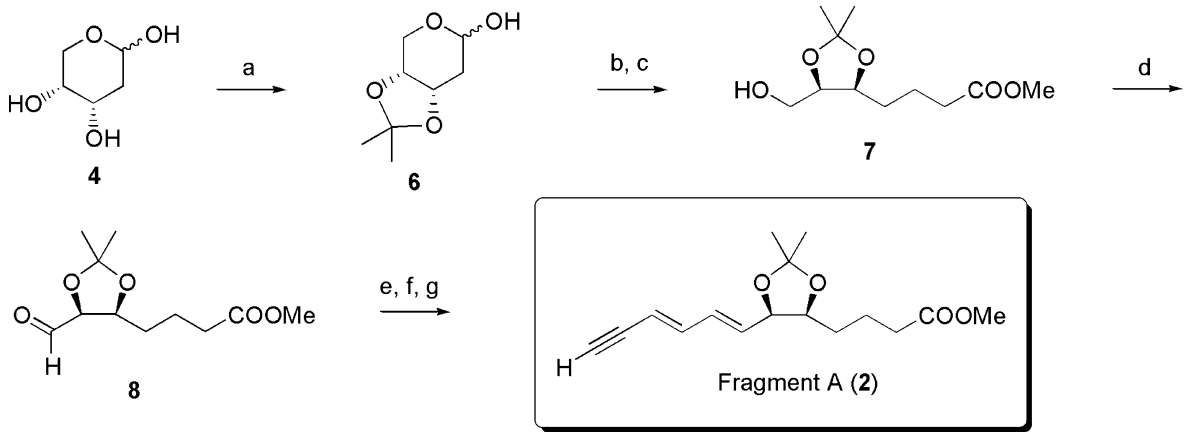


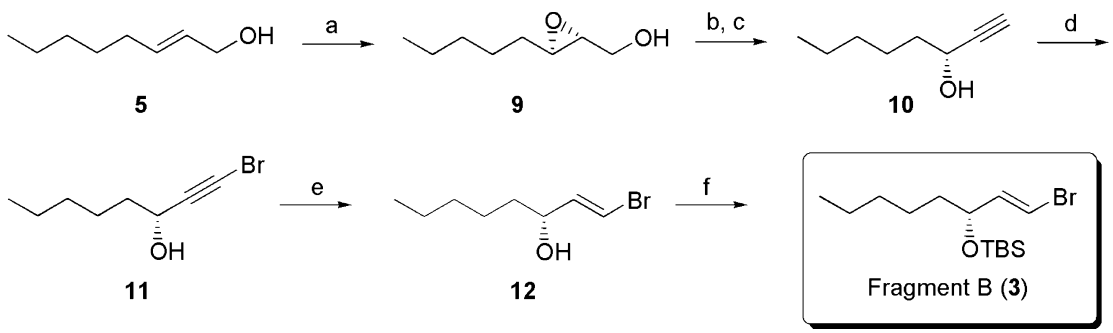
Scheme 1. *Reagents and conditions*: (a) 2-Methoxypropene, PPTS cat., EtOAc, rt; (b) $Ph_3P{=}CH{-}COOMe$, benzoic acid cat., THF, reflux; (c) H_2, Rh (5 wt.% on alumina), MeOAc, rt; (d) $SO_3{\cdot}Py$, DMSO, Et_3N, CH_2Cl_2, 0°C; (e) (*E*)-TMS–C≡C–CH=CH–CH_2–$P^+Ph_3Br^-$, *n*-BuLi, THF, −78°C; (f) I_2, benzene, rt; (g) KF, 18-crown-6, DMF, rt.

trimethylsilyl-2-penten-4-ynyl] triphenylphosphonium bromide/*n*-BuLi in THF at −78°C,[3] followed by isomerization with a catalytic amount of iodine in benzene and cleavage of the TMS-group with KF and 18-crown-6 (5%) in DMF gave fragment A (**2**) in 75% yield.

