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Total synthesis of lipoxin A_4 and lipoxin B_4 from butadiene

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Abstract

The total synthesis of LXA_4 and LXB_4 has been achieved starting from butadiene via palladium catalyzed telomerization. Sharpless catalytic AE and C-2 inversion of the 2(*S*),3(*S*)-epoxy alcohols, using Myers CO_2/Cs_2CO_3 procedure, generated the asymmetric centers. The flexibility of the strategy allows an easy access to the linear eicosanoids.

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

Samuelsson and Serhan investigated the interaction between lipoxygenase pathways and isolated two new compounds, lipoxin A_4 (**1**) and lipoxin B_4 (**2**).[1,2] These metabolites of arachidonic acid contain a conjugated tetraene structure. Earlier reports showed that LXA_4 and LXB_4 blocked the effects of PAF and LTB_4 in human cells.[3–6] In animal models of inflammation the activity of LXA_4 was comparable to corticosteroids.[7] LXA_4 was identified in the bronchoalveolar lavage fluid of humans with different lung diseases.[8] We could demonstrate that inhaled lipoxin A_4 blocked the bronchoconstriction of leukotrienes in asthmatic subjects.[9]

Chemical syntheses of LXA_4 (**1**) and LXB_4 (**2**) are required to produce sufficient quantities to study their biological and pharmacological properties.[10–15] 2-Deoxy-D-ribose has been used in the chiral pool synthesis of lipoxins.[12,16] In this communication we describe a convenient synthesis of LXA_4 (**1**) and LXB_4 (**2**) starting from butadiene via palladium catalyzed telomerization.

The dimerization of butadiene with acetic acid in the presence of $Pd(Acac)_2$ (0.2%), tri-*o*-tolylphosphite (0.2%) and NaOAc (3%) at room temperature produced a mixture of the octadienol acetates **4** (13%), **5** (76%) and **6** (11%) in 90% yield after distillation (the ratio of isomers was determined by ^{1}H NMR) (Scheme 1).[17–19]

The chiral building block **7** was obtained directly from the mixture of octadienols **4a**, **5a** and **6a** by Sharpless cat. AE[20] at −25°C to −15°C for 6 h (60% isolated yield, 79% based on **5a**). The epoxidation

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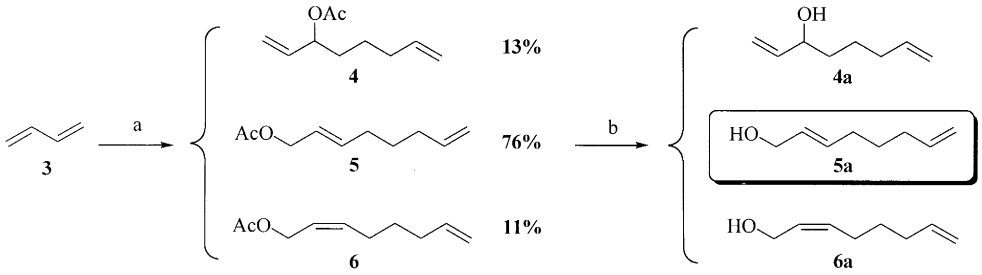
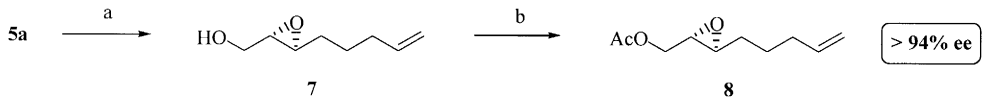


Scheme 1. (a) AcOH, $Pd(Acac)_2$ cat., tri-*o*-tolylphosphite cat., NaOAc cat., rt; (b) K_2CO_3, Na_2SO_4, MeOH, rt

of the *trans* allyl alcohol **5a** was preferred over the *cis* **6a** and the 3-hydroxy allyl isomer **4a** under these reaction conditions. Compound **7** was transformed to the acetate **8** with Ac_2O in pyridine at 0°C (Scheme 2) [>94% ee determined by ^1H NMR using $Eu(hfc)_3$ shift reagent in C_6D_6]. The transformation of **8** to the epoxy acetate **9** was carried out as described by Sharpless ($RuCl_3$, $NaIO_4$) followed by treatment with CH_2N_2 (71% yield).[21] The cleavage of the acetate in the presence of the epoxide and the methyl ester in **9** was readily achieved with cat. K_2CO_3 in the presence of anhydrous Na_2SO_4 in MeOH. Under these conditions neither ester cleavage nor Payne rearrangements were observed. Simple filtration of the Na_2SO_4 and normal work up gave **9a** in 69% yield and >94% ee (Scheme 3).



