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Synthesis of Methyl (5*S*,6*R*,7*E*,9*E*,11*Z*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-7,9,11,13-hexadecatetraenoate, an Analogue of 15*R*-Lipoxin A_4

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Abstract—We describe a method for the synthesis of methyl (5*S*,6*R*,7*E*,9*E*,11*Z*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-7,9,11,13-hexadecatetraenoate, a compound that has been described as a metabolically stable analogue of 15*R*-lipoxin A_4.

Lipid mediators play key roles in inflammation and other physiological and pathophysiological responses. Among these, lipoxin A_4 (**1**) and other lipoxins serve to dampen immune responses, and mediate the resolution of inflammation, in contrast to the roles of other 'proinflammatory' mediators.[1–6] These compounds are rapidly inactivated in vivo; thus lipoxin A_4 is rapidly metabolized, primarily to the C15 ketone.[7,8] As a result, there has been interest in the development of metabolically stable lipoxin A_4 analogues as tools to study the effects of these mediators, and metabolically stable lipoxin analogues formed by modification in the region of the metabolically labile C15 hydroxyl, have been described.[9] Among these, compound **2**, methyl (5*S*,6*R*,7*E*,9*E*,11*Z*,13*E*,15*S*,)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-hexadeca-7,9,11,13-tetraenoate, '15-*epi*-16-(*para*-fluoro)-phenoxy-LXA_4', has been identified as being of particular interest,[1,4–6] and reported to show both enhanced metabolic stability and activity in vivo. For example, compound **2** has been reported to inhibit TNF-α-induced neutrophil recruitment in vivo,[10] and to inhibit inflammatory angiogenesis.[11] Other studies have demonstrated the activity of the compound in reducing disease severity in a dextran sulfate model of colitis,[12] and that the compound is protective in ischemic acute renal failure.[13] However, while compound **2** has been identified as an important pharmacological tool for studying the activity of lipoxins in vivo, with reports of interesting biological properties, no method for its synthesis has been described to date. In this communication, we describe a synthesis of compound **2** (Fig. 1).

Our synthesis follows the approach illustrated in Figure 2, involving a *cis* reduction of the acetylenic precursor **3**, which is prepared through the formation of the C12-C13 bond via a cross-coupling of the two fragments **4** and **5**. Similar synthetic strategies have been successfully applied in previous syntheses of lipoxins and lipoxin analogues.[14–18]

The synthesis of the carboxy terminus fragment **4** from 2-deoxy-D-ribose (**6**) has been described previously in the context of lipoxin synthesis[18, 19] and was performed as shown in Scheme 1. Thus, **6**, protected as its isopropylidine acetal derivative **7**, was converted to aldehyde **10** via a Wittig reaction with methyl (triphenylphosphoranylidine)acetate to give unsaturated ester **8**, catalytic hydrogenation over 10% Pd/C to give compound **9**, followed by Swern oxidation[20] of the

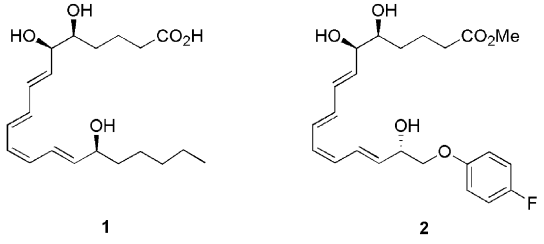

Figure 1.