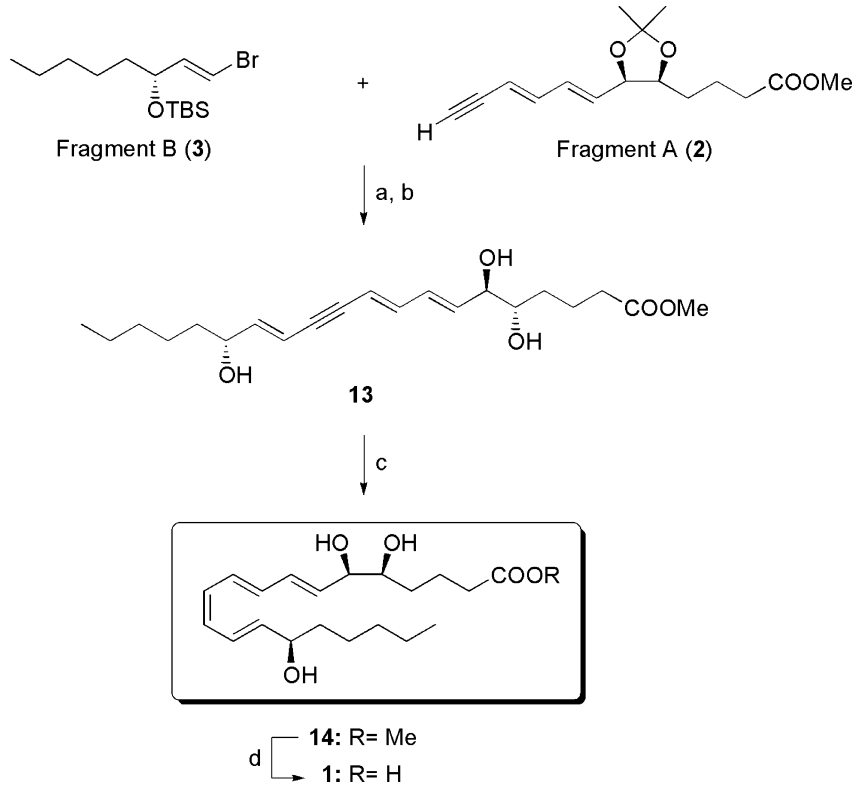
The second required fragment, fragment B (**3**), was readily available from 2(*E*)-octen-1-ol (**5**) as outlined in Scheme 2. Sharpless cat. AE gave the epoxy alcohol **9** which was obtained with >98% ee after simple recrystallization from hexane at 4°C.[21] Compound **9** was converted to (*R*)-1-octyn-3-ol (**10**), similar as described by Yadav,[22,23] and further transformed into the 1-bromo-1-alkyne **11** with NBS, in the presence of a cat. amount of $AgNO_3$, in quantitative yield.[24] The stereoselective reduction to the *trans*-vinylbromide **12** was accomplished with $LiAlH_4/AlCl_3$ in ether at 0°C in 83% yield.[25] Neither $LiAlH_4$ alone nor Red–Al® gave satisfactory results.[26] Standard silyl protection of the hydroxy group in **12** with TBSCl and imidazole in DMF gave **3** in 84% yield.

Coupling of **2** with **3** in the presence of $Pd°/Cu^I$,[3,27] followed by simultaneous deprotection of the isopropylidene and silyl groups with 2N HCl in $THF/CH_3OH/H_2O$ afforded crystalline **13** in 71% yield. The semihydrogenation of triple bonds in the presence of conjugated double bonds is still a challenging task. Lindlar reduction and modifications produced to some extent the all *trans* isomer and/or the over-reduced products.[3,28,29] However, the method introduced by Boland using Zn(Cu/Ag) in aq. MeOH at rt gave excellent results.[30,31] No sign of over-reduction was observed even after 36 h reaction. The preparation of the Zn(Cu/Ag) had to be modified, only if the Zn was activated with 2N HCl for 1–2 min, prior to the preparation of the alloy, a clean reaction occurred.[32,33] The so prepared alloy was dried under vacuum and could be stored for extended periods of time at −20°C under argon. Mild alkaline hydrolysis of 15-*epi*-LXA_4 methyl ester (**14**) at 0°C in THF followed by acidification and extraction with EtOAc gave 15-*epi*-lipoxin A_4 (**1**) (Scheme 3).

In conclusion, a concise total synthesis of aspirin-triggered 15-*epi*-LXA_4 has been achieved,[34] which makes this interesting compound available for further biological and pharmacological testing.



Scheme 2. *Reagents and conditions*: (a) Dimethyl D-(−) tartrate (15%), Ti(*i*-PrO)$_4$ (10%), TBHP, CH_2Cl_2, −25 to 15°C; (b) CCl_4, Ph_3P, $NaHCO_3$ cat., reflux; (c) LDA (5 equiv.), THF, −30°C→rt; (d) NBS, $AgNO_3$ cat., acetone, rt; (e) $LiAlH_4$, $AlCl_3$, ether, 0°C; (f) TBSCl, imidazole, DMF, 0°C→rt.



Scheme 3. *Reagents and conditions*: (a) $Pd(PPh_3)_4$, CuI, *n*-$PrNH_2$, benzene, rt; (b) 2N HCl, THF/CH_3OH/H_2O, rt; (c) Zn(Cu/Ag), aq. CH_3OH, 25–30°C; (d) 1N LiOH, THF, 0°C, then H^+ pH 5.5.

