Stereocontrolled Total Synthesis of Lipoxins A

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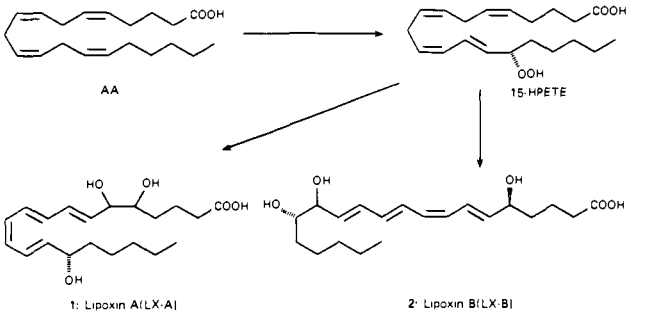
Abstract: A stereocontrolled total synthesis of lipoxin A and a number of its isomers is reported. The strategy involves Sharpless asymmetric epoxidation and pinylborane asymmetric reduction to build the hydroxy-bearing stereocenters and a Wittig-type as well as a Pd(0)–Cu(I) coupling reaction to construct the chain of the target molecules.

A new series of linear trihydroxy eicosanoids with a conjugated tetraene system was reported in 1984 from Samuelsson's group.[1,2] This novel series of oxygenated compounds was formed from arachidonic acid (AA) in human leukocytes via 15(*S*)-hydroperoxy-5,8,11,13-eicosatetraenoic acid (15-HPETE).[1,2] The two major compounds of this cascade were characterized as 5,6,15-(*S*)-trihydroxy-7,9,11,13-eicosatetraenoic acid and 5(*S*),14,15-(*S*)-trihydroxy-6,8,10,12-eicosatetraenoic acid and given the trivial names of lipoxin A (LX-A) and lipoxin B (LX-B), respectively (Scheme I).[1,2]

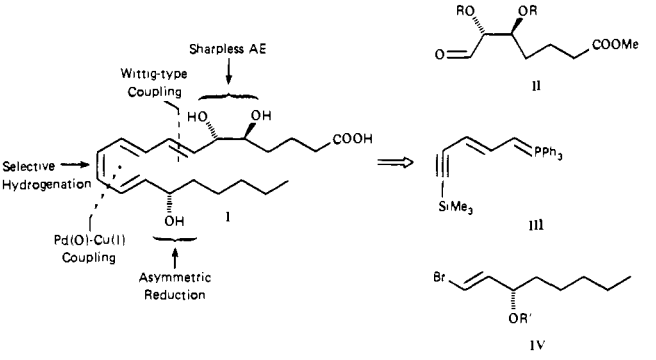
Samuelsson's partial assignments were based on biosynthetic considerations and degradation studies. They left, however, open the question of configuration at C-5 and C-6 for LX-A and C-14 for LX-B. Furthermore, the geometry of the double bonds, particularly that indicated as *Z*, was tentative. In view of these uncertainties and the important biological activities of the lipoxins we initiated in mid-1984 a program directed toward their total synthesis. In this article we describe stereocontrolled total syntheses of a series of lipoxins A. Other routes to lipoxins A were recently reported by Corey and Su[3] and by Adams et al.[4,5]

Lipoxin A (LX-A) added to human neutrophils provokes superoxide anion generation and degranulation at submicromolar concentrations without inducing substantial aggregation.[2] In this respect LX-A proved to be as potent as leukotriene B_4 (LTB_4) but showed much less potency than LTB_4 at inducing degranulation.[2] Furthermore, LX-A was found to stimulate lysosomal elastase release from human neutrophils.[2] This physiological profile coupled with the extreme scarcity of the natural compound and the structural novelty and uncertainties mentioned above dictated the synthetic studies described below.

Scheme I. Biosynthesis of Lipoxins A (LX-A) and B (LX-B)



Scheme II. Retrosynthetic Analysis of Lipoxins A



Strategy

At the outset of this program the stereochemistries of LX-A (**1**) at C-5, C-6, and Δ^{11} were uncertain, giving rise to 8 possible stereoisomers. We, therefore, sought to design a general and flexible strategy that would allow us to produce, stereoselectively, each of these compounds for comparisons with natural samples and for biological investigations. Our recently proposed general strategy toward linear eicosanoids,[6] seemed to be ideal for the present targets. Thus, focusing on the conjugated cis, trans diene system shown (Scheme II) and disconnecting of its central bond accompanied by converting the cis double bond to a triple bond led to a terminal acetylene and a vinyl bromide as potential precursors, whereas a further disconnection of the indicated trans double bond revealed the three key intermediates II–IV as the requisite building blocks. It was expected that this strategy would allow us to generate sequentially and cleanly a cis and a trans double bond in the final structure. This analysis also makes it possible to apply the Sharpless' AE procedure[7] to obtain all 4 possible stereoisomers of II by utilizing an allylic alcohol and varying the geometry of the double bond and the absolute configuration of the chiral auxiliary ((+)- or (−)-tartrate). Below we describe the total synthesis of the 5(*S*), 6(*S*), 15(*S*) and 5(*R*), 6(*S*), 15(*S*) series of lipoxins A.

Total Synthesis

Scheme III presents the synthesis of the requisite building block **14** for the 5(*S*),6(*S*)-lipoxin A series. Thus, Sharpless AE[7] of the (*Z*)-allylic alcohol **3**[8] employing (−)-DET led to the highly enriched epoxide **4** (86% ee, see Experimental) which was then converted to urethane **5** by reaction with phenyl isocyanate. Regioselective intramolecular epoxide opening[9] by the urethane oxygen accompanied by the expected inversion of configuration at the point of attack was effected in the presence of $BF_3{\cdot}Et_2O$ leading, after mild acid hydrolysis, to the terminal 5-membered-ring hydroxy carbonate **6** (IR (neat) ν_{max} 1805 cm^{-1}). Basic hydrolysis of **6** led to the triol **7**, the hydroxy groups of which were

† Recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1985; J. S. Guggenheim Fellow, 1984–1985.