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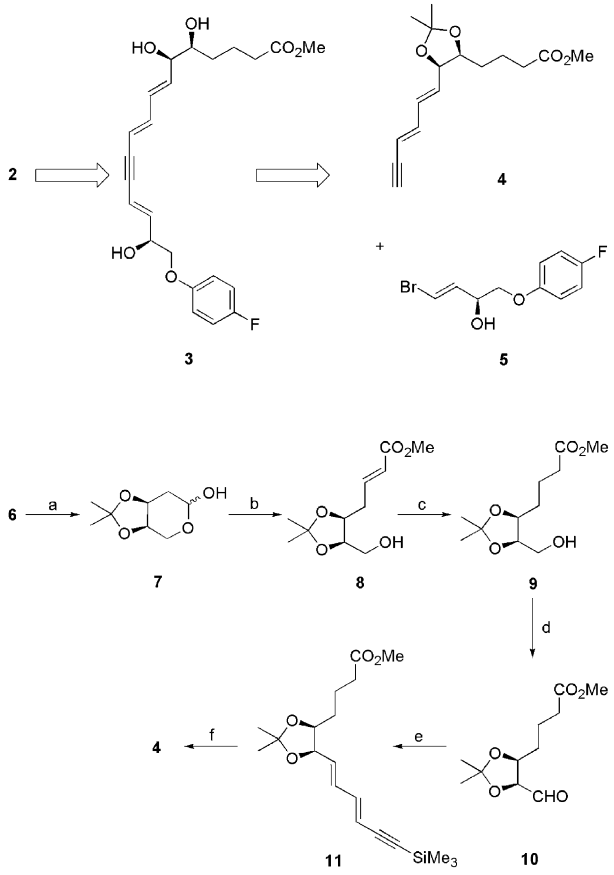
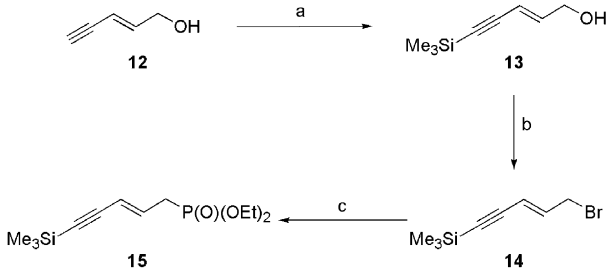


Scheme 1. Reagents and conditions: (a) 2-methoxypropene, PPTS, EtOAc, rt (43% yield); (b) $Ph_3P{=}CHCO_2Me$, BzOH (cat.), THF, Δ (81% yield) (c) H_2, 10% Pd/C (cat.), EtOH (87% yield); (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 °C→rt (86% yield); (e) 15, $LiNTMS_2$, toluene, −78 °C (36% yield); (f) KF, 18-crown-6, DMF, rt (99% yield).

resulting alcohol. In literature syntheses,[14–18] the lipoxin A_4 C7–C8 double bond has then been formed by a Wittig reaction of aldehyde **10** (or the corresponding intermediate with a bis-(*t*-butyldimethylsilyl)-protected C5–C6 diol) giving largely the undesired *cis* C7–C8 geometry, followed by isomerization with iodine to the desired *trans* geometry. In our hands, the isomerization proceeded only slowly and with significant decomposition. However, a useful variant to this procedure was adopted in which a Wadsworth–Emmons alkene formation[21] with phosphonate **15** formed the desired *trans*-stereoisomer (**11**) exclusively. Phosphonate **15** was prepared by the route shown in Scheme 2. Thus, protection of the terminal acetylene of **12** by treatment with ethylmagnesium chloride, followed by chlorotrimethylsilane gave alcohol **13**. Treatment of **13** with NBS/triphenylphosphine gave bromide **14**. Phosphonate **15** was then formed by the Arbusov reaction[22] of bromide **14** with triethylphosphite.

The synthesis of the *p*-fluorophenoxy fragment **5** was achieved using the route shown in Scheme 3. 2-(*p*-Fluorophenoxy)acetaldehyde (**18**) was prepared[23] by alkylation of *p*-fluorophenol with 3-chloropropane-1,2-diol (**16**) (K_2CO_3, DMF), followed by oxidative cleavage of the resulting diol (**17**) with silica-supported