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32. Zn (1.05 g, 16.1 mmol) was stirred for 2 min with 2N HCl (5 mL) under argon. The residue was washed with 2N HCl (3×5 mL) and H_2O (5×5 mL) before it was resuspended in H_2O (6 mL) under argon. $Cu(OAc)_2 \cdot H_2O$ (105 mg, 0.53 mmol) was added and stirred for 15 min, then $AgNO_3$ (105 mg, 0.62 mmol) was added and stirred for 15 additional min. The Zn(Cu/Ag) alloy was filtered through a glass frit and washed successively with H_2O (20 mL), CH_3OH (20 mL), acetone (20 mL) and ether (20 mL). The powder was dried under vacuo and stored at −20°C under argon. To a solution of **13** (10 mg, 0.027 mmol) in CH_3OH (10 mL) under argon was added H_2O (5 mL) followed by Zn(Cu/Ag) (300 mg). The suspension was stirred in the dark at 25–30°C for 15 h. HPLC/API–ES/MS showed complete transformation to **14**. The suspension was diluted with CH_3CN (20 mL) and filtered. Evaporation under reduced pressure followed by HPLC purification gave **14** in 77% yield. [Column: Zorbax SB–C18 21.2×250 mm; CH_3OH/H_2O 65/35; flow: 10 mL/min; R_t 53 min]. UV (CH_3CN) λ_{max} 289, 302, 316 nm (ε= 70000).
33. When the reaction was performed in CD_3OD/D_2O the 11,12-dideuterio-15-*epi*-LXA_4 methyl ester was cleanly produced.
34. Satisfactory spectroscopic data were obtained for all compounds. Selected spectra: Compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.4 (t, J=6.6 Hz, 1H), 2.0 (br. s, 1H), 1.8–1.6 (m, 2H), 1.5–1.4 (m, 2H), 1.4–1.2 (m, 4H), 0.9 (t, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 81.28, 63.41, 44.76, 37.54, 31.30, 24.58, 22.40, 13.81. Compound **3**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.2 (m, 2H), 4.2–4.0 (m, 1H), 1.6–1.2 (m, 8H), 1.0–0.8 (s overlapping t, 12H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 141.17, 105.48, 73.09, 37.70, 31.65, 25.72 (3C), 24.45, 22.48, 18.07, 13.90, −4.64, −4.99. Compound **2**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.7 (dd, J= 15.6, 10.8 Hz, 1H), 6.3 (dd, J=15.3, 10.8 Hz, 1H), 5.7 (dd, J=15.3, 7.8 Hz, 1H), 5.6 (dd, J=15.6, 2.3 Hz, 1H), 4.5 (t, J=7.8 Hz, 1H), 4.2–4.1 (m, 1H), 3.6 (s, 3H), 3.0 (d, J=2.3 Hz, 1H), 2.3 (t, J=7.5 Hz, 2H), 1.9–1.6 (m, 2H), 1.5 (s, 3H), 1.5–1.3 (m, 2H), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.82, 142.33, 132.41, 131.93, 111.03, 108.49, 82.57, 80.01, 78.61, 78.16, 51.39, 33.64, 29.90, 28.07, 25.47, 21.61. Compound **13**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.6 (dd, J=15.6, 10.8 Hz, 1H), 6.4–6.3 (dd, J=15.0, 10.8 Hz, 1H), 6.2–6.1 (dd, J=15.9, 6.3 Hz, 1H), 5.9–5.7 (m, 3H), 4.2–4.1 (m, 2H), 3.8–3.6 (m, 1H), 3.7 (s, 3H), 2.4–2.3 (t, J=7.0 Hz, 2H), 1.9–1.6 (m, 5H), 1.6–1.2 (m, 10H), 0.9 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.28, 145.90, 140.52, 133.26, 132.27, 112.34, 109.91, 90.79, 89.28, 75.23, 73.80, 72.37, 51.55, 36.94, 33.62, 31.63, 31.30, 24.84, 22.48, 20.96, 13.89. Compound **14**: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.9–6.7 (m, 2H), 6.5–6.3 (m, 2H), 6.2–6.0 (m, 2H), 5.9–5.7 (m, 2H), 4.2–4.1 (m, 1H), 4.1–3.9 (m, 1H), 3.6 (s, 3H), 3.6–3.4 (m, 1H), 3.1 (d, J=5.4 Hz, 1H), 2.9–2.8 (m, 2H), 2.4–2.3 (t, J=7.2 Hz, 2H), 1.9–1.6 (m, 2H), 1.6–1.4 (m, 2H), 1.4–1.2 (m, 8H), 0.9 (t, J=6.9 Hz, 3H); ^{13}C NMR (CD_3CN, 75.5 MHz): δ 174.27, 139.34, 134.32, 133.61, 131.91, 129.73, 129.26, 128.22, 124.93, 75.37, 74.17, 71.84, 51.13, 37.47, 33.70, 31.78, 31.73, 25.12, 22.56, 21.44, 13.53. Compound **1**: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.8–6.6 (m, 2H), 6.4–6.2 (m, 2H), 6.1–5.9 (m, 2H), 5.9–5.7 (2 dd, J=14.4, 6.6 Hz and J=15.3, 6.6 Hz, 2H), 4.1–4.0 (m, 1H), 4.0–3.9 (m, 1H), 3.5–3.4 (ddd, J=9.3, 4.5, 3.3 Hz, 1H), 2.3–2.2 (t, J=7.2 Hz, 2H), 1.8–1.6 (m, 2H), 1.6–1.4 (m, 2H), 1.4–1.2 (m, 8H), 0.9 (t, J=6.9 Hz, 3H); ^{13}C NMR (CD_3CN, 75.5 MHz): δ 174.85, 139.57, 134.58, 133.86, 132.12, 129.96, 129.50, 128.44, 125.18, 75.57, 74.44, 72.05, 37.69, 33.64, 31.98, 31.94, 25.30, 22.74, 21.56, 13.69.