(1) Serhan, C. N.; Hamberg, M.; Samuelsson, B. *Biochem. Biophys. Res. Commun.* **1984**, *118*, 943.
(2) Serhan, C. N.; Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 5335.
(3) Corey, E. J.; Su, W. *Tetrahedron Lett.* **1985**, *26*, 281.
(4) Adams, J.; Fitzimmons, B. J.; Firard, Y.; Leblanc, Y.; Evans, J. F.; Rokach, J. *J. Am. Chem. Soc.* **1985**, *107*, 464.
(5) Adams, J.; Fitzimmons, B. J.; Rokach, J. *Tetrahedron Lett.* **1984**, *25*, 4713.
(6) Nicolaou, K. C.; Webber, S. E. *J. Am. Chem. Soc.* **1984**, *106*, 5734.
(7) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
(8) Compound **3** was prepared from 5-hexyn-1-ol (Favchan) by the following sequence: (i) 1.0 equiv KH, 1.05 equiv $PhCH_2Br$, 0.01 equiv n-Bu_4NI, THF, 25 °C, 83%; (ii) 1.05 equiv n-BuLi, THF, −78 → 25 °C then $(CH_2O)_n$, 60 °C, 98%; (iii) Lindlar catalyst, quinoline, H_2, hexane, 25 °C, 100%. The corresponding *E* isomer of **3** was obtained by utilizing 1.2 equiv of $LiAlH_4$ in Et_2O, 0 °C–reflux in step (iii) of this sequence (95%).
(9) Roush, W. R.; Brown, R. j.; DiMare, M., *J. Org. Chem.*, *1983*, *48*, 5083.

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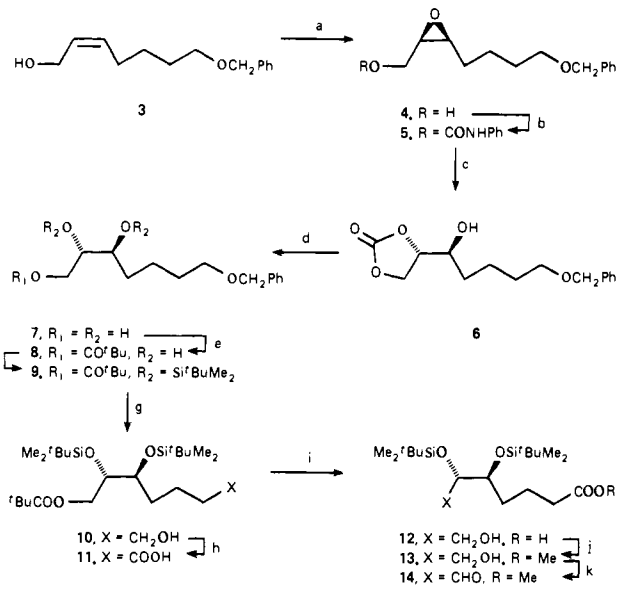
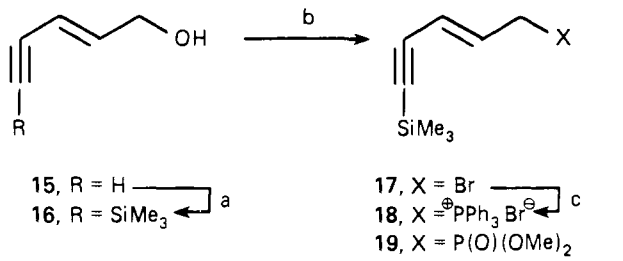
Scheme III. Synthesis of Key Intermediate 14



(a) 2.0 equiv of t-BuOOH, 1.0 equiv of (−)-DET, 1.0 equiv of $Ti(i\text{-}PrO)_4$, CH_2Cl_2, −20 °C, 73%. (b) 2.5 equiv of PhN=C=O, 5.0 equiv of pyridine, CH_2Cl_2, 25 °C, 98%. (c) 1.1 equiv of $BF_3{\cdot}Et_2O$, Et_2O, 0 °C then 1.0 N H_2SO_4 aqueous, 25 °C, 88%. (d) 3.0 equiv of NaOMe, MeOH, 25 °C, 98%. (e) 1.05 equiv of t-BuCOCl, 2.2 equiv of pyridine, CH_2Cl_2, 25 °C, 89%. (f) 2.5 equiv of t-$BuMe_2SiCl$, 5.0 equiv of imidazole, DMF, 0–25 °C. (g) H_2, 10% Pd-C, EtOH, 25 °C, 91% overall from 8. (h) 2% by mol RuO_2, 4.1 equiv of $NaIO_4$, CCl_4:MeCN:H_2O (1:1:1.5), 25 °C, 87%. (i) 2.0 equiv of Dibal, CH_2Cl_2, −78 °C, 87%. (j) CH_2N_2, Et_2O, 0 °C, 100%. (k) 1.5 $(COCl)_2$, 2.0 DMSO, 3.0 equiv of Et_3N, CH_2Cl_2, −78–25 °C.