Scheme 2. (a) Dimethyl-L-(+)tartrate (12%), Ti(*i*-PrO)$_4$ (10%), TBHP, −25°C→−15°C, 6 h; (b) Ac_2O, pyridine, 0°C, 12 h

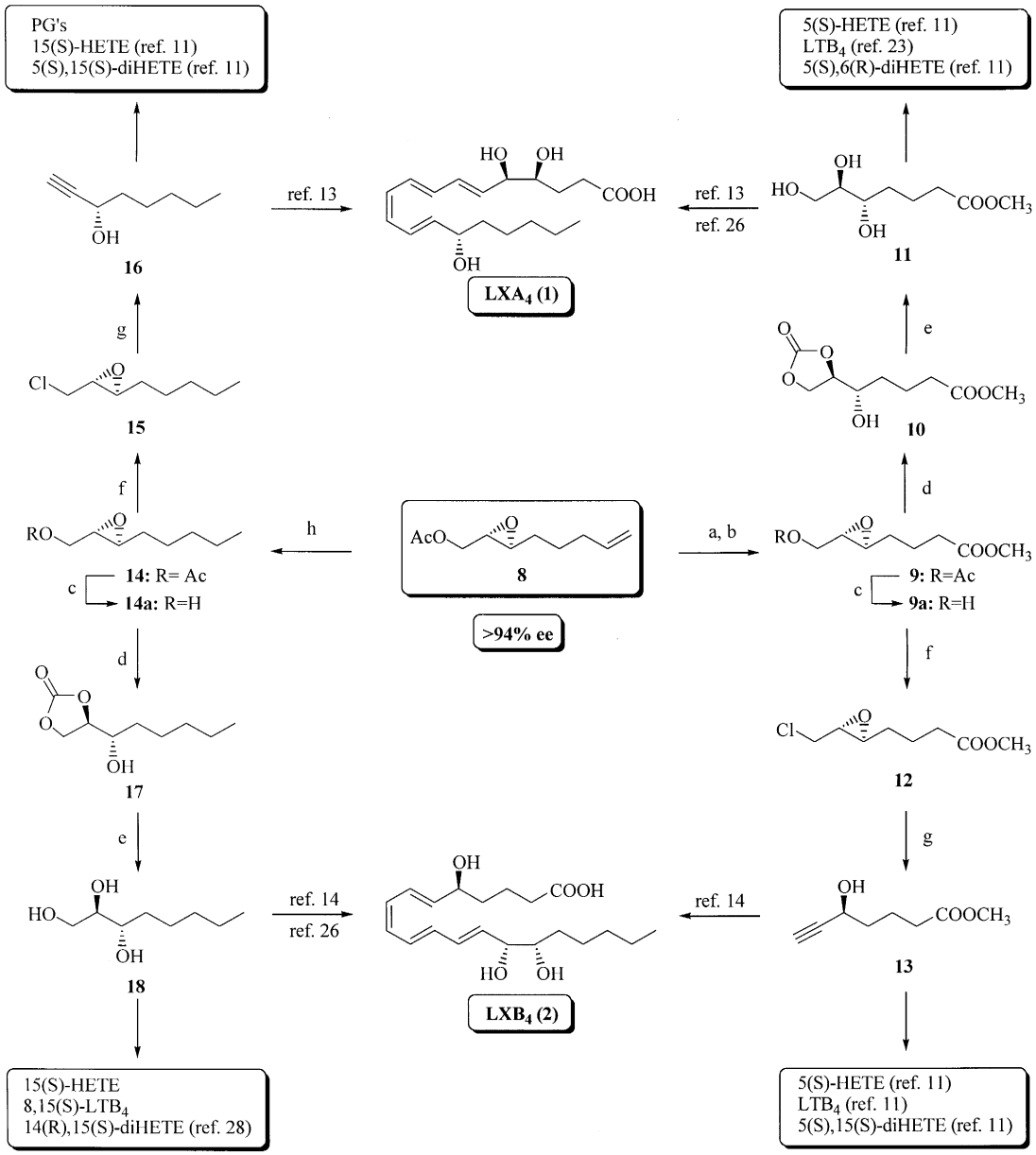
The direct conversion of **9a** to the C-2 inverted hydroxy carbonate **10**, bearing the required 5*S*,6*R*-configuration of LXA_4, was achieved with 1 atm CO_2 using Myers procedure (Cs_2CO_3 and 3 Å molecular sieves in DMF at 40°C in 40% yield).[22] Small quantities of the internal carbonate were detected but were easily removed by flash chromatography. The hydrolysis of the cyclic carbonate in the presence of the methyl ester in **10** could be accomplished by base catalyzed transesterification with cat. NaOMe in MeOH at rt to give **11**, the C_1–C_7 building block of LXA_4, identical with material prepared from 2-deoxy-D-ribose.[16,23]

The epoxy alcohol **9a** was converted to the chloro epoxide **12** with Ph_3P in CCl_4 at reflux in the presence of a small quantity of $NaHCO_3$ (52% isolated yield). Base catalyzed elimination with excess of LDA at −70°C to rt, similar to Yadav procedure,[24] afforded **13** (C_1–C_7 synthon of LXB_4) in 86% isolated yield. Other reaction conditions produced mixtures of *Z* and *E*-vinyl chlorides, besides starting material and the required alkyne **13**, similar as reported by Takano et al.[25]

The C_{13}–C_{20} building block of LXA_4 **16** was obtained from **8** via hydrogenation to **14** [Rh (5 wt% on alumina), 1 atm H_2, 95% isolated yield]. Compound **14a** was converted to **16** using the same reagents and conditions as described for the transformation of **9a** to **13** (Scheme 3). The C_{13}–C_{20} building block of LXB_4 **18** was obtained from **14a** similar to the transformation of **9a** to **11** (Scheme 3).

