intensity) 139 (M + $NH_4^+$, 78), 122 ($M^+$ + H, 50), 104 (100); HRMS calcd for $C_6H_8D_5O_2$ ($M^+$ + H) 122.1229, found 122.1223.

**Methyl (7*E*,9*E*,11*Z*,13*E*,5*S*,6*R*,15*S*)-5,6,15-Trihydroxy-19,19,20,20,20-pentadeuterio-7,9,11,13-eicosatetraenoate (19,19,20,20,20-Pentadeuteriolipoxin $A_4$ Methyl Ester) (2).** To a stirred solution of acetylene **34** (50.3 mg, 0.136 mmol) in $CH_2Cl_2$ (4.5 mL) was added Lindlar catalyst (Fluka, 15 mg, 30% w/w). The mixture was stirred under a hydrogen atmosphere at room temperture with monitoring by HPLC (Altex reverse phase-ODS C-18 column, MeOH/$H_2O$ 70:30, flow rate 5 mL/min, $\lambda_{max}$ 300 nm, UV detector) and allowed to proceed to ca. 85% completion (2.5 h). The catalyst was filtered off through Celite and the solvent was evaporated. The resulting oil was dissolved in MeOH (2 mL) and purified by reverse-phase HPLC (same conditions as above, $t_R$ 11.6 min) to give, after removal of the solvents, compound **2** (27.3 mg, 54%). **2**: white waxy solid; $R_f$ 0.31 (silica, 5% MeOH in $CH_2Cl_2$); $[\alpha]^{24}_D$ +23.7° (*c* 0.63, $CH_2Cl_2$); UV (MeOH) $\lambda_{max}$ 288, 300, 315 nm; IR ($CH_2Cl_2$) $\nu_{max}$ 3558, 3027, 2960, 2867, 2210, 2115, 1740, 1613, 1460, 1440, 1240, 1005, 985 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.67 (m, 2 H, olefinic), 6.35 (m, 1 H, olefinic), 6.25 (m, 2 H, olefinic), 6.03 (m, 2 H, olefinic), 5.78 (m, 2 H, olefinic), 4.20 (m, 1 H, C*H*OH), 4.15 (m, 1 H, C*H*OH), 3.70 (m, 4 H, C*H*OH, COOC$H_3$), 2.36 (t, $J$ = 6.6 Hz, $CH_2$COOMe), 1.35–1.26 (multiplets 13 H, O*H*, $CH_2$).

**Gas Chromatography–Mass Spectroscopy Methods.** Gas chromatography–mass spectrometry was performed with a Hewlett-Packard 5988A MS instrument equipped with a 59970A workstation and 5890 GC. A fused capillary column (SE-30 2-40004, 30 m, 0.25-mm i.d., 0.25 $\nu$M *df*; Supelco, Inc., Bellefonte, PA) was employed with a temperature program. The splitless on time was 0.9; initial temperature was 150 °C (1 min), followed by 230 °C (4 min), 250 °C (8 min), and 245 °C (12.0). The retention times for standard fatty acid methyl esters (carbons 20–26) in this system were 9.1 min (C20), 13.1 min (C22), 18.8 min C24), and 28.2 min (C26). Samples were treated with diazomethane, and trimethylsilyl ($Me_3Si$) derivatives were prepared (3) just prior to analysis on GC-MS.

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**Supplementary Material Available:** $^1H$ NMR and IR spectra of compounds **1**, **2**, **8**, **10**, **13**, **19**, **20**, **24**, **25**, **27–31**, **33**, and **33**; D and $^{13}C$ NMR spectra of compound **20** (17 pages). Ordering information is given on any current masthead page.

# Total Synthesis of Novel Geometric Isomers of Lipoxin $A_4$ and Lipoxin $B_4$

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Methyl esters of the geometric isomers of lipoxin $A_4$ and lipoxin $B_4$ **1–4** were synthesized by stereoselective routes. Compound **1** was constructed from key intermediates **13** and **20** by phosphonate–aldehyde condensation followed by deprotection and Lindlar hydrogenation. Compound **2** was synthesized by Pd(0)–Cu(I)-catalyzed coupling of fragments **25** and **26** followed by deprotection and selective reduction. Compound **3** was prepared via phosphonate–aldehyde coupling of intermediates **34** and **35** followed by deprotection and selective reduction. Compound **4** was synthesized via Pd(0)–Cu(I) coupling of key segments **41** and **42** followed by deprotection and selective hydrogenation.

## Introduction

In 1984, the isolation of a novel series of linear trihydroxy eicosanoids that contain a conjugated tetraene system in their structure was reported.[1] This series of oxygenated products of arachidonic acid was first isolated from human leukocytes incubated with 15(*S*)-hydroperoxy-5,8,11,13-eicosatetraenoic acid (15-HPETE).[1] Subsequent findings indicate that they can also be generated from 15(*S*)-hydroxy-5,8,11,13-eicosatetraenoic acid (15-HETE) by human neutrophils[2] and from endogenous arachidonic acid upon activation of human granulocytes from eosinophilic donors.[3]

Studies with isotopic oxygen ($^{18}O_2$) and intact human leukocytes revealed that lipoxin $A_4$ and lipoxin $B_4$ each carried an $^{18}O$ atom at carbon 5 and that oxygen substituents at carbon 6 of lipoxin $A_4$ and carbon 14 of lipoxin $B_4$ were not derived exclusively from molecular oxygen.[2,4] These results together with those obtained from alcohol trapping experiments indicated the involvement of a 5,6-epoxy tetraene intermediate (Scheme I) in the formation of lipoxin $A_4$ and lipoxin $B_4$ as well as their nonenzymatically derived isomers.[2,4,5] Total synthesis[6] of this epoxide followed by biogenetic studies with human leukocytes[5] as well as results obtained with 15-HETE and human neutrophils[7] revealed the generation of additional compounds

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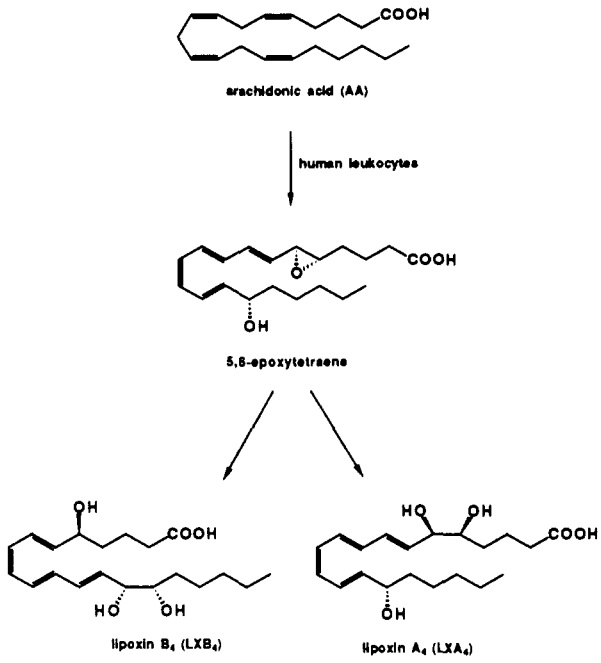
**Scheme I. Biosynthesis of Lipoxins $A_4$ and $B_4$**




that contained the basic lipoxin structure (i.e., trihydroxy tetraenes). Further studies with the new compounds indicated that at least one of the neutrophile-derived products was a geometric isomer of lipoxin $A_4$ and that they displayed biological activities.[7] In order to aid in the complete stereochemical assignment of their structure as well as to make them available for further biological investigations, we set out to synthesize several new geometric isomers of lipoxin $A_4$ and lipoxin $B_4$. It is now clear that lipoxin $A_4$ and lipoxin $B_4$ display highly stereospecific biological responses.[1c,8] Therefore, availability of geometric isomers in the tetraene system will also provide materials for detailed evaluation of the structure–activity relationships for lipoxins in various tissues. In this paper, we report stereoselective syntheses of four such isomers (compounds 1–4, Scheme II).

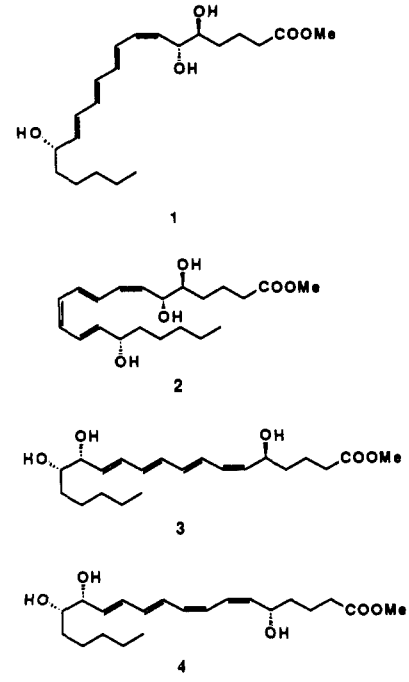
## General Strategy

On the basis of biosynthetic considerations and hydrogenation experiments the four geometrical isomers of lipoxins $A_4$ and $B_4$ shown in Scheme II were chosen as the initial targets for synthesis. These targets retain the 5*S*,6*R*,15*S* and the 5*S*,14*R*,15*S* stereochemistry of lipoxins $A_4$ and $B_4$, respectively, but differ from the original lipoxins in the geometry of their tetraene system. The construction of these new lipoxins was based on our previously outlined strategy toward linear eicosanoids[9] in which both the absolute stereochemistry of the stereogenic centers and the geometry of the double bonds is controlled in a predictable manner. As previously,[9] the powerful Pd(0)–Cu(I)-catalyzed coupling reaction between terminal acetylenes and vinyl halides features heavily in these syntheses.

## Total Synthesis

### Methyl 5(*S*),6(*R*),15(*S*)-Trihydroxy-9,13-*trans*,-7,11-*cis*-eicosatetraenoate (7-*cis*,11-*trans*-LXA$_4$ Methyl Ester) (1).

**Scheme II. Newly Synthesized Geometrical Lipoxin Isomers**




The total synthesis of 7-*cis*,11-*trans*-lipoxin $A_4$ methyl ester (1) is detailed in Scheme III. It began with the previously synthesized aldehyde **5**,[9] which was transformed to acetylene **8** by the Corey–Fuchs[10] procedure. Thus, condensation of **5** with $Ph_3P$–$CBr_4$ resulted in the formation of dibromo olefin **6** (83%), the methyl ester of which was temporarily reduced with DIBAL (**6** → **7**, 94%) to allow methyllithium-induced acetylene formation (**8**, 91%) via compound **7**. Reoxidation of the primary alcohol in **8** with pyridinium dichromate (PDC) followed by methylation with $CH_2N_2$ led to the requisite acetylene **9** in 78% overall yield. Coupling of **9** with vinyl bromide **10**[11] under the influence of Pd(0)–Cu(I) catalysis[12] produced exclusively the trans enyne **11** (89%). It was found necessary to carry out this coupling reaction with excess vinyl bromide (3 equiv) and in a relatively concentrated solution in $Et_2NH$ (2.4 M) in order to avoid dimerization of the acetylene. Transformation of the allylic alcohol **11** to the bromide **12** and subsequently to phosphonate **13** followed standard conditions (67% overall yield).