Scheme IV. Synthesis of Key Intermediates 18 and 19

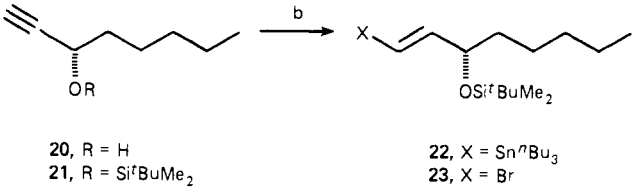


(a) 2.2 equiv of EtMgBr, THF, 0 °C then 2.2 equiv of Me_3SiCl, 50 °C, 92%. (b) 1.1 equiv of NBS, 1.2 equiv of PPh_3, CH_2Cl_2, 0–25 °C, 86%. (c) 1.2 equiv of Ph_3P, PhH, 25 °C, 88%. (d) 10.0 equiv of $P(OMe)_3$, MeCN, 80 °C, 84%.

differentiated by selective blocking of the primary position as pivalate ester followed by engagement of the secondary groups as *tert*-butyldimethylsilyl ethers. This standard sequence furnished compound **9** via derivative **8**. Removal of the benzyl ether by catalytic hydrogenation then liberated primary alcohol **10** which was oxidized to carboxylic acid **11** by the Sharpless method (catalyst RuO_2, $NaIO_4$).[10] Exposure of **11** to 2.2 equiv of Dibal at −78 °C followed by aqueous workup and diazomethane treatment produced the hydroxymethyl ester **13**, via the corresponding acid (**12**) which was oxidized under Swern conditions to the desired subtarget aldehyde **14** in excellent overall yield and in multigram quantities.

The second requisite building block was designed as the phosphonium bromide **18** (mp 182–184 °C dec) or phosphonate **19** (Scheme IV) in order to allow exploration of efficiency and geometrical selectivity in the coupling reaction with aldehyde **14**. A highly efficient preparation of these intermediates from 1-hydroxy-2(*E*)-penten-4-yne (**15**), involving the intermediacy of

Scheme V. Synthesis of Vinylbromide 23



(a) 1.5 equiv of t-$BuMe_2SiOSO_2CF_3$, 2.2 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 96%. (b) 1.5 equiv of n-Bu_3SnH, cat. AIBN, 130 °C. (c) 1.0 equiv of Br_2, CCl_4, −20 °C, 94% overall from **21**, ≥98% *E*.

compounds **16** and **17**, is detailed in Scheme IV.

The third required fragment, vinyl bromide **23** (Scheme V) is readily available in multigram quantities as previously communicated.[6] Thus, the known acetylenic alcohol **20** (Scheme V) was silylated to **21** which reacted with excess n-Bu_3SnH in the presence of the radical initiator AIBN at 130 °C to afford vinylstannane **22**. Brominolysis of **22** then furnished vinyl bromide **23** in high chemical yield and geometrical purity (≥98% *E*).

The coupling of the major building blocks and the final stages of the synthesis are presented in Scheme VI. It was, thus, observed that coupling of the phosphorane derived from phosphonium salt **18** and n-BuLi led, in excellent yield, to a mixture of *Z* and *E* products **24** and **25** in ca. 1:1 ratio (^1H NMR and isolation), whereas the utilization of the phosphonate **19** under similar basic conditions furnished a 1:3 ratio of **24** to **25**, again in excellent chemical yield. Isomerization of **24** to **25** with iodine, however, was easily effected, producing an equilibrium of ca. 1:11 of *Z*:*E* isomers. Flash column chromatography then allowed isolation of pure **25** which was then selectively desilylated at carbon to afford terminal acetylene **26**. The final coupling of **26** with vinyl bromide **23** proceeded smoothly and in high yield under the catalytic influence of Pd(0) and Cu(I),[6,11] furnishing the complete carbon assembly of lipoxin A as derivative **27**. Subsequent desilylation of **27** with fluoride anion gave the trihydroxy compound **28** together with δ-lactone **29** (ca. 1:1). Opening of this lactone with $LiOH/H_2O/THF$, followed by CH_2N_2 treatment, gave methyl ester **28** in high yield, thus funnelling this intermediate back to the main pathway. Finally, selective, catalytic hydrogenation (Lindlar catalyst, quinoline) generated lipoxin A methyl ester **30** (5(*S*),6(*S*),15(*S*)) (together with small amounts of its all-trans isomer (**32**)) purified by HPLC (reverse phase, ultra sphere ODS, MeOH–H_2O (70:30)). Methyl ester **30** then served as a precursor to sodium salt **31** and lipoxin A (**1**) under standard alkaline conditions. Furthermore, isomerization of **30** by catalytic amounts of iodine smoothly generated the all-trans lipoxin A methyl ester **32** (≥98% *E*) from which the sodium salt **33** and carboxylic acid **34** were similarly obtained.

Starting with the *E* isomer[8] of allylic alcohol **3** (Scheme III) and following the same strategy and similar methodology the 5(*R*),6(*S*),15(*S*)-lipoxins A, **35–40** (Scheme VII), were also synthesized in similar overall yields and selectivties. In this sequence, it was interesting to observe an ca. 20:1 ratio of *Z*:*E* olefins in the Wittig coupling employing phosphonium salt **18**. This result, however, was easy to correct, since iodine-induced isomerization favored the required *E* isomer as in the previous synthesis.