Compounds **11** and **18** were transformed to their tri-TES ethers and selectively oxidized in the primary position as previously described.[26] The synthesis of LXA_4 (**1**) and LXB_4 (**2**) were completed using Nicolaou's route [13,14] and were identical in all aspects with material prepared from 2-deoxy-D-ribose.[12,16,26]

In summary, the total synthesis of LXA_4 and LXB_4 from butadiene has been achieved.[27] The flexibility of the strategy allows an easy access to the linear eicosanoids as shown in Scheme 3.[11–14,23,26,28]



Scheme 3. (a) $NaIO_4$, $RuCl_3$ cat., $CCl_4/CH_3CN/H_2O$, 0°C; (b) CH_2N_2, Et_2O, 0°C; (c) K_2CO_3 cat., Na_2SO_4, MeOH, rt; (d) CO_2 (1 atm), Cs_2CO_3, 3 Å molecular sieves, DMF, 40°C; (e) NaOMe cat., MeOH; (f) CCl_4, Ph_3P, $NaHCO_3$ cat., reflux; (g) LDA (15 equiv.), THF, −70°C→rt; (h) H_2, Rh (5 wt% on alumina), EtOAc, rt

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27. Satisfactory spectroscopic data were obtained for all compounds. Selected spectra: **5**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.8–5.6 (m, 2H), 5.5 (dtt, *J*=15.4, 6.4, 1.4 Hz, 1H), 5.0–4.8 (m, 2H), 4.4 (dd, *J*=6.3, 0.9 Hz, 2H), 2.0–1.9 (m and s, 7H), 1.4 (quint., *J*=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.6, 138.2, 135.8, 124.0, 114.5, 64.9, 32.9, 31.3, 27.8, 20.6. **8**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.9–5.7 (ddt, *J*=17.2, 10.4, 6.7 Hz, 1H), 5.1–4.9 (m, 2H), 4.4–4.3 (dd, *J*=12.3, 3.3 Hz, 1H), 3.9 (dd, *J*=12.3, 6.3 Hz, 1H), 3.0–2.9 (ddd, *J*=6.3, 3.3, 2.1 Hz, 1H), 2.9–2.8 (m, 1H), 2.1–2.0 (m, 2H), 2.1 (s, 3H), 1.7–1.4 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.8, 138.2, 115.0, 64.6, 56.4, 55.1, 33.2, 30.8, 24.9, 20.6. **9a**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.8 (dd, *J*=12.6, 2.4 Hz, 1H), 3.6 (s, 3H), 3.5 (dd, *J*=12.6, 4.5 Hz, 1H), 2.9–2.8 (m, 2H), 2.8–2.7 (br. s, 1H), 2.3 (t, *J*=7.3 Hz, 2H), 1.8–1.6 (m, 2H), 1.6–1.4 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.7, 61.6, 58.2, 55.3, 51.3, 33.2, 30.6, 21.1. **11**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.9–3.7 (m, 3H), 3.7 (s, 3H), 3.6–3.5 (m, 1H), 2.4 (t, *J*=7.2 Hz, 2H), 1.9–1.6 (m, 2H), 1.6–1.4 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.4, 73.7, 73.2, 63.3, 51.6, 33.5, 32.3, 20.9. **12**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.7 (s, 3H), 3.6–3.5 (dd AB system, *J*=11.7, 5.7 Hz, 1H), 3.5–3.4 (dd AB system, *J*=11.7, 5.4 Hz, 1H), 3.0 (ddd, *J*=5.7, 5.4, 2.1 Hz, 1H), 2.9–2.8 (ddd, *J*=6.3, 4.8, 2.1 Hz, 1H), 2.4–2.3 (t, *J*=7.3 Hz, 2H), 1.9–1.7 (m, 2H), 1.7–1.5 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.6, 58.3, 56.8, 51.5, 44.5, 33.3, 30.7, 21.1. **17**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.6 (ddd, *J*=8.4, 6.5, 3.8 Hz, 1H), 4.5 (dd, *J*=8.4, 6.5 Hz, 1H), 4.4 (t, *J*=8.4 Hz, 1H), 3.9 (m, 1H), 2.7 (br. d, *J*=4.2 Hz, 1H), 1.5–1.2 (m, 8H), 0.9 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 155.4, 78.7, 70.2, 65.1, 31.7, 31.4, 24.8, 22.3, 13.8. **18**: ^{1}H NMR ($CDCl_3$/CD_3OD, 300 MHz): δ 3.6–3.5 (dd AB system, *J*=11.4, 4.2 Hz, 1H), 3.5 (dd AB system, *J*=11.4, 5.4 Hz, 1H), 3.5–3.4 (m, 1H), 3.4–3.3 (m, 1H), 1.5–1.1 (m, 8H), 0.8–0.7 (t, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD, 75.5 MHz): δ 74.0, 73.0, 63.0, 32.6, 31.5, 25.1, 22.2, 13.4.
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