The other requisite fragment, aldehyde **20**, was synthesized from epoxide **14** (obtained from 2(*E*)-octen-1-ol by Sharpless asymmetric epoxidation[13]) by the sequence shown in Scheme III. Thus, reductive opening of **14** with DIBAL led to a mixture of 1,2-(**15**) and 1,3-diols (80% total yield, ca. 1.8:1 ratio) that was monopivalated and chromatographically separated to its components (**16**, 51%, 1,3-isomer of **16**, 29%). Pure **16** was then silylated with $^t$BuMe$_2$SiOTf and treated with DIBAL to afford primary alcohol **18** (87% overall yield). Swern[14] oxidation of **18** followed by condensation with (triphenylphosphoranylidene)acetaldehyde gave the $\alpha,\beta$-unsaturated

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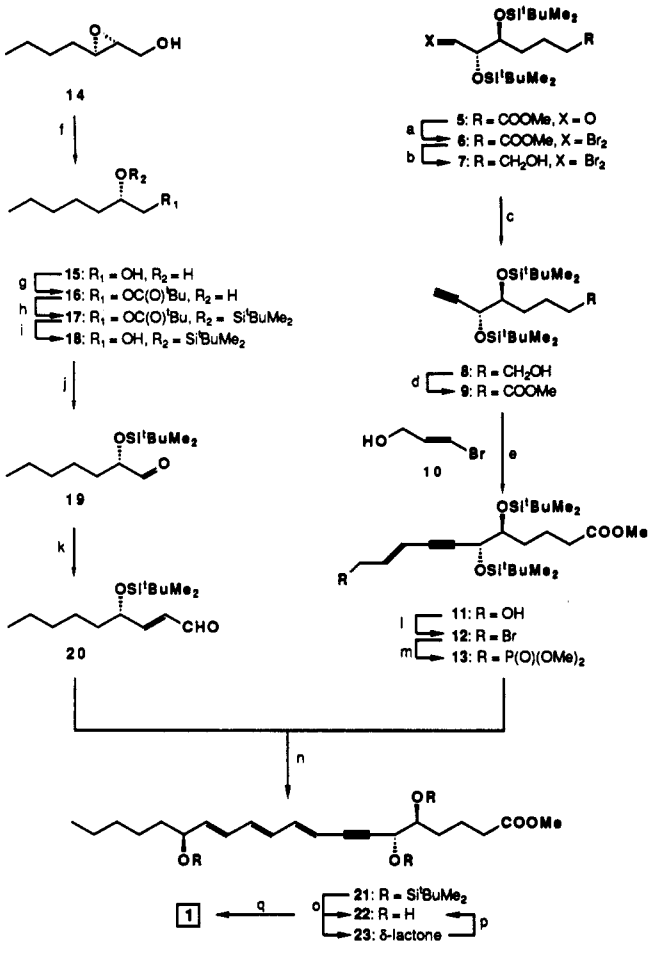
**Scheme III. Total Synthesis of 7-*cis*,11-*trans*-Lipoxin $A_4$ Methyl Ester (1)[a]**




[a] Reagents and conditions: (a) 4.5 equiv of $Ph_3P$, 2.2 equiv of $CBr_4$, $CH_2Cl_2$, 0 °C, 2 h, 83%; (b) 2.5 equiv of DIBAL, $CH_2Cl_2$, −78 °C, 0.5 h, 94%; (c) 3.0 equiv of MeLi, THF, −78 °C, 1 h, 91%; (d) 5.0 equiv of PDC, DMF, 25 °C, 12 h, then $CH_2N_2$, $Et_2O$, 0 °C, 78% overall; (e) 0.05 equiv of $Pd(PPh_3)_4$, 0.16 equiv of CuI, $Et_2NH$ (2.4 M solution), 25 °C, 4 h, 89%; (f) 3.5 equiv of DIBAL, $CH_2Cl_2$–hexanes (1:3), −10 °C, 1 h, 80%; (g) 1.05 equiv of $^t$BuCOCl, 1.1 equiv of DMAP, $CH_2Cl_2$, 0 °C, 10 h, 51% (15), 29% (1,3-isomer of 15); (h) 1.6 equiv of $^t$BuMe$_2$SiOTf, 2.1 equiv of 2,6-lutidine, $CH_2Cl_2$, 0 °C, 6 h, 100%; (i) 2.4 equiv of DIBAL, $CH_2Cl_2$, −78 °C, 1 h, 87%; (j) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, 5.0 equiv of $Et_3N$, −78 → 0 °C, 1 h; (k) 1.0 equiv of $Ph_3P$=CHCHO, benzene, 25 °C, 4 h, 50% overall; (l) 1.3 equiv of $Ph_3P$, 1.2 equiv of $CBr_4$, $CH_2Cl_2$, −40 → 0 (°C, 1 h, 95% (m) 1.2 equiv of $P(OMe)_3$, 110 °C, 4 h, 71%; (n) 0.9 equiv of LDA, 0.95 equiv of **20**, THF, −78 °C, 1 h, 67%; (o) 3.1 equiv of KF·2$H_2O$, DMF, 48 h, 82%; (p) 3.0 equiv of $Et_3N$, MeOH, 25 °C, 0.5 h, 100%; (q) $H_2$, 10% weight Lindlar cat., $CH_2Cl_2$, 25 °C, 4 h, 47%.

aldehyde **20** in 50% overall yield.

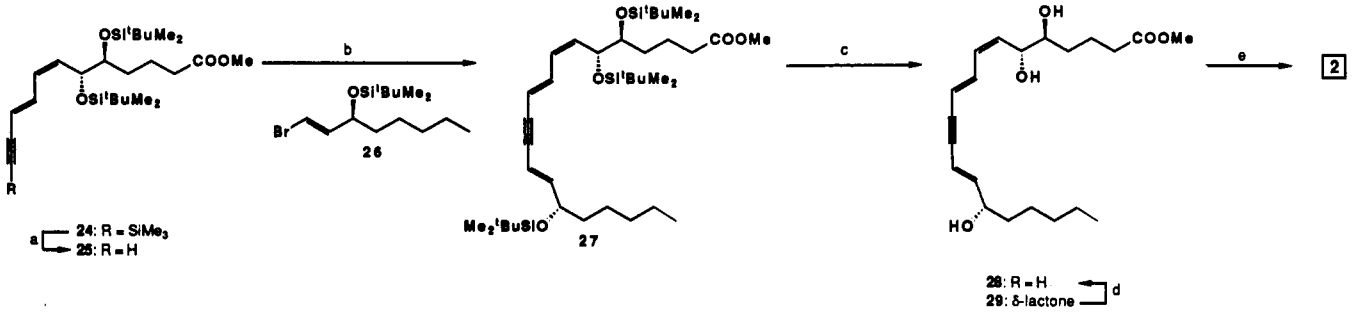
A Horner–Emmons reaction was then used to couple phosphonate **13** with aldehyde **20**, leading to the *E,E,E*-trienyne **21** (67% yield). Evidence for the trans geometry for the newly generated double bond was obtained from the $^1$H NMR spectrum of **21**, which revealed a coupling constant ($J$) of 15.3 Hz for $H_{11}$ and $H_{12}$. Desilylation of **21** with KF in DMF resulted in the formation of triol **22** and δ-lactone **23** (**22**:**23** ca. 3:1), which was dissolved in methanol and treated with $Et_3N$, leading exclusively to triol **22** (82%). Finally selective hydrogenation of **22** under Lindlar conditions led to the desired 7-*cis*,11-*trans*-lipoxin $A_4$ methyl ester (**1**) (47% yield after HPLC purification; Altex semipreparative, reverse-phase ODS column, MeOH/$H_2O$ 70:30, 3 mL/min flow rate, $t_R$ 19.9 min).

**Methyl 5(*S*),6(*R*),15(*S*)-Trihydroxy-9,13-*trans*-,7,11-*cis*-eicosatetraenoate (7-*cis*-Lipoxin $A_4$ Methyl Ester) (2).** The total synthesis of 7-*cis*-lipoxin $A_4$ as its methyl ester **2** is outlined in Scheme IV. Thus, the previously reported trimethylsilylated acetylenic compound **24**[9] was deprotected with $AgNO_3$–KCN to afford the free terminal acetylene **25** in 96% yield. Coupling of **25** with known[9] *trans*-vinyl bromide **26** under the standard Pd(0)–Cu(I) conditions led to compound **27** in 90% yield. Removal of the silyl protecting groups from **27** with excess HF·pyr led to triol **28** (65%) accompanied by the corresponding δ-lactone **29** (21%). δ-Lactone **29** was treated with $Et_3N$ in methanol as described above to afford triol **28** (86%). Semihydrogenation of **28** under the conditions described above for **1** led to the targeted 7-*cis*-lipoxin $A_4$ methyl ester (**2**) in 41% yield after HPLC (conditions as described above, $t_R$ 14.8 min).

The two new lipoxin $A_4$ isomers as their methyl esters (**1** and **2**) were compared with the 5(*S*),6(*R*),15(*S*)-lipoxin $A_4$ methyl ester derived from a biological source (diazomethane treatment, hydrogenation experiments had established the location and sterochemistry of the hydroxy groups in the naturally occurring material). These comparisons showed that the biologically derived material was identical with synthetic 7-*cis*,11-*trans*-lipoxin $A_4$ methyl ester (**1**) by UV, HPLC, GC, GC-MS, and bioassay.[7] With the identification of the new lipoxin $A_4$ isomer **1** as a natural product, we then proceeded to synthesize the lipoxin $B_4$ isomers **3** and **4** (Scheme II) in the hope that they might match biologically derived materials.

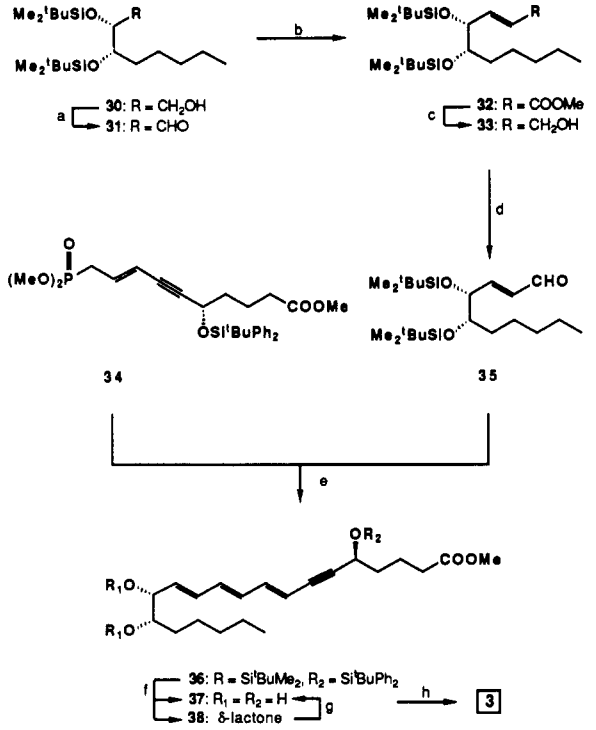
**Methyl 5(*S*),14(*R*),15(*S*)-Trihydroxy-6-*cis*,8,10,12-*trans*-eicosatetraenoate (6-*cis*,8-*trans*-Lipoxin $B_4$ Methyl Ester) (3).** Scheme V outlines the synthesis of the 6-*cis*,8-*trans*-lipoxin $B_4$ methyl ester (**3**). Thus, the previously reported alcohol **30**[15] was oxidized with $SO_3$·pyr

**Scheme IV. Total Synthesis of 7-*cis*-Lipoxin $A_4$ Methyl Ester (2)[a]**




[a] Reagents and conditions: (a) 4.0 equiv of $AgNO_3$, then 7.0 equiv of KCN, EtOH/THF/$H_2O$ (1:1:1), 0 → 25 °C, 2 h, 96%; (b) 1.2 equiv of **27**, 0.04 equiv of $(Ph_3P)_4Pd$, 0.16 equiv of CuI, 1.4 equiv of $^n$PrNH$_2$, benzene, 25 °C, 5 h, 90%; (c) 10 equiv of HF·pyr, THF, 0 → 25 °C, 4 h, 65% (**28**), 21% (**29**); (d) 3.0 equiv of $Et_3N$, MeOH, 25 °C, 0.5 h, 100%; (e) $H_2$, 20% by weight Lindlar cat., quinoline, $CH_2Cl_2$, 3 h, 41%.