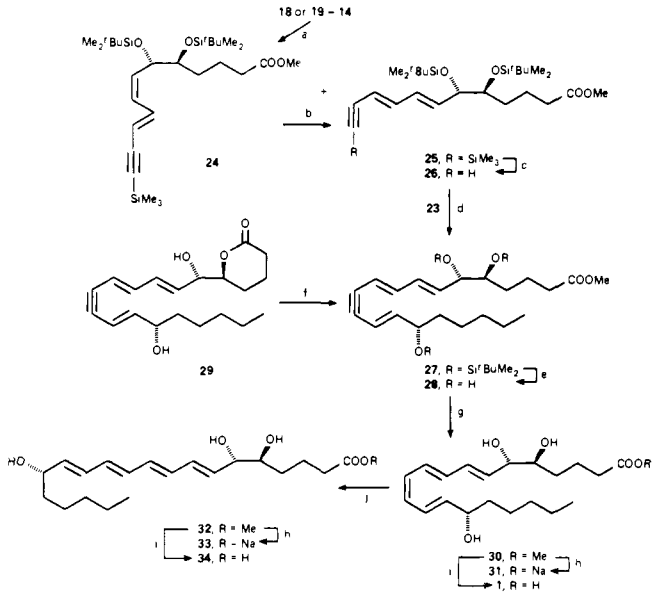
Conclusions

A general, Pd(0)–Cu(I) catalyzed, strategy for the total synthesis of the lipoxin A family of linear eicosanoids was developed. Four of these compounds, including the one (structure **1**, Scheme VI) claimed to be the natural product by the Merck Frosst[4] and the Harvard[3] groups, were produced by a stereocontrolled and efficient synthesis. The reported synthetic route renders the lipoxin A series of compounds (natural, isomers and analogues) readily accessible for biological investigations. In contrast to previous syntheses of these compounds,[3,4] the present strategy is charac-

(10) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B., *J. Org. Chem.*, *1981*, *46*, 3936.

(11) (a) Sonogashira, K.; Tohda, Y.; Hogihara, N. *Tetrahedron Lett. 1975*, 4467. (b) Ratovelomana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917.

Scheme VI. Total Synthesis of Lipoxin A and Its All-Trans Isomer



(a) 1.6 equiv of 18, 1.5 equiv of *n*-BuLi, THF, −78 to 25 °C then 1.0 equiv of 14, THF, −78 to 25 °C, 98%, *E*:*Z* ca. 1:1 or 1.5 equiv 19, 1.4 equiv *n*-BuLi, THF, 90%, *E*:*Z* ca. 3:1. (b) 0.01 equiv of I_2, C_6H_6, 25 °C, 98%, *E*:*Z* ca. 11:1. (c) 4.0 equiv of $AgNO_3$, then 7.0 equiv of KCN, EtOH:THF:H_2O (1:1:1), 0–25 °C, 85%. (d) 1.0 equiv of vinyl bromide **23**, 0.04 equiv of $Pd(PPh_3)_4$, 1.4 equiv of $nPrNH_2$, 0.16 equiv of CuI, PhH, 25 °C, 96%. (e) 3.1 equiv of KF·$2H_2O$, 0.1 equiv of 18-C-6, DMF, 25 °C, 83%. (f) 2.0 equiv of 2 N aqueous LiOH, MeOH, 25 °C, then dilute H_2SO_4, pH 5–6, then CH_2N_2, Et_2O, 90%. (g) H_2, Lindlar catalyst, quinoline, CH_2Cl_2, 25 °C, 53%. (h) 2.0 equiv of NaOEt, 95% aqueous EtOH, 25 °C, 100%. (i) 2.0 equiv of LiOH, THF:H_2O (4:1), 25 °C, then dilute H_2SO_4, pH 5–6, 90%. (j) 0.01 equiv of I_2, CH_2Cl_2, 25 °C, 60%, ≥98% *E*.

terized by (a) high stereocontrol and (b) wide scope of flexibility which leads selectively to any desired lipoxin A, thus avoiding isomeric mixtures. Furthermore, the described sequence secures all elements of stereochemistry from achiral and simple starting materials and could be used to synthesize numerous analogues of these substances with varying chains and substituents for biological evaluation.

Experimental Section

General. ^1H NMR spectra were recorded on a Bruker WH-250 MHz spectrometer in $CDCl_3$ and are reported in δ from Me_4Si. IR spectra were recorded on a Perkin-Elmer Model 781 infrared spectrophotometer and the IR figures reported are ν_{max} in cm^{-1}. UV spectra were recorded on a Perkin-Elmer Model 553 ultraviolet and visible spectrophotometer, and the UV figures reported are λ_{max} in nm. High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under Chemical Ionization (CI) conditions. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) using UV light and 7% phosphomolybdic acid in ethanol–heat as developing agent or HPLC Varian Model 5000 (reverse phase, ultrasphere ODS, UV detector). Preparative layer chromatography was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography .

All reactions were carried out under an argon atmosphere with dry freshly distilled solvents under anhydrous conditions unless otherwise noted. Ethereal solvents were dried and distilled under nitrogen from sodium benzophenone ketyl. Methylene chloride was distilled under nitrogen from calcium hydride. Amines were distilled under argon from calcium hydride. Reaction temperatures were externally measured. NMR multiplicities were reported by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad, *J* = coupling constant (Hz). Only the strongest and/or structurally most important peaks are reported for the IR. All yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials.