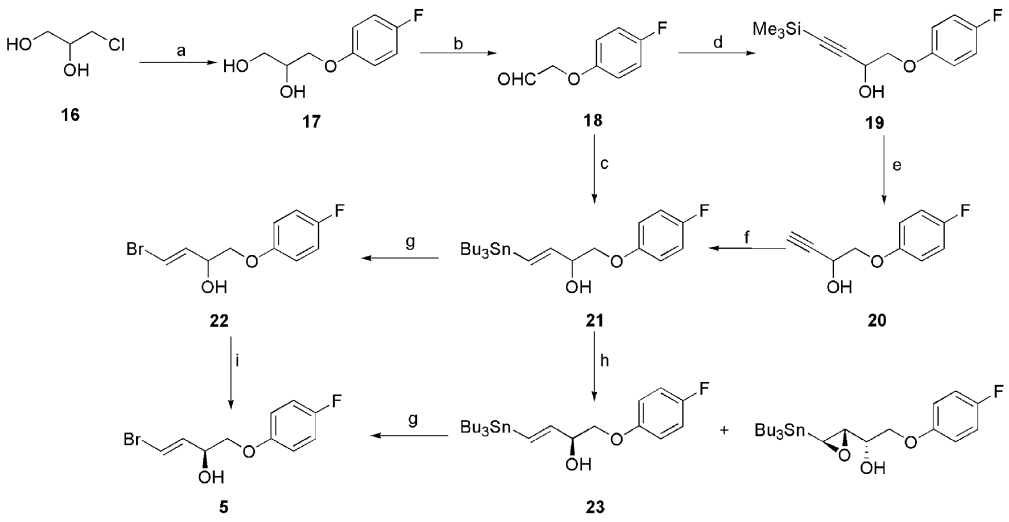


Scheme 2. Reagents and conditions: (a) (i) EtMgCl, THF, 0 °C; (ii) TMSCl, 50 °C; (iii) SiO_2 chromatography (90% yield); (b) NBS, Ph_3P, CH_2Cl_2, 0 °C→rt (74% yield); (c) $P(OEt)_3$, toluene, Δ (90% yield).

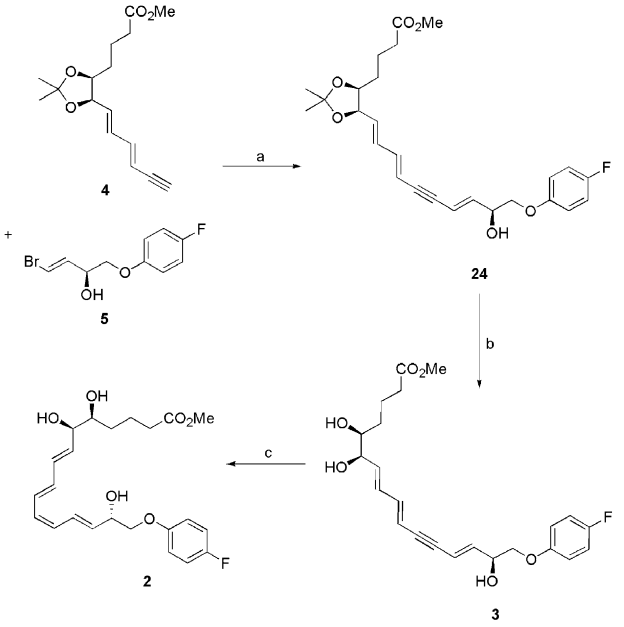
sodium periodate in dichloromethane. Addition of *E*-2-(tri-*n*-butylstannyl)vinyllithium, prepared in situ from *E*-1,2-bis(tri-*n*-butylstannyl)ethylene[24] by treatment with *n*-butyllithium (THF, −78→16 °C, 30 min) then gave the racemic vinylstannane **21**. Due to its high molecular weight, relatively large quantities of bis(tri-*n*-butylstannyl)ethylene were needed in the preparation of **21** by this procedure. Therefore **21** was more conveniently prepared by addition of lithium 2-trimethylsilylacetylide to **18** to give **19**, TMS deprotection to give the acetylenic alcohol **20**, followed by selective *trans* addition of tri-*n*-butyltin hydride under free radical conditions. Vinylstannane **21** was then converted to the racemic vinylic bromide **22** by treatment with NBS in dichloromethane.