**Scheme V. Total Synthesis of 6-*cis*,8-*trans*-Lipoxin $B_4$ Methyl Ester (3)[a]**

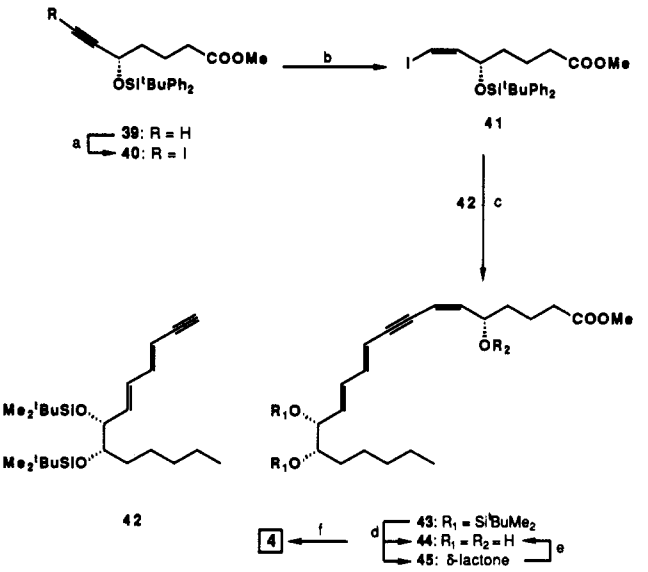



[a] Reagents and conditions: (a) 2.5 equiv of $SO_3$·pyr, 5 equiv of $Et_3N$, DMSO, $CH_2Cl_2$, 0 °C, 12 h; (b) 2 equiv of $Ph_3P$=CHCOOMe, 25 °C, 14 h, 79.1% two steps, trans:cis ca. 9:1; (c) 2.4 equiv of DIBAL, $CH_2Cl_2$, −78 °C, 2 h, 94%; (d) 2.2 equiv of $CrO_3$·pyr-HCl, 1.1 equiv of 3,5-dimethylpyrazole, $CH_2Cl_2$, 0 °C, 2 h, 99%; (e) 1.3 equiv of **34**, 1.2 equiv of $LiN(SiMe_3)_2$, THF, −78 °C, 10 min, 85%, trans:cis > 20:1; (f) 10 equiv of HF·pyr, THF, 0 → 25 °C, 61% (**37**), 17% (**38**); (g) 3 equiv of $Et_3N$, MeOH, 25 °C, 15 min; 100%; (h) $H_2$, 20% by weight Lindlar cat., quinoline, $CH_2Cl_2$, 2.5 h, 57%.

to aldehyde **31**, which was then condensed with the appropriate stabilized phosphorane to afford the $\alpha,\beta$-unsaturated ester **32** (79% yield, *E*:*Z* ca. 9:1 ratio). Reduction of the ester **32** with excess DIBAL resulted in the formation of allylic alcohol **33** (94%), which was oxidized back to the aldehyde **35** with PCC–3,5-dimethylpyrazole in 99% yield. Aldehyde **35** was then condensed with the lithio anion of phosphonate **34**,[16] leading to compound **36** in 85% yield (*E*:*Z* > 20:1). Desilylation of **36** with excess HF·pyr led to triol **37** (61% yield) together with the corresponding δ-lactone **38** (17% yield). Treatment of **38** with $Et_3N$ in methanol gave quantitatively triol **37**. Finally hydrogenation of **37** with Lindlar catalyst in the presence of quinoline led to the desired lipoxin $B_4$ isomer methyl ester **3** (57% yield after HPLC purification as described above, $t_R$ 13.4 min).

**Methyl 5(*S*),14(*R*),15(*S*)-Trihydroxy-6,8-*cis*,10,12-*trans*-eicosatetraenoate (6-*cis*-Lipoxon $B_4$ Methyl Ester) (4).** The construction of the 6-*cis*-lipoxin $B_4$ methyl ester isomer (**4**) is shown in Scheme VI. Thus, iodonation of acetylene **39**[16] with iodine in the presence of morpholine[17] yielded iodoacetylene **40** (93%), which was selectively reduced with diimide to the *cis*-vinyl iodide **41** (99%). Coupling of **41** with the acetylenic compound **42** under the influence of $Pd(PPh_3)_4$–CuI catalysis in $Et_2NH$ gave streoselectively compound **43** in 92% yield. Deprotection

**Scheme VI. Total Synthesis of 6-*cis*-Lipoxin $B_4$ Methyl Ester (4)[a]**




[a] Reagents and conditions: (a) 3.5 equiv of morpholine, 1.1 equiv of $I_2$, benzene, 45 °C, 2.5 h, 93%; (b) 1.1 equiv of KOOCN=NCOOK, 2.1 equiv of AcOH, 5.7 equiv of pyridine, MeOH, 25 °C, 2 h, 99%; (c) 0.05 equiv of $Pd(PPh_3)_4$, 0.16 equiv of CuI, $Et_2NH$, 25 °C, 10 min, 92%; (d) 10 equiv of HF·pyr, THF, 0 → 25 °C, 4 h, 52% (**44**), 23% (**45**); (e) 3.0 equiv of $Et_3N$, MeOH, 25 °C, 15 min, 100%; (f) $H_2$, 10% by weight Lindlar cat., quinoline, $CH_2Cl_2$, 25 °C, 2 h, 69%.

of **43** with excess HF·pyr resulted in the formation of triol **44** (52%) and its corresponding δ-lactone **45** (23%), which were separated chromatographically. Conversion of **45** to **44** was easily achieved by the action of $Et_3N$ as described above (100% yield). Lindlar hydrogenation of **44** in the presence of quinoline completed the synthesis of **4** (69% yield after HPLC purification under the above-mentioned conditions, $t_R$ 16.2 min).

## Conclusion

Four new isomers of lipoxin $A_4$ and lipoxin $B_4$ were synthesized as their methyl esters (**1**–**4**). A powerful strategy based on Pd(0)–Cu(I) coupling reactions of terminal acetylene with vinyl halides was employed to deliver these compounds in stereocontrolled fashion. Comparisons of these compounds with biologically derived materials established the complete structure of a new naturally occurring lipoxin $A_4$ as **1**.[7] Investigations for the identification of further naturally occurring lipoxins and relating to the biological activities of the synthesized compounds are in progress and will be reported in due course. The availability of these stereoisomers has already provided further evidence for the high degree of stereospecificity involved in evoking biological responses by lipoxins.[18]

## Experimental Section

**General.** NMR spectra were recorded on an IBM AF-250 or a Bruker AM-500 instrument. IR spectra were recorded on a Perkin-Elmer Model 781 infrared spectrophotometer. UV spectra were recorded on a Perkin-Elmer Model 553 ultraviolet–visible spectrophotomer.

High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VC ZAB E instrument under FAB conditions. Elemental analyses were performed by Galbraith Laboratories

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(17) Southwick, P. L.; Kirchner, J. R. *J. Org. Chem.* **1962**, *27*, 3305.
(18) Dahlen, S.-E.; Veale, C. A.; Webber, S. E.; Marron, B. E.; Nicolaou, K. C.; Serhan, C. N. *Agents Actions*, in press.

Inc., Knoxville, TN, or Robertson Laboratories, Inc., Madison, NJ.

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% ethanolic phorphomolybdic acid–heat as developing agent. Preparative layer chromatography was performed on 0.5 or 0.25 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.063) 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. Yields refer to chromatographically and spectroscopically ($^1$H NMR) homogeneous materials, unless otherwise stated.

**Methyl (5*S*,6*R*)-5,6-Bis(*tert*-butyldimethylsiloxy)-8,8-dibromo-7-octenoate (6).** To a solution of triphenylphosphine (3.5 g, 13.5 mmol) in $CH_2Cl_2$ (12 mL) at 0 °C was added carbon tetrabromide (2.2 g, 6.7 mmol) in three equal portions over a period of 0.5 h. The resulting solution was allowed to stir at 0 °C for a further 0.5 h. To this mixture was then added a solution of aldehyde **5** (1.25 g, 3.0 mmol) in $CH_2Cl_2$ (5 mL), and the resulting solution was stirred for 1 h at 0 °C. The reaction mixture was diluted with ether (200 mL) and the precipitated triphenylphosphine oxide was removed by filtration. The filtrate was washed with saturated $NaHCO_3$ (2 × 100 mL), $H_2O$ (2 × 100 mL), and brine (100 mL). The solution was dried ($MgSO_4$) and the solvent was removed to give an oil, which was chromatographed (silica, 5% ether in petroleum ether) to give pure dibromo olefin **6** (1.47 g, 83%). **6**: colorless oil; $R_f$ 0.40 (silica, 5% ether in petroleum ether); $[\alpha]^{21}_D$ −5.59° (*c* 0.55, $CHCl_3$); IR (neat) $\nu_{max}$ 3450, 2960, 2920, 2860, 1740, 1625, 1480, 1475, 1250, 1100, 840 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 6.31 (d, *J* = 8.6 Hz, 1 H, olefinic), 4.17 (dd, *J* = 8.6, 5.0 Hz, 1 H, -C*H*O-), 3.64 (s, 3 H, $COOCH_3$), 3.61 (dd, *J* = 9.0, 5.0 Hz, 1 H, -C*H*O-), 2.29 (t, *J* = 7.4 Hz, 2 H, $CH_2COOCH_3$), 1.70 (m, 2 H, -$CH_2$-), 1.55 (m, 1 H, -$CH_2$-), 1.49 (m, 1 H, -$CH_2$-), 0.87 (s, 9 H, Si$^t$*Bu*), 0.86 (s, 9 H, Si$^t$*Bu*), 0.08, 0.06, 0.05, 0.03 (singlets, 3 H each, $SiCH_3$); MS *m*/*e* (rel intensity) 517 ($M^+$ + H, 30), 445 (45), 385 (65), 245 (100), 213 (50), 147 (100); HRMS calcd for $C_{21}H_{43}O_4Br_2$ ($M^+$ + H) 517.1528, found 517.1531. Anal. Calcd: C, 43.92; H, 7.32; Br, 27.84. Found: C, 44.13; H, 7.08; Br, 27.61.

**(5*S*,6*R*)-5,6-Bis(*tert*-butyldimethylsiloxy)-8,8-dibromo-7-octen-1-ol (7).** To a solution of ester **6** (1.41 g, 2.5 mmol) in $CH_2Cl_2$ (12 mL) at −78 °C was added dropwise a solution of DIBAL (1.0 M in $CH_2Cl_2$, 6.3 mL, 6.3 mmol). The resulting solution was allowed to warm to 0 °C (20 min) and then recooled to −78 °C before quenching with methanol (5 mL). The mixture was warmed to room temperature, diluted with EtOAc (100 mL), washed with saturated sodium potassium tartrate (3 × 100 mL), dried ($MgSO_4$), and concentrated. The resulting oil was flash chromatographed (silica, 30% ether in petroleum ether) to give pure alcohol **7** (1.28 g, 94%). **7**: colorless oil; $R_f$ 0.8 (silica, 50% ether in petroleum ether); $[\alpha]^{21}_D$ −5.1° (*c* 2.65, $CHCl_3$); IR (neat) $\nu_{max}$ 3350, 2940, 2910, 2840, 1600, 1465, 1455, 1250, 1100, 840, 760 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, *J* = 8.5 Hz, 1 H, olefinic), 4.18 (dd, *J* = 8.5, 6.0 Hz, 1 H, -C*H*O-), 3.61 (m, 3 H, -C*H*O- and $CH_2$OH), 1.62–1.40 (m, 6 H, -$CH_2$-), 0.86 (s, 9 H, Si$^t$*Bu*), 0.84 (s, 9 H, Si$^t$*Bu*), 0.08, 0.07, 0.04, 0.01 (singlets, 3 H each, $SiCH_3$); MS *m*/*e* (rel intensity) 545 ($M^+$ + H), 489 (10), 415 (10), 357 (42), 283 (33), 147 (100); HRMS calcd for $C_{20}H_{42}O_3Si_2Br_2$ ($M^+$ + H) 545.1117, found 545.1124.