Epoxidation of Compound 3 to 2(*R*),3(*S*) Epoxide 4. Into a 1-L flask were added allylic alcohol **3** (12.3 g, 55.0 mmol), $Ti(iPrO)_4$ (16.6 mL, 55.0 mmol), (−)-diethyl tartrate (9.5 mL, 55.0 mmol), *t*-BuOOH (25.6 mL, 112.0 mmol), and CH_2Cl_2 (500 mL). The homogenous solution was kept at −20 °C for 48 h and then quenched (−20 °C) by addition of 10% aqueous tartaric acid solution (200 mL) and stirring for an additional 0.5 h. The organic phase was separated from the aqueous, washed with brine (100 mL), dried (Na_2SO_4), and evaporated to an oil. This oil was dissolved in ether (425 mL) and cooled to 0 °C. NaOH (1 N, 180 mL) was added and stirred for 0.5 h. The organic phase was separated from the aqueous, washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), evaporated, and flash-chromatographed (silica, ether-petroleum ether, 70:30) to give **4** (9.6 g, 73% yield). This material was found to have an 86% ee by the Mosher ester method[12] (two distinct signals in the ^{19}F NMR spectrum (49.3 and 35.8) for both enriched and racemic material) **4**: R_f 0.17 (silica, ether–petroleum ether, 70:30); $[\alpha]^{23}_D$ + 1.55° (*c* 1.1, CH_2Cl_2); IR (neat) ν_{max} 3450, 2955, 2880, 1460, 1110, 1050, 750, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5 H, aromatic), 4.50 (s, 2 H, PhCH_2O–), 3.81 (ddd, *J* = 12.0, 7.4, 4.4 Hz, 1 H, CH_2OH), 3.65 (ddd, *J* = 12.0, 6.8, 5.1 Hz, 1 H, CH_2OH), 3.49 (t, *J* = 6.0 Hz, 2 H, CH_2OCH_2Ph), 3.13 (m, 1 H, epoxide), 3.02 (m, 1 H, epoxide), 1.94 (t, *J* = 5.0 Hz, 1 H, O*H*), 1.52 (m, 6 H, CH_2); HRMS calcd for $C_{14}H_{20}O_3$ 236.1412, found for (M + 1) 237.1490. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.15; H, 8.53; Found: C, 71.02; H, 8.56.

Oxidation of 12 to 5(*S*),6(*R*) Aldehyde 14. In a flame-dried flask under an argon atmosphere at −78 °C was placed Me_2SO (0.17 mL, 2.42 mmol) in CH_2Cl_2 (3 mL) and to this was added oxalyl chloride (0.16 mL, 1.82 mmol). The solution was stirred for 0.25 h and then alcohol **13** (506 mg, 1.21 mmol) in CH_2Cl_2 (3 mL) was added. This solution was stirred for 0.75 h and then triethylamine (0.84 mL, 6.05 mmol) was added followed by warming to room temperature. The reaction was quenched by addition of water (5 mL) and diluted with ether (50 mL). The ether layer was washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), and evaporated to give an oil which was flash-chromatographed (silica, ether–petroleum ether, 5:95) to give **14** as a colorless oil (481 mg, 96% yield). **14**: R_f 0.55 (silica, ether–petroleum ether, 30:70); $[\alpha]^{23}_D$ −50.0° (*c* 0.50, CH_2Cl_2); IR (neat) ν_{max} 2980, 2940, 2880, 2730, 1750, 1265, 840, 780 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.73 (d, *J* = 0.7 Hz, 1 H, CHO), 4.01 (dd, *J* = 4.65, 0.7 Hz, 1 H, CH–O), 3.85 (5-line multiplet, 1 H, CH–O), 3.63 (s, 3 H, $COOCH_3$), 2.27 (t, *J* = 7.0 Hz, 2 H, CH_2COOCH_3), 1.80–1.10 (m, 4 H, CH_2), 0.89 (s, 9 H, *t*-Bu), 0.87 (s, 9H, *t*-Bu); 0.64 (s, 9 H, (Me_2Si)), 0.18 (s, 3 H, (Me_2Si)). Anal. Calcd for $C_{20}H_{42}O_5Si_2$: C, 57.37; H, 10.11. Found: C, 57.18; H, 9.97.

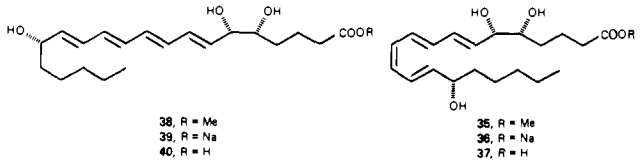
Preparation of Phosphonium Salt 18. The allylic alcohol **16** (7.7 g, 50.0 mmol) was dissolved in dry methylene chloride (100 mL) and cooled to −30 °C under argon. To this magnetically stirred solution was added triphenylphosphine (15.73 g, 60.0 mmol) followed by recrystallized *N*-bromosuccinimide (9.79 g, 55.0 mmol). The course of the reaction was followed by TLC. Upon completion (1 h), ether (300 mL) was added and the organic phase was washed with saturated bicarbonate (2 × 100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), concentrated, and treated with petroleum ether (200 mL), precipitating triphenylphosphine oxide and succinimide which were filtered off. Concentration of the solution followed by flash column chromatography gave pure bromide **17** (9.33 g, 86%) as a colorless oil. **17**: R_f = 0.16 (silica, petroleum ether); IR (neat) ν_{max} 3045, 3010, 2965, 2900, 2100, 1035, 1255, 845 cm^{-1}; ^1H NMR (250 MHz $CDCl_3$) δ 6.28 (dt, *J* = 15.6, 7.75 Hz, 2 H), 5.73 (d, *J* = 15.6 Hz, 1 H), 3.94 (d, *J* = 7.75 Hz, 2 H), 0.17 (s, 9 H, $SiMe_3$).

Allyl bromide **17** (8.68 g, 40.0 mmol) was dissolved in anhydrous benzene (80 mL) and recrystallized triphenylphosphine (48.0 mmol) was added under argon at 25 °C. The mixture was stirred at 25 °C for 18 h and then diluted with anhydrous ether (200 mL). The colorless solid was collected by filtration, washed with anhydrous ether (2 × 100 mL), and dried over P_2O_5, giving pure phosphonium salt **18** (17.25 g, 90% yield). **18**: mp 182–184 °C dec; IR ($CHCl_3$) ν_{max} 3070, 3020, 2940, 2450, 2160, 1600, 1440, 1250, 1115, 840; ^1H NMR (250 MHz, $CDCl_3$) δ 7.90–7.65 (m, 15 H, aromatic), 6.24 (dd, *J* = 16.0, 5.4 Hz, 1 H), 5.92 (m, 2 H), 5.09 (ddd, *J* = 16.0, 7.5, 1.0 Hz, 2 H), 0.14 (s, 9 H, (Me_3Si)). Anal. Calcd for $C_{26}H_{28}BrPSi$: C, 65.63; H, 5.89; Br, 16.66; P, 6.46; Si, 5.85. Found: C, 65.37; H, 6.05; Br, 16.22; P, 6.46; Si, 5.85.