In an attempt to obtain the *S* enantiomer (**5**) of bromide **22** required for the coupling with **4**, kinetic resolution of the stannane **21** was performed by subjecting this racemic allylic alcohol to Sharpless epoxidation[25] conditions using (+)-diisopropyl L-tartrate and recovering the unreacted *S*-enantiomer **23** (38% yield, 67% ee).[26] Compound **21** was then converted to bromide **5** by treatment with NBS, as described above. Optimization of the conditions for the kinetic resolution of **21** to give improved ee would be needed to provide an acceptable synthesis of bromide **5**. However, we found that the racemic vinylic bromide **22** could be conveniently and effectively resolved directly by chiral supercritical fluid chromatography (SFC) performed using Chiral Technologies Chiralpak® AD™ columns. Analytical separations were carried out on a Berger Analytical SFC instrument with a 4.6×250 mm 10 μm particle size column using 20% MeOH in CO_2 as the eluant at 2.2 mL/min flow, giving a resolution of $R = 7$ in a run time of 6 min. Preparative chromatography was performed on a Berger PrepSFC™ instrument with a 21×250 mm 10 μm particle size column, using the same eluant at a 50 mL/min flow and a compound loading of the racemic mixture of 30 mg per injection. The later eluting, desired, *S* enantiomer (**5**) was collected with 84% recovery and in >99% ee, as determined either by analytical chiral SFC or by ^1H NMR in $CDCl_3$ using the chiral shift reagent (*S*)-1-anthracen-9-yl-2,2,2-trifluoroethanol-d_{11}.

Completion of the synthesis then required the organometallic cross-coupling of the fragments **4** and **5**,



Scheme 3. Reagents and conditions: (a) *p*-FC_6H_4OH, K_2CO_3, MeCN, Δ (56% yield); (b) $NaIO_4/SiO_2$, CH_2Cl_2 (98% yield); (c) *E*-*n*Bu_3SnCH=CHLi, THF, −20 °C (45% yield); (d) $Me_3SiC{\equiv}CLi$, Et_2O, −30 °C→rt (71% yield); (e) NaOH (76% yield); (f) *n*Bu_3SnH, AIBN, 150 °C (50% yield); (g) NBS, CH_2Cl_2, 0 °C (95% yield); (h) *t*BuOOH, $Ti(OiPr)_4$, (+)-DIPT, CH_2Cl_2, −20 °C (67% ee, 38% yield); (i) chiral supercritical fluid chromatography (99% ee, 42% yield).



Scheme 4. Reagents and conditions: (a) $Pd(PPh_3)_4$, CuI, *n*$PrNH_2$, PhH, rt (75%); (b) 0.5 N HCl, MeOH, 2 min, then quench $NaHCO_3$ (90%); (c) Zn (Cu/Ag), aq MeOH, 45 °C, 36 h (80%).

deprotection, and *cis* reduction of the resulting conjugated acetylene **3** to give the C11–C12 *cis* double bond (Scheme 4). Coupling of **4** and **5** was achieved by cross-coupling mediated by $Pd(PPh_3)_4$/CuI in the presence of *n*-propylamine to give **24**. Deprotection of the acetal group had to be performed carefully, by brief treatment with dilute methanolic HCl, to avoid decomposition of the product. The selective *cis* reduction of compound **3** to give **2** was then performed by reduction with an activated zinc alloy. This latter procedure, introduced by Boland[27] and recently employed by Rodriguez and Spur[18] in a synthesis of 15*R*-lipoxin A_4 avoids the problems of over-reduction and isomerization to the all *trans* isomer which may be observed when Lindlar reduction is used to form the C11–C12 *cis* double bond.

In summary, methyl (5*S*,6*R*,15*S*,7*E*,9*E*,11*Z*,13*E*,15*S*)-16 - (4 - fluorophenoxy) - 5,6,15 - trihydroxyhexadeca-7,9,11,13-tetraenoate, '15-*epi*-16-(*para*-fluoro)-phenoxy-LXA_4', has been described as a compound that acts as a metabolically stable, biologically active, analogue of lipoxin A_4. This communication provides a concise, practical, route for the synthesis of this compound.

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