**(5*S*,6*R*)-5,6-Bis(*tert*-butyldimethylsiloxy)-7-octyn-1-ol (8).** To a solution of dibromo olefin **7** (958 mg, 1.76 mmol) in THF (6 mL) at −78 °C was added dropwise a solution of methyllithium (1.55 M in ether, 4 mL, 6.2 mmol), and the resulting solution was allowed to stir at that temperature for 1 h. The reaction mixture was then quenched with methanol (5 mL) and brought to room temperature. Dilution with ether (100 mL) followed by washing with saturated $NH_4Cl$ (50 mL) and $H_2O$ (50 mL), drying ($MgSO_4$), and removal of the solvent gave an oil, which was flash chromtographed (silica, 30% ether in petroleum ether) to give pure acetylene **8** (618 mg, 91%). **8**: colorless oil; $R_f$ 0.6 (silica, 30% ether in petroleum ether); $[\alpha]^{21}_D$ −27.7° (*c* 0.69, $CHCl_3$); IR (neat) $\nu_{max}$ 3400, 3340, 3100, 3040, 2980, 2950, 2880, 1485, 1475, 1280, 1100, 850, 790 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 4.20 (dd, *J* = 4.9, 2.1 Hz, 1 H, -C*H*O-), 3.69 (dd, *J* = 10.7, 4.9 Hz, 1 H, -C*H*O-), 3.62 (t, *J* = 6.6 Hz, 2 H, $CH_2$OH), 2.32 (d, *J* = 2.1 Hz, 1 H, acetylene), 1.61–1.39 (series of multiplets, 6 H, -$CH_2$-), 1.23 (br s, 1 H, O*H*), 0.88 (s, 9 H, Si$^t$*Bu*), 0.87 (s, 9 H, Si$^t$*Bu*), 0.12, 0.09, 0.07, 0.05 (singlets, 3 H each, $SiCH_3$); MS *m*/*e* (rel intensity) 387 ($M^+$ + H, 25), 371 (15), 337 (12), 329 (100), 313 (20); HRMS calcd for $C_{20}H_{42}O_3Si_2$ ($M^+$ + H) 387.2751, found 387.2784.

**Methyl (5*S*,6*R*)-5,6-Bis(*tert*-butyldimethylsiloxy)-7-octynoate (9).** To a solution of alcohol **8** (585 mg, 1.52 mmol) in DMF (5 mL) at 25 °C was added pyridinium dichromate (2.9 g, 7.6 mmol), and the resulting dark solution was allowed to stir at that temperature for 12 h. The solution was then diluted with ether (200 mL) and washed with $H_2O$ (5 × 50 mL) and brine (50 mL). Drying ($MgSO_4$) followed by solvent removal gave an oil, which was redissolved in ether (200 mL), cooled to 0 °C, and reacted with ethereal diazomethane until no more acid was present as indicated by TLC (silica, ether). The excess diazomethane was decomposed by addition of acetic acid (100 μL), and the solvent was removed to give an oil, which was chromatographed (silica, 5% ether in petroleum ether) to give pure ester **9** (490 mg, 78%). **9**: colorless oil; $R_f$ 0.3 (silica, 3% ether in petroleum ether); $[\alpha]^{24}_D$ −9.1° (*c* 0.61, $CHCl_3$); IR (neat) $\nu_{max}$ 3310, 2960, 2940, 2860, 1745, 1485, 1475, 1250, 1100, 840, 790 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 4.19 (m, 1 H, -C*H*O-), 3.68 (m, 1 H, -C*H*O-), 3.64 (s, 3 H, $COOCH_3$), 2.32 (m, 1 H, acetylenic), 2.28 (t, *J* = 7.1 Hz, 2 H, $CH_2COOCH_3$), 1.75–1.52 (series of multiplets, 4 H, -$CH_2$-), 0.87 (s, 18 H, 2 × Si$^t$*Bu*), 0.12, 0.09, 0.08, 0.05 (singlets, 3 H each, $SiCH_3$); MS *m*/*e* (rel intensity) 415 ($M^+$, 35), 399 (15), 357 (62), 283 (82), 245 (100), 225 (35); HRMS calcd for $C_{21}H_{43}O_4Si_2$ ($M^+$ + H) 415.2700, found 415.2681. Anal. Calcd: C, 60.86; H, 10.14. Found: C, 60.57; H, 10.07.

**Methyl (9*E*,5*S*,6*R*)-5,6-Bis(*tert*-butyldimethylsiloxy)-11-hydroxyundec-9-en-7-ynoate (11).** To a deoxygenated solution of vinyl bromide **10** (737 mg, 5.4 mmol), $Pd(PPh_3)_4$ (28 mg, 0.02 mmol), and CuI (150 mg, 0.78 mmol) in diethylamine (1 mL) was added a solution of acetylene **9** (2.01 g, 4.9 mmol) in diethylamine (2 mL), and the resulting solution was allowed to stir at 25 °C for 1 h. The solution was diluted with ether (250 mL) and then washed sequentially with saturated $NH_4Cl$ (100 mL), $H_2O$ (100 mL), and brine (50 mL). Drying ($MgSO_4$) and removal of the solvent gave an oil, which was flash chromatographed (silica, 20% ether in petroleum ether) to afford pure alcohol **11** (2.05 g, 89%). **11**: colorless oil; $R_f$ 0.4 (silica, 30% ether in petroleum ether); $[\alpha]^{24}_D$ −24.4° (*c* 0.92, $CHCl_3$); IR (neat) $\nu_{max}$ 3450, 2960, 2940, 2860, 1740, 1485, 1475, 1250, 1100, 840, 790 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 6.18 (dt, *J* = 15.9, 5.2 Hz, 1 H, $CH_2CH$=CH), 5.73 (dd, *J* = 15.9, 1.8 Hz, 1 H, $CH_2CH$=C*H*), 4.28 (dd, *J* = 5.4, 4.2 Hz, 1 H -C*H*O-), 4.19 (dd, *J* = 5.2, 1.7 Hz, 2 H, allylic $CH_2$OH), 3.68 (dd, *J* = 9.9, 5.2 Hz, 1 H, -C*H*O-), 3.63 (s, 3 H, $COOCH_3$), 2.28 (t, *J* = 7.3 Hz, 2 H, $CH_2COOCH_3$), 1.71–1.48 (series of multiplets, 5 H, -$CH_2$- and O*H*), 0.87 (s, 9 H, Si$^t$*Bu*), 0.86 (s, 9 H, Si$^t$*Bu*), 0.11, 0.08, 0.06, 0.04 (singlets, 3 H each, $SiCH_3$); HRMS calcd for $C_{24}H_{47}O_7Si_2$ ($M^+$ + H) 503.2860, found 503.2869.

**Methyl (9*E*,5*S*,6*R*)-5,6-Bis(*tert*-butyldimethylsiloxy)-11-bromoundec-9-en-7-ynoate (12).** To a solution of alcohol **11** (356 mg, 0.76 mmol) and triphenylphosphine (238 mg, 0.91 mmol) in $CH_2Cl_2$ (4 mL) at −40 °C was added carbon tetrabromide (328 mg, 1.0 mmol), and the resulting solution was stirred at that temperature for 2 h. The reaction mixture was then diluted with ether (100 mL), washed with saturated $NaHCO_3$ (2 × 50 mL) and $H_2O$ (50 mL), and dried ($MgSO_4$) and the solvent was removed under vacuum. The resulting oil was chromatographed (silica, 5% ether in petroleum ether) to furnish pure bromide **12** (385 mg, 95%). **12**: colorless oil; $R_f$ 0.5 (silica, 5% ether in petroleum ether); $[\alpha]^{24}_D$ −24.0° (*c* 1.12, $CHCl_3$); IR (neat) $\nu_{max}$ 2960, 2940, 2860, 1745, 1630, 1485, 1475, 1250, 1100, 840, 780 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 6.19 (dt, *J* = 15.4, 7.7 Hz, 1 H, -$CH_2CH$=CH-), 5.71 (d, *J* = 15.4 Hz, 1 H, $CH_2CH$=C*H*), 4.30 (d, *J* = 5.3 Hz, 1 H, -C*H*O-), 3.96 (d, *J* = 7.7 Hz, 2 H, $CH_2$Br), 3.69 (dd, *J* = 10.2, 5.3 Hz, 1 H, -C*H*O-), 3.64 (s, 3 H, $COOCH_3$), 2.29 (t, *J* = 7.1 Hz, 2 H, $CH_2COOCH_3$), 1.71–1.52 (series of multiplets, 4 H, -$CH_2$-), 0.87 (s, 18 H, 2 × Si$^t$*Bu*), 0.11, 0.09, 0.07, 0.05 (singlets, 3 H each, $SiCH_3$); MS *m*/*e* (rel intensity) 565 ($M^+$ + H, 5), 415 (35), 341 (60), 183 (100), 145 (72); HRMS calcd for $C_{24}H_{45}O_6Si_2Br$ ($M^+$ + H) 565.1938, found 565.2021.

**Methyl (9*E*,5*S*,6*R*)-5,6-Bis(*tert*-butyldimethylsiloxy)-11-(dimethylphosphono)undec-9-en-7-ynoate (13).** A solution

of bromide **12** (799 mg, 1.5 mmol) in trimethyl phosphite (3 mL) was heated at 100 °C for 5 h. Excess trimethyl phosphite was removed by distillation under aspirator vacuum at 60 °C. The resulting oil was purified by flash chromatography (silica, gradient elution, 1 → 3% MeOH in ether) to give pure phosphonate **13** (598 mg, 71%). **13**: colorless oil; $R_f$ 0.5 (silica, 1.5% MeOH in ether); $[\alpha]^{24}_D$ −22.0° (*c* 1.41, $CHCl_3$); IR (neat) $\nu_{max}$ 2980, 2960, 2875, 1750, 1485, 1475, 1270, 1100, 840, 790 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.97 (dt, *J* = 15.6, 7.7 Hz, 1 H, -$CH_2CH$=CH-), 5.60 (ddd, *J* = 15.6, 5.5, 1.6 Hz, 1 H, -$CH_2CH$=C*H*-), 4.28 (d, *J* = 5.5 Hz, 1 H, -C*H*O-), 3.74 (s, 3 H, $COOCH_3$), 2.67 (dd, *J* = 7.7, 1.2 Hz, 1 H, -$CH_2$P-), 2.63 (dd, *J* = 7.7, 1.2 Hz, 1 H, -$CH_2$P-), 2.28 (t, *J* = 7.2 Hz, 2 H, $CH_2COOCH_3$), 1.70–1.53 (series of multiplets, 4 H, -$CH_2$-), 0.87 (s, 18 H, 2 × Si*t*Bu), 0.10, 0.08, 0.06, 0.04 (singlets, 3 H each, $SiCH_3$); MS *m/e* (rel intensity) 563 ($M^+$ + H, 5), 547 (20), 531 (18), 505 (100), 473 (30), 432 (100); HRMS calcd for $C_{26}H_{51}O_7Si_2P$ ($M^+$ + H) 563.2911, found 563.3081. Anal. Calcd: C, 55.52; H, 9.08; P, 5.51. Found: C, 55.78; H, 9.25; P, 5.03.

**1,2(*S*)-Dihydroxyheptane (15) and Its 1,3-Regioisomer.** To a stirred solution of epoxy alcohol **14** (10.2 g, 78 mmol) in a mixture of $CH_2Cl_2$ and hexane (1:3, 150 mL) at −10 °C was added dropwise a solution of DIBAL (1.0 M in hexanes, 30.3 mL, 30.3 mmol), and stirring was continued for 0.5 h. The reaction was quenched by addition at −10 °C of a solution of NaF (96.6 g, 2.3 mol) in $H_2O$ (42 mL), and the resulting solution was stirred at ambient temperature for 1 h over which time a white solid separated from the solution. The solid was removed by filtration and excess $H_2O$ was removed by drying ($MgSO_4$) followed by a second filtration. The solvent was removed and the resulting material was chromatographed (silica, gradient elution, 5 → 7% MeOH in $CH_2Cl_2$) to give an inseparable mixture (ca. 1.8:1) of 1,2-diol **15** and its 1,3-regioisomer (8.2 g, 80%). **15 + regioisomer**: colorless oil; $R_f$ 0.7 (silica, 3% methanol in ether); IR (neat) $\nu_{max}$ 3400, 2980, 2955, 2880, 1470, 1140, 1080, 890 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 3.85 (multiplets, 1 H, -C*H*O-), 3.71 (m, 1 H, -C*H*O-), 3.63 (ddd, *J* = 11.0, 2.9, 1.1 Hz, 2 H, -$CH_2$O-), 3.40 (ddd, *J* = 11.0, 7.6, 1.1 Hz, 2 H, -$CH_2$O-), 2.10 (br s, 4 H, 4 × O*H*), 1.65 (m, 2 H, $CH_2CH_2OH$), 1.6–1.3 (series of multiplets, 14 H, -$CH_2$-), 0.87 (m, 6 H, $CH_3$); MS *m/e* (rel intensity) 150 (M + $NH_4^+$, 22), 133 (50), 115 (100); HRMS calcd for $C_7H_{20}O_2N$ (M + $NH_4^+$) 150.1478, found 150.1481.