Wittig Reaction of Phosphonium Salt 18 with Aldehyde 14. Preparation of 24 and 25. In a 100-mL flask under an argon atmosphere was placed phosphonium salt **18** (3.5 g, 7.2 mmol) in THF (30 mL) and the mixture was cooled to −78 °C. *n*-BuLi (1.6 M in hexane, 4.2 mL, 6.7 mmol) was added and the solution was allowed to warm to 0 °C and then recooled to −78 °C. The aldehyde **14** (1.87 g, 4.5 mmol) in THF (18

(12) Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543.

Scheme VII. (5*S*,6*R*,15*R*)-Lipoxins A



mL) was added and the cooling bath removed. When TLC (silica, ether–petroleum ether, 5:95) showed the reaction to be complete (ca. 2 h), saturated NH_4Cl(aq.) (15 mL) was added and the product extracted into ether (200 mL). The ether layer was washed with water (2 × 50 mL) and brine (25 mL) and then dried ($MgSO_4$). The solution was evaporated to an oil which was flash-chromatographed (silica, ether–petroleum ether, 3:97) to give the coupling product (2.63 g, 98% yield) as a 1:1 mixture of *E* and *Z* isomers **24** and **25**.

24 (*Z* isomer): R_f 0.31 (silica, ether–petroleum ether, 5:95) $[\alpha]^{25}_D$ −113° (*c* 1.1, ether); IR(neat) ν_{max} 2965, 2940, 2865, 2160, 1750, 1260, 850, 780 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.94 (dd, *J* = 15.0, 11.0 Hz, =C*H*—), 6.05 (t, *J* = 11.0 Hz, 1 H, =C*H*—), 5.53(d, *J* = 15.0 Hz, 1 H, =C*H*—), 5.44 (dd, *J* = 11.0, 8.0 Hz, 1 H, =C*H*—), 4.46 (m, 1 H, C*H*–O), 3.63 (s, 3 H, COOCH_3) 3.59 (m, 1 H, C*H*–O), 2.27 (t, *J* = 7.0 Hz, 2 H, CH_2COOCH$_3$), 1.80–1.10 (m, 4 H, CH_2), 0.87 (s, 9 H, *t*-Bu), 0.86 (s, 9 H, *t*-Bu), 0.17 (s, 9 H (*Me*$_3$Si)), 0.09 (s, 3 H, (*Me*$_2$Si)), 0.05 (s, 3 H, (*Me*$_2$Si)), 0.03 (s, 3 H, (*Me*$_2$Si)), 0.01 (s, 3 H, (*Me*$_2$Si)). Anal. Calcd for $C_{28}H_{54}O_4Si_3$: C, 62.40; H, 10.09. Found: C, 62.38, H, 9.85.

25 (*E* isomer): R_f 0.36 (silica, ether–petroleum ether, 5:95) $[\alpha]^{25}_D$ −44° (*c* 1.5, ether); IR (neat) ν_{max} 2975, 2940, 2865, 2180, 2130, 1750, 1255, 1120, 840, 780 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.65 (dd, *J* = 15.0, 11.0 Hz, 1H, –C*H*–), 6.22 (dd, *J* = 15.0, 11.0 Hz, 1 H, =C*H*—), 5.90 (dd, *J* = 15.0, 4.0 Hz, 1 H, =C*H*—), 5.53 (d, *J* = 15.0 Hz, 1 H, =C*H*—) 3.63 (m, 1 H, C*H*–O), 3.62 (s, 3 H, COOCH_3), 3.55 (m, 1 H, C*H*–O), 2.24 (t, *J* = 7.0 Hz, 2 H, CH_2COOCH$_3$), 1.80–1.10 (m, 4H, CH_2), 0.86 (s, 9 H, *t*-Bu), 0.85 (s, 9 H, *t*-Bu), 0.16 (s, 9 H, (*Me*$_3$Si)), 0.04 (s, 6 H, (2*Me*$_2$Si)), 0.02 (s, 3 H, (*Me*$_2$Si)), 0.00 (s, 3 H, (*Me*$_2$Si)). Anal. Calcd for $C_{28}H_{54}O_4Si_3$: C, 62.40; H, 10.09. Found: C, 62.37; H, 9.57.

Preparation of Vinyl Bromide 23 from Acetylene 20. To a magnetically stirred solution of acetylenic alcohol **20** (2.52 g, 20.0 mmol, ≥90% ee)[6] in dry CH_2Cl_2 (20 mL) at 0 °C was sequentially and dropwise added 2,6-lutidine (5.2 mL, 44.0 mmol) and *tert*-butyldimethylsilyl triflate (6.9 mL, 30.0 mmol). The cooling was ended and the reaction mixture was stirred for 1 h before it was diluted with ether (100 mL) and poured into ice–water (25 mL). The organic solution was separated, washed with 10% aqueous HCl (25 mL) and saturated brine (25 mL), and dried ($MgSO_4$). Concentration followed by flash column chromatography (silica, ether–petroleum ether, 1:99) gave silyl ether **21** as a colorless oil (4.60 g, 96% yield). **21**: R_f 0.26 (silica, ether–petroleum ether, 1:99); $[\alpha]^{23}_D$ −41.7° (*c* = 1.0, $CHCl_3$); IR (neat) ν_{max} 3320, 2960, 2940, 2860, 1475, 1360, 1090, 840, 775, 625 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.32 (m, 1 H, C*H*OSi), 2.36 (d, *J* = 2.0 Hz, 1 H, C≡C*H*), 1.65 (m, 2 H, CH_2), 1.50–1.20 (m, 6 H, CH_2), 0.89 (m, 12 H, *t-Bu*, CH_3), 0.11 (singlets, 6 H, *Me*$_2$Si); HRMS Calcd for $C_{14}H_{28}$OSi 240.1909, found for (M + 1) 241.1976.

Acetylene **21** (2.40 g, 10.0 mmol), *n*-Bu_3SnH (4.37 g, 15.0 mmol), and AIBN (25 mg) were stirred under argon at 130 °C for 2 H. The mixture so obtained containing the vinylstannane **22** was cooled to −20 °C and treated dropwise with a solution of bromine (1.6 g, 10.0 mmol) in dry CCl_4 (11.0 mL) until a faint yellow color persisted. Concentration followed by flash column chromatography (silica, petroleum ether) furnished **23** as a colorless oil (3.0 g, 94% yield). **23**: R_f 0.32 (silica, petroleum); $[\alpha]^{22}_D$ −19.9° (*c* = 1.0, $CHCl_3$); IR (neat) ν_{max} 2960, 2930, 2860, 1625, 1475, 1360, 1090, 935, 835, 765 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.16 (m, 2 H, olefinic), 4.09 (m, 1 H, CHOSi), 1.46 (m, 2 H, CH_2), 1.27 (m, 6 H, CH_2), 0.88 (m, 12 H, *t-Bu*, CH_3), 0.05 (singlets, 6 H, Me_2Si); HRMS calcd for $C_{14}H_{29}$ ^{79}BrOSi 320.1170, found for (M + 1) 321.1181. ^{1}H NMR data of desilylated **23** (1.1 equiv of *n*-Bu_4NF, THF, 0 °C) established its *E* geometry and purity. ^{1}H NMR (250 MHz, $CDCl_3$) of desilylated **23**: δ 6.31 (d, *J* = 13.7 Hz, 1 H, =C*H*Br), 6.20 (dd, *J* = 13.6, 6.2 Hz, 1H, =C*H*—), 4.09 (m, 1 H, C*H*OH), 1.60 (br s, 1 H, O*H*), 1.57–1.28 (m, 8 H, CH_2), 0.87 (t, *J* = 6.6 Hz, 3 H, CH_3).

Coupling of Acetylene 26 with Vinyl Bromide 23. Preparation of Compound 27. In a 100-mL flask under an argon atmosphere was placed vinyl bromide **23** (860 mg, 2.68 mmol) in degassed benzene (19 mL). To this was added *n*-propylamine (0.31 mL, 3.75 mmol) and $(Ph_3P)_4Pd$ (123 mg, 0.017 mmol), and the resulting solution was protected from light and stirred for 0.75 h. Acetylene **26** (1.25 g, 2.68 mmol) and CuI (82 mg, 0.43 mmol) were added and the progress of the reaction was followed by TLC (silica, ether–petroleum ether, 5:95) to completion (ca. 3 h). The solution was diluted with ether (100 mL) and extracted with saturated NH_4Cl (25 mL), water (2 × 25 mL), and brine (25 mL). Drying of the solution ($MgSO_4$) followed by evaporation gave an oil which was immediately flash-chromatographed (silica, ether–petroleum ether, 3:97) to give **27** (1.81 g, 96% yield). **27**: R_f 0.57 (silica, ether–petroleum ether, 5:95); $[\alpha]^{23}_D$ +12° (*c* 0.20, CH_2Cl_2); UV (MeOH) λ_{max} 205, 285, *J* 313; IR (neat) ν_{max} 3060, CH_2COOCH$_3$), 2880, 1755, 1480, 1475, 1260, 1100, 840, 780 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.58 (dd, *J* = 15.0, 10.0 Hz, 1 H, =C*H*—), 6.24 (dd, *J* = 15.0, 10.0 Hz, 1 H, =C*H*—), 6.07 (dd, *J* = 15.0, 5.0 Hz, 1 H, =C*H*—), 5.87 (dd, *J* = 15.0, 4.0 Hz, 1 H, =C*H*—), 5.73 (br d, *J* = 15.0 Hz, 1 H, =C*H*—), 5.63 (br d, *J* = 15.0 Hz, 1 H, =C*H*—), 4.15 (m, 2 H, C*H*–O), 3.62 (s, 3 H, COOCH_3), 3.56 (m, 1 H, C*H*–O), 2.25 (t, *J* = 8.0 Hz, 2 H, CH_2COOCH$_3$), 1.57–1.01 (m, 12 H, CH_2), 0.88 (br s, 27 H, 3 *t*-Bu), 0.86 (m, 3 H, CH_3), 0.05 (s, 6 H (2*Me*$_2$Si)), 0.03 (s, 6 H (2*Me*$_2$Si)), 0.01 (s, 6 H (2*Me*$_2$Si)). Anal. Calcd for $C_{39}H_{74}O_5Si_3$: C, 66.21; H, 10.55. Found: C, 66.17; H, 10.65.