**(2*S*)-1-(Trimethylacetoxy)heptan-2-ol (16).** To a stirred, cold (−10 °C) solution of diol **15** and its regioisomer obtained above (10.0 g, 76 mmol) and (*N*,*N*-dimethylamino)pyridine (10.2 g, 84 mmol) in $CH_2Cl_2$ (400 mL) was added, dropwise, over a period of 1 h, a solution of trimethylacetyl chloride (9.9 mL, 80 mmol) in $CH_2Cl_2$ (100 mL). The resulting solution was allowed to stir at that temperature for 2 h (TLC monitoring) and then quenched by addition of saturated $NaHCO_3$ (100 mL). Extraction with ether (1 L) followed by washing with $H_2O$ (200 mL) and brine (100 mL), drying ($MgSO_4$), and solvent evaporation gave a mixture of monopivalates, which were separated by chromatography (silica, 30% ether in petroleum ether) leading to pure pivalate **16** (8.42 g, 51%) and its isomeric compound (4.75 g, 29%). **16**: colorless oil; $R_f$ 0.3 (silica, 30% ether in petroleum ether); $[\alpha]^{21}_D$ 4.63° (*c* 0.95, $CHCl_3$); IR (neat) $\nu_{max}$ 3500, 2990, 2960, 2880, 1745, 1500, 1410, 1300, 1280 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.12 (dd, *J* = 11.4, 3.2 Hz, 1 H, -$CH_2$O-), 3.95 (dd, *J* = 11.4, 7.0 Hz, 1 H, -$CH_2$O-), 3.83 (m, 1 H, -C*H*O-), 1.96 (d, *J* = 4.1 Hz, 1 H, O*H*), 1.56–1.18 (series of multiplets, 8 H, -$CH_2$-), 0.87 (t, *J* = 6.8 Hz, 3 H, $CH_3$); MS *m/e* (rel intensity) 217 ($M^+$ + H, 45), 199 ($M^+$ − OH), 131 (15); HRMS calcd for $C_{12}H_{25}O_3$ ($M^+$ + H) 217.1804, found 217.1823.

**2(*S*)-(*tert*-Butyldimethylsiloxy)heptan-1-ol (18).** To a solution of ester **16** (8.42 g, 39 mmol) and 2,6-lutidine (9.6 mL, 82.4 mmol) in $CH_2Cl_2$ (80 mL) at 0 °C was added $^t$BuMe$_2$SiOTf (14.2 mL, 62 mmol), and the resulting solution was allowed to stir at that temperature for 1 h. The reaction was quenched by addition of saturated $NaHCO_3$ (50 mL) followed by extraction with ether (500 mL). The organic phase was washed with $H_2O$ (2 × 100 mL) and brine (100 mL) and dried ($MgSO_4$), and the solvent was removed under vacuum. The crude silyl ether was dissolved in $CH_2Cl_2$ (210 mL), cooled to −78 °C, and treated with DIBAL (1.0 M in $CH_2Cl_2$, 95 mL, 95 mmol). The reaction mixture was stirred at −78 °C for 1 h and then quenched with a saturated solution of sodium potassium tartrate (200 mL). The solution was allowed to warm to room temperature and then was extracted with EtOAc (1 L). The organic phase was washed with an additional portion of saturated sodium potassium tartrate (300 mL) and dried ($MgSO_4$), and the solvent was evaporated. The resulting crude material was chromatographed (silica, 10% ether in petroleum ether) to give pure alcohol **18** (8.33 g, 87% yield). **18**: colorless oil; $R_f$ 0.6 (silica, 20% ether in petroleum ether); $[\alpha]^{21}_D$ +10.5° (*c* 2.55, $CHCl_3$); IR (neat) $\nu_{max}$ 3400, 2980, 2945, 2880, 1480, 1475, 1270, 1100, 840, 790 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 3.70 (m, 1 H, -C*H*O-), 3.53 (m, 1 H, -C*H*O-), 3.41 (m, 1 H, -C*H*O-), 1.87 (t, *J* = 5.2 Hz, 1 H, O*H*), 1.45 (m, 2 H, -$CH_2$-), 1.35 (m, 6 H, -$CH_2$-), 0.87 (m, 12 H, overlapping $CH_3$ and Si*t*Bu), 0.06 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$); MS *m/e* (rel intensity) 247 ($M^+$ + H, 48), 215 ($M^+$ − $CH_2OH$, 100), 189 (50), 131 (15); HRMS calcd for $C_{13}H_{31}O_2Si$ ($M^+$ + H) 247.2093, found 247.2106.

**4(*S*)-(*tert*-Butyldimethylsiloxy)-2(*E*)-nonenal (20).** To a solution of oxalyl chloride (0.28 mL, 3.2 mmol) in $CH_2Cl_2$ (2 mL) at −78 °C was added dropwise DMSO (0.3 mL, 4.2 mmol), and the resulting solution was allowed to stir for 15 min. A solution of alcohol **18** (516 mg, 2.1 mmol) in $CH_2Cl_2$ (8 mL) was then added dropwise and the resulting solution was allowed to stir at −78 °C for 0.5 h. Triethylamine (1.5 mL, 10 mmol) was then added and the resulting mixture was stirred for 20 min followed by warming to room temperature. The reaction mixture was diluted with ether (100 mL) and washed with $H_2O$ (2 × 50 mL) and brine (50 mL). The solution was dried ($MgSO_4$) and the solvent was removed by evaporation. The crude aldehyde **19** was dissolved in benzene (5 mL), (triphenylphosphoranylidine)acetaldehyde (640 mg, 2.1 mmol) was added, and the resulting solution was allowed to stir for 12 h. The solvent was then removed by evaporation and the crude product was chromatographed (silica, 5% ether in petroleum ether) to give pure aldehyde **20** (284 mg, 50%). **20**: colorless oil; $R_f$ 0.5 (silica, 5% ether in petroleum ether); $[\alpha]^{21}_D$ +16.0° (*c* 1.66, $CHCl_3$); IR (neat) $\nu_{max}$ 2960, 2940, 2720, 1700, 1480, 1475, 1250, 1100, 840, 790 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 9.56 (d, *J* = 7.9 Hz, 1 H, -C*H*O-), 6.79 (dd, *J* = 15.5, 4.5 Hz, 1 H, C*H*=CHCHO), 6.22 (ddd, *J* = 15.5, 7.9, 1.5 Hz, 1 H, CH=C*H*CHO), 4.38 (ddd, *J* = 10.5, 6.0, 1.5 Hz, 1 H, -C*H*O-), 1.53 (m, 2 H, -$CH_2$-), 1.26 (m, 6 H, -$CH_2$-), 0.87 (m, 12 H, overlapping $CH_3$ and Si*t*Bu), 0.04 (s, 3 H, $SiCH_3$), 0.003 (s, 3 H, $SiCH_3$); MS *m/e* (rel intensity) 271 ($M^+$ + H, 10), 213 (100), 199 (30), 143 (30), 129 (65); HRMS calcd for $C_{15}H_{31}O_2Si$ ($M^+$ + H) 271.2093, found 271.2061. Anal. Calcd: C, 66.67; H, 11.11. Found: C, 66.32; H, 10.98.

**Methyl (9*E*,11*E*,13*E*,5*S*,6*R*,15*S*)-5,6,15-Tris(*tert*-butyldimethylsiloxy)-9,11,13-eicosatrien-7-ynoate (21).** To a solution of phosphonate **13** (590 mg, 1.05 mmol) in THF (3 mL) at −78 °C was added dropwise LDA (0.67 mL, 1.0 mmol, 1.5 M in THF), and the resulting solution was allowed to stir for 3 min. Aldehyde **20** (256 mg, 0.95 mmol) in THF (3 mL) was then added at −78 °C and stirring was continued for 2 h at that temperature before being warmed to room temperature. The reaction was then quenched by addition of saturated $NH_4Cl$ (5 mL) and diluted with ether (100 mL). The organic phase was washed with $H_2O$ (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated to give an oil. Flash chromatography (silica, 3% ether in petroleum ether) gave pure **21** (451 mg, 67%). **21**: colorless oil; $R_f$ 0.3 (silica, 3% ether in petroleum ether); $[\alpha]^{21}_D$ −15.5° (*c* 0.86, $CHCl_3$); IR (neat) $\nu_{max}$ 3140, 2980, 2940, 2780, 1755, 1485, 1475, 1270, 1100, 1000, 840, 780 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.52 (dd, *J* = 15.4, 10.5 Hz, 1 H, H-10), 6.25 (dd, *J* = 14.5, 10.5 Hz, 1 H, H-11), 6.17 (overlapping multiplets, 2 H, H-12, H-13), 5.71 (dd, *J* = 14.9, 6.3 Hz, 1 H, H-14), 5.54 (d, *J* ≈ 15.4 Hz, 1 H, H-9), 4.31 (dd, *J* = 5.5, 1.1 Hz, 1 H, H-6), 4.13 (dd, *J* = 12.2, 6.3 Hz, 1 H, H-15), 3.68 (dd, *J* = 9.9, 5.8 Hz, 1 H, H-5), 3.63 (s, 3 H, $COOCH_3$), 2.29 (t, *J* = 7.2 Hz, 2 H, H-2), 1.75–1.2 (series of multiplets, 14 H, -$CH_2$-), 0.87 (m, 12 H, overlapping $CH_3$, Si*t*Bu), 0.11–0.03 (series of singlets, 18 H, $SiCH_3$); MS *m/e* (rel intensity) 707 ($M^+$ + H, 20), 649 (60), 575 (100), 517 (55), 329 (45); HRMS calcd for $C_{39}H_{75}O_5Si_3$ ($M^+$ + H) 707.4922, found 707.4961. Anal. Calcd: C, 66.28; H, 10.48. Found: C, 65.95; H, 10.69.