Hydrogenation of Compound 28. Preparation of Lipoxin A Methyl Ester 30 and Its All-Trans Isomer 32. In a 25-mL flask was placed acetylene **28** (112 mg, 0.30 mmol), CH_2Cl_2 (5 mL), quinoline (50 μL), and Lindlar catalyst (11.2 mg). The mixture was stirred at 25 °C under a hydrogen atmosphere and the reaction was monitored by HPLC (reverse phase–ODS Column, MeOH:H_2O, 70:30) and allowed to proceed to ca. 70% completion. The catalyst was then filtered off and the solvent removed. The product was flash-chromatographed (silica, MeOH:CH_2Cl_2, 5:95) to remove quinoline and the resulting oil was purified by HPLC to give, after removal of solvents, compound **30** (47.4 mg, 43% yield), its all-trans isomer **32** (10.7 mg, 10% yield), and recovered starting material (25 mg, 23%). **27**: R_f 0.31 (silica, MeOH:CH_2Cl_2, 5:95) $[\alpha]^{24}_D$ +6.00° (*c* 0.08, CH_2Cl_2); UV (MeOH) λ_{max} 275, 288, 301, 315; IR (CH_2Cl_2) ν_{max} 3610, 3460, 3110, 2940, 2875, 1740 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.66 (m, 2 H, olefinic), 6.38 (dd, *J* = 14.7, 10.9 Hz, 1 H, olefinic), 6.21 (dd, *J* = 14.3, 10.7 Hz, 1 H, olefinic), 6.01 (m, 2 H, olefinic), 5.70 (m, 2 H, olefinic), 4.17 (m, 1 H, C*H*–O), 3.96 (t, *J* = 6.0Hz, 1 H, C*H*–O), 3.65 (s, 3 H, COOCH_3), 3.45 (m, 1 H, C*H*–O), 2.33 (t, *J* = 7.0 Hz, 2 H, CH_2COOCH$_3$), 2.50–2.20 (m, 2 H, O*H*), 1.90–1.20 (m, 13 H, CH_2 and *O*H), 0.87 (t, *J* = 7.0 Hz, 3 H, CH_3); HPLC data (MeOH:H_2O, 70:30, Ultrasphere ODS Column 1.0 cm × 25 cm, 2.0 mL/min, 0.1 AUFS, 300NM detector) R_t 9.5 min; HRMS calcd for $C_{30}H_{58}O_5Si_3$ (tris–TMS ethers) 582.3592, found for (M + 1) 583.3676.

All-trans isomer **32**: R_f 0.31 (silica, MeOH–CH_2Cl_2, 5:95); $[\alpha]^{23}_D$ −2.42° (*c* 1.0, CH_2Cl_2); UV (MeOH) λ_{max} 275, 290, 301, 315; IR (C-H_2Cl_2) ν_{max} 3600, 3450, 2960, 2940, 2860, 1735, 1005, 910 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.33–6.14 (m, 5 H, olefinic), 5.90–5.60 (m, 3 H, olefinic), 4.15 (m, 1 H, C*H*–O), 3.97 (m, 1 H, C*H*–O), 3.65 (s, 3 H, COOCH_3), 3.60 (m, 1 H, C*H*—O) 2.45 (br s, 1 H, O*H*), 2.35 (t, *J* = 6.0 Hz, 2 H, CH_2COOCH$_3$), 2.22 (br s, 1 H, O*H*), 1.90–1.10 (m, 13 H, CH_2 and O*H*), 0.85 (br t, *J* = 7.0 Hz, 3 H, CH_3); HRMS calcd for $C_{30}H_{58}O_5Si_3$ 582.3592, found for (M + 1) 583.3676; HPLC data (conditions same as above) R_t 7.8 min.

Data for 5(*R*),6(*S*),15(*S*),Δ^{11} Cis Isomer 35: R_f 0.35 (silica, MeOH–CH_2Cl_2, 5:95); $[\alpha]^{25}_D$ +25.90° (*c* 0.27, $CHCl_3$); UV (MeOH) λ_{max} 275, 286, 299, 313 nm; IR ($CHCl_3$) ν_{max} 3610, 3460, 3010, 2940, 2870, 1735, 1250, 1000 cm^{-1}; H^1 NMR (250 MHz, $CDCl_3$) δ 6.71–6.62 (m, 2 H, olefinic), 6.41–6.17 (m, 2 H, olefinic), 6.02–5.98 (m, 2 H, olefinic), 5.78–5.72 (m, 2 H, olefinic), 4.20–4.12 (m, 2 H, C*H*–O), 3.65 (m, 3 H, COOCH_3), 3.57 (m, 1 H, C*H*–O), 2.34 (t, *J* = 7.1, 2 H, CH_2COOCH$_3$), 2.21 (br s, 1 H, O*H*), 2.08 (br s, 1 H, O*H*), 1.86–1.16 (m, 13 H, CH_2, O*H*), 0.84 (t, *J* = 8.6 Hz, 3 H, CH_3); HPLC R_t 7.8 min (same conditions as for compound **30**); HRMS calcd for $C_{30}H_{58}O_5Si_3$ (tris–TMS ether) 582.3592, found for (M + 1) 583.3572.

Data for 5(*R*),6(*S*),15(*S*),Δ^{11} Trans Isomer 38: R_f 0.35 (silica, MeOH–CH_2Cl_2, 5:95); $[\alpha]^{25}$D +1.50 (*c* 0.2, $CHCl_3$); UV (MeOH) λ_{max} 275, 288, 301, 315 nm; IR ($CHCl_3$) ν_{max} 360, 3010, 3930, 2860, 1730, 1230, 1005 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.28–6.21 (m, 6 H, olefinic), 5.75–5.28 (m, olefinic), 4.14 (m, 2 H, C*H*–O), 3.75–3.57 (m, 1 H, C*H*–O), 3.65– (s, 3 H, COOCH_3), 2.34 (t, *J* = 7.1 Hz, 2 H, CH_2COOCH$_3$), 2.10 (m, 1 H, O*H*), 1.94 (m, 1 H, OH), 1.93–1.19 (m, 13 H, C*H*OH), 0.87 (br t, *J* = 5.7 Hz, 3 H, CH_3); HPLC R_t 10.2 min (same conditions as for compound **30**); HRMS Calcd for $C_{30}H_{58}O_5Si_3$ (tris–TMS ether) 582.3592, found for (M + 1) 583.3586.

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