**Methyl (9*E*,11*E*,13*E*,5*S*,6*R*,15*S*)-5,6,15-Trihydroxy-9,11,13-eicosatrien-7-ynoate (22).** To a solution of tris(silyl ether) **21** (353 mg, 0.5 mmol) and 18-crown-6 (53 mg, 0.2 mmol) in DMF (5 mL) was added KF·2$H_2O$ (150 mg, 1.6 mmol), and the resulting solution was stirred at 25 °C for 48 h. The reaction was quenched

by dilution with EtOAc (100 mL) and the solution was washed with a pH 5.0 phosphate buffer (2 × 50 mL) and brine (50 mL). Drying ($MgSO_4$) followed by solvent evaporation gave an oily mixture of **22** and **23** and saponified **22**. This mixture was dissolved in ether (100 mL), cooled to 0 °C, and treated with diazomethane ethereal solution). Evaporation of the solvent, dissolution in methanol (50 mL), and addition of triethylamine (5 mL) resulted in the formation of **22**, which was purified by evaporation and flash chromatography (silica, 5% MeOH in $CH_2Cl_2$) (150 mg, 82% yield). **22**: colorless oil; $R_f$ 0.6 (silica, 3% MeOH in ether); $[\alpha]^{21}_D$ +26.1° (*c* 0.49, $CHCl_3$); IR (neat) $\nu_{max}$ 3140, 2980, 2940, 2780, 1755, 1485, 1475, 1270, 1100, 1000, 840, 780 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.59 (dd, *J* = 15.6, 10.5 Hz, 1 H, H-10), 6.26 (dd, *J* = 15.3, 10.5 Hz, 1 H, H-11), 6.20 (m, 2 H, H-12, H-13), 5.77 (dd, *J* = 14.8, 6.6 Hz, 1 H, H-14), 5.59 (dd, *J* = 15.6, 1.7 Hz, 1 H, H-9), 4.44 (br s, 1 H, H-6), 4.15 (dd, *J* = 8.5, 6.6 Hz, 1 H, H-15), 3.68 (m, 1 H, H-5), 3.65 (s, 3 H, $COOCH_3$), 2.62 (d, *J* = 6.6 Hz, 1 H, O*H*), 2.36 (t, *J* = 7.3 Hz, 2 H, $CH_2COOCH_3$), 2.25 (d, *J* = 6.6 Hz, 1 H, O*H*), 1.95–1.2 (series of multiplets, 12 H, -$CH_2$-), 0.86 (t, *J* = 7.6 Hz, 3 H, $CH_3$); MS *m/e* (rel intensity) 365 ($M^+$ + H, 5), 347 (15), 329 (20), 216 (25), 131 (100); HRMS calcd for $C_{21}H_{33}O_5$ ($M^+$ + H) 365.2328, found 365.2311.

**Methyl (7*Z*,9*E*,11*E*,13*E*,5*S*,6*R*,15*S*)-5,6,15-Trihydroxy-7,9,11,13-eicosatetraenoate (1).** A mixture of acetylene **22** (21 mg, 0.06 mmol) and Lindlar's catalyst (palladium on calcium carbonate poisoned with lead, 11 mg) in $CH_2Cl_2$ (2 mL) was placed under a hydrogen atmosphere and stirred at 25 °C. The reaction was followed by HPLC (Altex C-18 semipreparative reverse-phase C-18 column, MeOH/$H_2O$ 70:30, flow rate 3.0 mL/min, $t_R$ (product) 19.9 min, UV detector at $\lambda_{max}$ 310 for product, 260 for overreduced product and 310 nm for starting material) monitoring. When the reaction was approximately 50% complete the hydrogen was replaced with an argon atmosphere, the catalyst was removed by filtration through Celite, and the solvent was evaporated. The crude material was dissolved in methanol (3 mL) and purified by HPLC (using the conditions above) to give tetraene **1** (9.8 mg, 47%). **1**: colorless oil; $R_f$ 0.35 (silica, 5% methanol in $CH_2Cl_2$); $[\alpha]^{21}_D$ +6.0° (*c* 0.4, $CH_2Cl_2$); UV (MeOH) $\lambda_{max}$ 288, 301, 315 nm; IR (neat) $\nu_{max}$ 3550, 3060, 2960, 2940, 2880, 1740, 1480, 1460, 1090, 850 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.47 (t, *J* = 12.6 Hz, 1 H, olefinic), 6.35–6.30 (m, 5 H, olefinic), 5.49 (t, *J* = 10.0 Hz, 1 H, H-7), 5.25 (dd, *J* = 14.0, 6.7 Hz, 1 H, H-14), 4.55 (m, 1 H, H-6), 4.20 (m, 1 H, H-15), 3.71 (m, 1 H, H-5), 3.64 (s, 3 H, $COOCH_3$), 2.34 (t, *J* = 7.0 Hz, 1 H, $CH_2COOCH_3$), 2.15 (br s, 1 H, O*H*), 2.0–1.2 (m, 14 H, -$CH_2$-, O*H*), 0.9 (t, *J* = 7.0 Hz, 3 H, $CH_3$); MS *m/e* (tris(trimethylsilyl ether) (rel intensity) 582 ($M^+$), 492, 482, 203 ($Me_3SiO^+$=$CH(CH_2)_3CO_2CH_3$, 100), 173 ($Me_3SiO^+$=$CH(CH_2)_4CH_3$, 60), 171 (203–32; elimination of $CH_3OH$, 25); HRMS (for triol) calcd for $C_{21}H_{35}O_5$ ($M^+$ + H) 367.2485, found 367.2413.

**Methyl (7*Z*,9*E*,11*Z*,13*E*,5*S*,6*R*,15*S*)-5,6,15-Trihydroxy-7,9,11,13-eicosatetraenoate (2).** Compound **2** was prepared according to Scheme IV. The proceudres were similar to the ones described for compounds **1**–**3**. HPLC purification (Altex C-18 ultrasphere semipreparative reverse-phase column, MeOH/$H_2O$ 70:30, flow rate 4.5 mL/min, $t_R$ 14.8 min) gave pure **2** (41%). **2**: white waxy solid; $R_f$ 0.35 (silica, 5% MeOH in $CH_2Cl_2$); $[\alpha]^{25}_D$ +6.0° (*c* 0.4, $CH_2Cl_2$); UV (MeOH) $\lambda_{max}$ 288, 302, 316 nm; IR ($CH_2Cl_2$) $\nu_{max}$ 3550, 2960, 2940, 2880, 1740, 1480, 1460, 1090, 850 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.47 (t, *J* = 12.6 Hz, 1 H, olefinic), 6.35–6.20 (m, 5 H, olefinic), 5.55 (dd, *J* = 14.0, 6.7 Hz, 1 H, H-14), 5.49 (t, *J* = 10 Hz, 1 H, H-7), 4.55 (m, 1 H, H-6), 4.20 (m, 1 H, H-15), 3.71 (m, 1 H, H-5), 3.64 (s, 3 H, $COOCH_3$), 2.34 (t, *J* = 7.0 Hz, $CH_2COOCH_3$), 2.15 (br s, 1 H, O*H*), 1.9–1.2 (m, 14 H, -$CH_2$-), 0.9 (t, *J* = 7.0 Hz, 3 H, $CH_3$); MS *m/e* (rel intensity) 582 ($M^+$), 203 ($Me_3SiO^+$=$CH(CH_2)_3CO_2CH_3$, 100), 173 ($Me_3SiO^+$=$CH(CH_2)_4CH_3$, 60), 171 (203 – 32; elimination of $CH_3OH$, 25).

**Methyl (2*E*,4*R*,5*S*)-4,5-Bis(*tert*-butyldimethylsiloxy)-2-decenoate (32).** To the known[15] primary alcohol **30** (2.729 g, 6.98 mmol) were added DMSO (17.5 mL), $CH_2Cl_2$ (17.5 mL), and $Et_3N$ (4.9 mL, 34.9 mmol). The mixture was cooled to 0 °C, $SO_3$·pyr complex (2.8 g, 17.6 mmol) was added in one portion, and the reaction mixture was stirred at 0 °C for 12 h to give aldehyde **31**, which was reacted without isolation. Methyl (triphenylphosphoranylidene)acetate (3.16 g, 9.45 mmol) was added directly to the mixture, and the reaction vessel was equipped with a reflux condenser and heated at reflux for 14 h. After cooling to room temperature, the mixture was diluted with petroleum ether (100 mL) and washed with water (4 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated, giving a yellow oil. Flash column chromatography (silica, 2.5% ether in petroleum ether) gave pure **32** (2.455 g, 79%). **32**: colorless oil; $R_f$ 0.25 (silica, 2.5% ether in petroleum ether); $[\alpha]^{25}_D$ −1.78° (*c* 4.24, $CH_2Cl_2$); IR (neat) $\nu_{max}$ 2950, 2901, 2864, 1735, 1668, 1473, 1442, 1265, 1172, 1118 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 7.00 (dd, *J* = 15.6, 5.3 Hz, 1 H, CH=C*H*COOCH$_3$), 6.00 (dd, *J* = 15.7, 1.5 Hz, 1 H, C*H*=CHCOOCH$_3$), 4.15 (m, 1 H, -C*H*(O)CH=C), 3.73 (s, 3 H, $COOCH_3$), 3.59 (m, 1 H, -C*H*OSi-), 1.50–1.15 (m, 8 H, -$CH_2$-), 0.88 (m, 21 H, 2 × Si$^t$*Bu*, $CH_3$), 0.85–0.10 (singlets, 12 H total, $SiCH_3$); MS *m/e* (rel intensity) 445 ($M^+$ + H, 15), 429 (42), 387 (100), 344 (43), 313 (100), 255 (52), 216 (100); HRMS calcd for $C_{23}H_{48}O_4Si_2$ ($M^+$ + H) 445.3169, found 445.3213.

**(2*E*,4*R*,5*S*)-4,5-Bis(*tert*-butyldimethylsiloxy)-2-decen-1-ol (33).** To a cold (−78 °C) stirred solution of **32** (2.27 g, 5.10 mmol) in $CH_2Cl_2$ (170 mL) was added DIBAL (1.0 M solution in hexanes, 12.2 mL, 12.2 mmol). The solution was allowed to warm to −20 °C over a 2-h period and stirring was continued at that temperature for 0.5 h before recooling to −78 °C and quenching by careful addition of methanol until gas evolution ceased. Ethyl acetate (100 mL) was added to the solution and the organic phase was washed with saturated aqueous sodium potassium tartrate (4 × 25 mL) and brine (25 mL). The solvent was evaporated in vacuo, giving a colorless oil. Flash column chromatography (silica, 20% ether in petroleum ether) gave the allylic alcohol **33** (2.00 g, 94% yield). **33**: colorless oil; $R_f$ 0.25 (silica, 20% ether in petroleum ether); $[\alpha]^{25}_D$ −5.40° (*c* 8.97, $CH_2Cl_2$); IR (neat) $\nu_{max}$ 3344, 2943, 2860, 1476, 1468, 1248, 1100 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 5.72 (m, 2 H, olefinic), 4.15 (m, 2 H, C=CHC*H*$_2$OH), 3.97 (m, 1 H, -C*H*OSi-), 3.56 (m, 1 H, -C*H*OSi-), 1.48–1.23 (m, 9 H, -$CH_2$-, O*H*) 0.86 (7, 21 H, $CH_3$, 2 × Si$^t$*Bu*), 0.03 (singlets, 12 H total, $SiCH_3$); MS *m/e* (rel intensity) 417 ($M^+$ + H, 74), 261 (100); HRMS calcd for $C_{22}H_{49}O_3$ ($M^+$ + H) 417.3220, found 417.3231.

**(2*E*,4*R*,5*S*)-4,5-Bis(*tert*-butyldimethylsiloxy)-2-decenal (35).** To the allylic alcohol **33** (1.0526 g, 2.623 mmol) were added $CH_2Cl_2$ (13 mL) and 3,5-dimethylpyrazole (257.0 mg, 2.676 mmol), and the stirred solution was cooled to 0 °C. Pyridinium chlorochromate (PCC, 1.696 g, 7.868 mmol, recrystallized from $CH_2Cl_2$) was added to the solution and stirring was continued for 2 h (0 → 10 °C). Celite was added to the reaction mixture and the solution was diluted with ether (30 mL) and filtered through a short pad of silica. Evaporation of the solvents and flash column chromatography (silica, 2.5% ether in petroleum ether) of the resultant brown residue provided the unsaturated aldehyde **35** (1.030 g, 98% yield). **35**: colorless oil; $R_f$ 0.20 (silica, 2.5% ether in petroleum ether); $[\alpha]^{25}_D$ +82.86° (*c* 1.05, $CH_2Cl_2$); IR (neat) $\nu_{max}$ 2965, 2912, 2855, 1700, 1465, 1250, 1102 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 9.8 (d, *J* = 8.0 Hz, 1 H, H-1), 6.88 (dd, *J* = 15.7, 5.3 Hz, 1 H, H-3), 6.24 (ddd, *J* = 15.7, 8.0, 1.4 Hz, 1 H, H-2), 4.27 (m, 1 H, H-4), 3.67 (dd, *J* = 10.4, 4.6 Hz, 1 H, H-5), 1.56–1.21 (m, 8 H, -$CH_2$-), 0.91 (s, 9 H, Si$^t$*Bu*), 0.87 (m, 12 H, Si$^t$*Bu*, H-10), 0.07, 0.06, 0.04, 0.02 (singlets, 3 H each, $SiCH_3$); MS *m/e* (rel intensity) 357 (M − $^t$Bu, 62), 314 (32), 281 (58), 255 (33), 215 (100), 147 (66); HRMS calcd for $C_{18}H_{37}O_3Si_2$ (M − $^t$Bu) 357.2281, found 357.2267.

**Methyl (8*E*,10*E*,12*E*,5*S*,14*R*,15*S*)-5-(*tert*-Butyldiphenylsiloxy)-14,15-bis(*tert*-butyldimethylsiloxy)-8,10,12-eicosatrien-6-ynoate (36).** Phosphonate **34**[16] (1.851 g, 3.339 mmol) was dissolved in anhydrous THF (12.6 mL) and cooled to −78 °C. To the stirred solution was added lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 2.9 mL, 2.9 mmol) dropwise over a 3-min period, and stirring was continued for an additional 2 min. Aldehyde **35** (899 mg, 2.520 mmol) in THF (3 mL) was slowly added to the yellow ylide at −78 °C and the mixture was stirred at that temperature for 1 h. The reaction was quenched by the addition of saturated ammonium chloride solution (15 mL) and after warming to room temperature the product was extracted with petroleum ether (100 mL). Washing of the organic phase with $H_2O$ (2 × 10 mL) and brine (20 mL) followed by drying ($MgSO_4$), evaporation, and flash column chromatography (silica, 2.5% ether in petroleum ether) gave product **36** (1.741 g, 83% yield). **36**: colorless oil that yellows on exposure to air; $R_f$ 0.16 (silica, 2.5% ether in petroleum ether);

$[\alpha]^{25}_D$ −7.38° (c 12.4, $CH_2Cl_2$); UV (MeOH) $\lambda_{max}$ 288 (shoulder), 301, 315 nm; IR (neat) $\nu_{max}$ 3088, 3021, 2942, 2860, 1743, 1472, 1465, 1430, 1364, 1250, 1105 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 7.76 (m, 4 H, Ar), 7.39 (m, 6 H, Ar), 6.39–6.11 (m, 4 H, H-8, H-9, H-10, H-11), 5.78 (dd, J = 14.9, 7.0 Hz, 1 H, H-12), 5.46 (dd, J = 15.1, 1.4 Hz, 1 H, H-13), 4.54 (m, 1 H, H-5), 4.03 (m, 1 H, H-14), 3.67 (s, 3 H, $COOCH_3$), 3.59 (m, 1 H, H-15), 2.31 (t, J = 6.9 Hz, H-2), 1.78 (m, 4 H, $-CH_2-$), 1.46–1.14 (m, 8 H, $-CH_2-$), 1.14 (s, 9 H, Si$^t$Bu), 0.92 (s, 9 H, Si$^t$Bu), 0.91 (s, 12 H, Si$^t$Bu, H-20), 0.07, 0.06, 0.05, 0.04 (singlets, 3 H each, $SiCH_3$); MS m/e (rel intensity) 831 ($M^+$ + H, 100), 731 (45), 579 (31), 515 (28); HRMS calcd for $C_{49}H_{79}O_5Si_3$ ($M^+$ + H) 831.5235, found 831.5238.

**Methyl (8*E*,10*E*,12*E*,5*S*,14*R*,15*S*)-5,14,15-Trihydroxy-8,10,12-eicosatrien-8-ynoate (37).** Acetylene **36** (519 mg, 0.626 mmol) was dissolved in THF (3 mL) and cooled to 0 °C. HF·pyr complex (0.3 mL) was added with stirring at 0 °C, and the solution was stirred at that temperature for 10 min and then at 25 °C for a further 30 min. The mixture was similarly treated with three additional portions of HF·pyr (0.3 mL each) and the reaction mixture was poured into ether (50 mL) and carefully neutralized (pH paper) with saturated aqueous $NaHCO_3$ solution. The organic phase was separated and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic extract was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 5% MeOH in $CH_2Cl_2$) gave, in order of elution, δ-lactone **38** (35.4 mg, 17% yield) and triol **37** (0.139 g, 61% yield). The δ-lactone **38** was converted to the triol **37** by dissolution in methanol (5 mL) and treatment with $Et_3N$ (34.7 mL, 0.318 mmol) (25 °C, 15 min). **37**: colorless oil that yellows on exposure to air; $R_f$ 0.17 (silica, 5% MeOH in $CH_2Cl_2$); $[\alpha]^{24}_D$ +6.95° (c 0.59, $CH_2Cl_2$); UV (MeOH) $\lambda_{max}$ 288 (shoulder), 301, 315 nm; IR (neat) $\nu_{max}$ 3390, 3023, 2928, 2857, 1740, 1440, 1380, 1250, 1075, 1000 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.59 (dd, J = 15.52, 10.1 Hz, 1 H, H-8), 6.33–6.25 (multiplets, 3 H, H-9, H-10, H-11), 5.85 (dd, J = 14.1, 6.9 Hz, 1 H, H-12), 5.62 (dd, J = 15.8, 1.4 Hz, 1 H, H-13), 4.54 (m, 1 H, H-5), 4.16 (dd, J = 6.8, 3.5 Hz, 1 H, H-14), 3.71 (m, 1 H, H-15), 3.68 (s, 3 H, $COOCH_3$), 2.39 (m, 2 H, $CH_2COOCH_3$), 2.03 (br s, 1 H, O*H*), 1.84–1.73 (m, 5 H, $-CH_2-$), 1.65 (br s, 1 H, O*H*), 1.48 (m, 1 H, $-CH_2-$), 1.39 (m, 2 H, $-CH_2-$), 1.29 (m, 5 H, $-CH_2-$), 0.89 (m, 3 H, $CH_3$); MS m/e (rel intensity) 347 ($M^+$ − OH, 11), 329 ($M^+$ − 2 × OH, 100), 297 (38), 246 (54), 215 (78), 155 (80), 129 (80); HRMS calcd for $C_{21}H_{31}O_5$ ($M^+$ − H) 363.2172, found 363.2143.

**Methyl (6*Z*,8*E*,10*E*,12*E*,5*S*,14*R*,15*S*)-5,14,15-Trihydroxy-6,8,10,12-eicosatetraenoate (3).** To a solution of acetylene **37** (58.0 mg, 0.162 mmol) in $CH_2Cl_2$ (3.2 mL) was added freshly distilled quinoline ($CaH_2$, 20 μL) and Lindlar catalyst (Fluka Chemical Co., 24.0 mg, 50% w/w). The mixture was stirred under a hydrogen atmosphere while being monitored by HPLC (Altex C-18 ultrasphere semipreparative reverse phase, MeOH/$H_2O$ 70:30, flow rate 3 mL/min, UV detector at $\lambda_{max}$ 301 for product and 260 nm for overreduced product and 310 nm for starting material). The reaction was also monitored by TLC (silica, 15% acetone in methylene chloride, three developments). Upon completion (3 h) the hydrogen atmosphere was removed and the solution was filtered through a short Celite pad with ether washings (3 × 5 mL). The solvent was carefully evaporated on a rotary evaporator at <10 °C to furnish a slightly yellow oil, which was dissolved in methanol (3 mL) and purified by reverse-phase HPLC (same conditions as above, $t_R$ 13.4 min.). Removal of the solvent under reduced pressure (dry ice condenser, 4 mmHg) provided the product **3** (33.8 mg, 57% yield). **3**: white waxy solid; $R_f$ 0.29 (silica, 5% MeOH in $CH_2Cl_2$); $[\alpha]^{25}_D$ 18.29 (c 0.48, $CH_2Cl_2$); UV (MeOH) $\lambda_{max}$ 288, 302, 316 nm; IR ($CH_2Cl_2$) $\nu_{max}$ 3395, 3011, 2915, 2829, 1730, 1480, 1072, 988 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.52 (m, 1 H, H-8), 6.29 (m, 4 H, H-9, H-10, H-11, H-12), 6.11 (t, J = 11.2 Hz, 1 H, H-7), 5.80 (dd, J = 14.6, 7.1 Hz, 1 H, H-13), 5.43 (t, J = 9.6 Hz, 1 H, H-6), 4.59 (m, 1 H, H-5), 4.15 (m, 1 H, H-14), 3.70 (m, 1 H, H-15), 3.67 (s, 3 H, $COOCH_3$), 2.36 (m, 2 H, $CH_2COOCH_3$), 2.21 (d, J = 3.4 Hz, 1 H, O*H*), 2.08 (d, J = 4.3 Hz, 1 H, O*H*), 1.77 (d, J = 3.3 Hz, 1 H, O*H*), 1.76–1.63 (m, 3 H, $-CH_2-$), 1.54–1.13 (m, 9 H, $-CH_2-$), 0.89 (t, J = 6.7 Hz, 3 H, $CH_3$); MS m/e (rel intensity) $C_{30}H_{56}O_5Si_3$ [tris(trimethylsilyl] 528 ($M^+$), 203, 173 (100); HRMS calcd for $C_{21}H_{35}O_5$ ($M^+$ + H) 367.2485, found 367.2496.

**Methyl (5*S*)-7-Iodo-5-(*tert*-butyldiphenylsiloxy)hept-6-ynoate (40).** Iodine (344 mg, 2.71 mmol) and morpholine (350 μL, 4.01 mmol) were dissolved in benzene (7.0 mL) and heated to 45 °C for 10 min. To the resulting red solution was added the acetylene **39**[16] (471 mg, 1.158 mmol) in benzene (1 mL) with stirring. Stirring was continued for 2.5 h at 45 °C and the solution was cooled to room temperature and filtered through a Celite pad. Washing the filtrate with 5% aqueous $Na_2HPO_4$ (15 mL), 10% aqueous $Na_2S_2O_3$ (2 × 15 mL), saturated aqueous $NaHCO_3$ (15 mL), and brine (15 mL) solutions followed by drying ($MgSO_4$) and evaporation gave a yellow oil. Flash column chromatography (silica, 5% ether in petroleum ether) furnished pure **40** (562 mg, 93% yield). **40**: colorless oil that yellows on exposure to air; $R_f$ 0.22 (silica, 5% ether in petroleum ether); $[\alpha]^{25}_D$ −5.52° (c 15.8, $CH_2Cl_2$); IR (neat) $\nu_{max}$ 3076, 3042, 2940, 2858, 1743, 1590, 1430, 1160, 1112, 1005 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.68 (m, 4 H, Ar), 7.40 (m, 6 H, Ar), 4.45 (t, J = 5.5 Hz, 1 H, -C*H*OSi-), 3.65 (s, 3 H, $COOCH_3$), 2.27 (m, 2 H, $CH_2COOCH_3$), 1.76 (m, 2 H, $-CH_2-$), 1.69 (m, 2 H, $-CH_2-$), 1.07 (s, 9 H, Si$^t$Bu); MS m/e (rel intensity) 489 ($M^+$ − $OCH_3$, 32), 464 ($M^+$ − $^t$Bu, 100), 431 (56), 385 (52), 337 (100), 305 (30), 265 (25); HRMS calcd for $C_{23}H_{26}O_2SiI$ ($M^+$ − $OCH_3$) 489.0747, found 489.0700.

**Methyl (5*S*)-7-Iodo-5-(*tert*-butyldiphenylsiloxy)hept-6-enoate (41).** Iodoacetylene **40** (573 mg, 1.08 mmol) was taken up in methanol (13 mL) and to this solution were added pyridine (0.5 mL) and dipotassium azodicarboxylate (238 mg, 1.23 mmol) at 25 °C. After stirring vigorously for 15 min, glacial acetic acid (130 μL, 2.3 mmol) was added dropwise over a period of 20 min and stirring was continued at ambient temperature for 1.5 h. Another portion of dipotassium aozdicarboxylate (246 mg, 1.27 mmol) was introduced to the solution followed by dropwise addition of acetic acid (130 μL, 2.3 mmol) over a 20-min period and stirring for an additional 1 h. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with 3 N aqueous HCl (2 × 5 mL), water (3 × 5 mL), and brine (10 mL). Drying ($MgSO_4$) followed by concentration gave a yellow oil. Flash column chromatography (silica, 5% ether in petroleum ether) gave pure *cis*-iodoolefin **41** (570 mg, 99% yield). **41**: colorless oil; $R_f$ 0.20 (silica, 5%, ether in petroleum ether); $[\alpha]^{25}_D$ +47.13° (c 0.505, $CH_2Cl_2$); IR (neat) $\nu_{max}$ 3075, 3051, 2941, 2860, 1740, 1613, 1594, 1466, 1430, 1365, 1109, 1090 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4 H, Ar), 7.39 (m, 6 H, Ar), 6.27 (t, J = 7.6 Hz, 1 H, CH=C*H*I), 6.08 (dd, J = 7.7 Hz, 1 H, C*H*=CHI), 4.42 (m, 1 H, -C*H*OSi-), 3.64 (s, 3 H, $COOCH_3$), 2.20 (m, 2 H, $CH_2COOCH_3$), 1.67–1.48 (m, 4 H, $-CH_2-$), 1.06 (s, 9 H, Si$^t$Bu); MS m/e (rel intensity 465 ($M^+$ − $^t$Bu, 100), 433 (31), 387 (52), 339 (46), 199 (83); HRMS calcd for $C_{20}H_{22}O_3SiI$ ($M^+$ − $^t$Bu) 465.0383, found 465.0348.

**Methyl (6*Z*,10*E*,12*E*,5*S*,14*R*,15*S*)-5-(*tert*-Butyldiphenylsiloxy)-14,15-bis(*tert*-butyldimethylsiloxy)-6,10,12-eicosatrien-8-ynoate (43).** To the vinyl iodide **41** (576 mg, 1.077 mmol) was added $Et_2NH$ (5.4 mL), and argon was bubbled through the solution at 25 °C for 20 min. The reaction flask was covered with aluminum foil, tetrakis(triphenylphosphine)palladium was added, and the solution was stirred for 30 min at ambient temperature. A degassed (Ar bubbling) solution of acetylene **42** (580 mg, 1.356 mmol) in $Et_2NH$ (4.5 mL) was added followed by CuI (32.8 mg, 0.172 mmol). The reaction mixture was stirred for 10 min at 25 °C and then diluted with EtOAc (40 mL). Washing with saturated aqueous $NH_4Cl$ (5 × 5 mL), $H_2O$ (5 mL), and brine (10 mL) was followed by drying ($MgSO_4$), filtration, and concentration, giving a reddish oil that was subjected to flash column chromatography (silica, 2.5% ether in petroleum ether) to furnish compound **43** (824 mg, 92%). **43**: pale yellow oil; $R_f$ 0.28 (silica, 5% ether in petroleum ether); $[\alpha]^{25}_D$ +59.80° (c 5.26, $CH_2Cl_2$); UV (MeOH) $\lambda_{max}$ 288 (shoulder), 301, 315 nm; IR (neat) $\nu_{max}$ 3080, 3038, 2942, 2860, 1745, 1475, 1468, 1430), 1254, 1111 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 4 H, Ar), 7.35 (m, 6 H, Ar), 6.28 (dd, J = 15.5, 10.9 Hz, 1 H, olefinic), 6.12 (dd, J = 15.1, 11.0 Hz, 1 H, olefinic), 5.89 (dd, J = 10.6, 8.8 Hz, 1 H, olefinic), 5.75 (dd, J = 15.1, 7.2 Hz, 1 H, olefinic), 5.48 (m, 2 H, olefinic), 4.71 (m, 1 H, -C*H*OSi-), 4.00 (m, 1 H, -C*H*OSi-), 3.62 (s, 3 H, $-COOCH_3$), 3.58 (dd, J = 9.7, 4.6 Hz, 1 H, -C*H*OSi-), 2.18 (m, 2 H, $CH_2COOCH_3$), 1.60 (m, 4 H, $-CH_2-$), 1.52–1.25 (m, 10 H, $-CH_2-$), 1.06 (s, 9 H, Si$^t$Bu), 0.91 (s, 9 H, Si$^t$Bu), 0.89 (m, 3 H, $CH_3$), 0.88 (s, 9 H, Si$^t$Bu), 0.08, 0.06, 0.04, 0.02 (singlets, 3 H each, $SiCH_3$); MS m/e (rel intensity) 831 ($M^+$ +

H, 32), 707 (100), 650 (18), 576 (31), 518 (27), 465 (28); HRMS calcd for $C_{49}H_{79}O_5Si_3$ ($M^+ + H$) 830.5157, found 830.5188.

**Methyl (6*Z*,10*E*,12*E*,5*S*,14*R*,15*S*)-5,14,15-Trihydroxy-6,10,12-eicosatrien-8-ynoate (44).** To a cooled (0 °C) solution of **43** (710 mg, 0.857 mmol) in THF (4.3 mL) under argon in a Nalgene bottle was added HF·pyr complex (0.2 mL). After being stirred at 0 °C for 5 min, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 30 min. This procedure was repeated four additional times until TLC monitoring (silica, 5% ether in petroleum ether and 5% MeOH in $CH_2Cl_2$) indicated that the reaction was complete. The reaction mixture was then poured into an Erlenmeyer flask, diluted with ether (10 mL), and neutralized (pH paper) by the cautious addition of a saturated aqueous $NaHCO_3$ solution. The phases were separated and the aqueous layer was extracted with ether (4 × 10 mL). The combined organic extract was dried ($MgSO_4$), filtered, and concentrated to provide a yellow oil. Radial preparative chromatography (chromatotron, Harrison Research, silica, 5% MeOH in $CH_2Cl_2$) gave, in order of elution, δ-lactone **45** (65.5 mg, 23% yield) and triol **44** (162.4 mg, 52% yield). The δ-lactone **45** was quantitatively converted to **44** by being dissolved in methanol (1 mL) and treatment with triethylamine (60 μL) (15 min, 25 °C). **44**: colorless oil that yellows upon exposure to air; $R_f$ 0.24 (silica, 7.5% MeOH in $CH_2Cl_2$); $[\alpha]^{25}_D$ −30.92° (*c* 0.60, $CH_2Cl_2$); UV (MeOH) $\lambda_{max}$ 283 (shoulder), 295, 314 nm; IR (neat) $\nu_{max}$ 3390, 3021, 2930, 2858, 1730, 1441, 1072 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.60 (dd, *J* = 15.5, 10.9 Hz, 1 H, olefinic), 6.35 (dd, *J* = 15.2, 10.9 Hz, 1 H, olefinic), 5.89 (m, 2 H, olefinic), 5.76 (dd, *J* = 15.5, 2.3 Hz, 1 H, olefinic), 5.69 (dd, *J* = 10.9, 2.3 Hz, 1 H, olefinic), 4.65 (m, 1 H, -C*H*(OH)CH=CH-), 4.17 (dd, *J* = 6.6, 3.4 Hz, 1 H, -C*H*(OH)CH=CH-), 3.70 (m, 1 H, C*H*OH), 3.67 (s, 3 H, $COOCH_3$), 2.39 (m, 2 H, $CH_2COOCH_3$), 2.25 (br s, 2 H, O*H*), 1.79–1.63 (m, 2 H, -$CH_2$-), 1.57 (m, 1 H, -$CH_2$-), 1.49 (m, 1 H, -$CH_2$-), 1.39 (m, 2 H, -$CH_2$-), 1.29 (m, 7 H, -$CH_2$-, O*H*), 0.89 (t, *J* = 6.7 Hz, $CH_3$); MS *m/e* (rel intensity) 387 ($M + NH_4^+$, 3), 365 ($M^+ + H$, 5), 347 ($M^+ - OH$, 68), 329 (100), 311 (55), 263 (90), 246 (95), 215 (33); HRMS calcd for $C_{21}H_{31}O_4$ ($M^+ - OH$) 347.2222, found 347.2224.

**Methyl (6*Z*,8*Z*,10*E*,12*E*,5*S*,14*R*,15*S*)-5,14,15-Trihydroxy-6,8,10,12-eicosatetraenoate (4).** The acetylene **44** (31.1 mg, 0.0865 mmol) in $CH_2Cl_2$ (1.7 mL) was selectively hydrogenated with Lindlar catalyst (Fluka Chemical Co., 9.4 mg, 30% by weight) in the presence of freshly distilled quinoline ($CaH_2$, 8.5 μL). The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 2.5 h and the reaction was monitored by HPLC as described for compound **3**. The resulting crude product was purified by reverse-phase HPLC (same conditions as above, $t_R$ 16.2 min) to give, after removal of the solvents, **4** (21.6 mg, 69.1% yield). **4**: white, waxy solid; $R_f$ 0.32 (silica, 5% MeOH in $CH_2Cl_2$); $[\alpha]^{25}_D$ +33.73° (*c* 0.257, $CH_2Cl_2$); UV (MeOH) $\lambda_{max}$ 285, 298, 314 nm; IR ($CH_2Cl_2$) $\nu_{max}$ 3390, 3031, 2914, 2835, 1732, 1482, 1392, 1170, 1072, $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 14.3, 11.9 Hz, 1 H, H-10), 6.53 (t, *J* = 11.4 Hz, 1 H, H-7), 6.39 (dd, *J* = 14.9, 10.9 Hz, 1 H, H-12), 6.28 (m, 2 H, H-8, H-11), 6.11 (t, *J* = 11.2 Hz, 1 H, H-13), 5.50 (t, *J* = 9.6 Hz, 1 H, H-6), 4.63 (m, 1 H, H-5), 4.16 (m, 1 H, H-14), 3.20 (m, 1 H, H-15), 3.67 (s, 3 H, $COOCH_3$), 2.34 (m, 2 H, H-2), 2.02 (s, 1 H, O*H*), 1.94 (s, 1 H, O*H*), 1.77–1.26 (m, 13 H, O*H*, -$CH_2$-), 0.89 (t, *J* = 6.8 Hz, 1 H, H-20); MS *m/e* (rel intensity) 366 ($M^+$), 203, 173 (100); HRMS calcd for $C_{21}H_{35}O_5$ ($M^+ + H$) 367.2485, found 367.2489.

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**Supplementary Material Available:** $^1H$ NMR and IR spectra of compounds 1–4, 6–9, 11–13, 15, 16, 18, 20–22, 32, 33, 35–37, 39, 41, and 43–45 (27 pages). Ordering information is given on any current masthead page.

# Carbenoid Properties of Phosphenium Salts. Synthesis of the First 1-Aza-3-phosphetine Cations

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Further examples of the synthetic utility of phosphenium cations are reported. They react with isocyanides to produce 1-aza-3-phosphetine cations **3a–f** or cyano- and dicyanophosphines **4**, **5**, and **7**, depending on the experimental conditions and on the nature of the substituents of each partner. The transient formation of hitherto unknown cationic phosphacumulenes $R_2P^+{=}C{=}NR'$ in resonance with the nitrilium salts $R_2PC{\equiv}N^+R'$ can explain the formation of this new series of phosphorus heterocycles.

## Introduction

It has been shown that low coordinated phosphorus cationic species, that is, the phosphenium salts $R_2P^+$, react as carbenoids with alkynes or 1,3- or 1,4-dienes to give the corresponding unsaturated three-, four-, or five-membered rings.[1] They can exhibit carbocation-like behavior toward 1,5-dienes.[2] Due to the fact that they possess a formal positive charge and a sextet of electrons on phosphorus, they can also function as Lewis acids; furthermore, the presence of a lone pair and a vacant π orbital render phosphenium ions excellent ligands[1] (Scheme I).

On the other hand, isocyanides can interact either with nucleophiles or with electrophiles. Moreover, by virtue of their carbenic character, isocyanides react easily with most of the common multiple bonds to give a range of heterocyclic systems often inaccessible by other methods.[3]

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