Levuglandin E_2: Enantiocontrolled Total Synthesis of a Biologically Active Rearrangement Product from the Prostaglandin Endoperoxide PGH_2[1]

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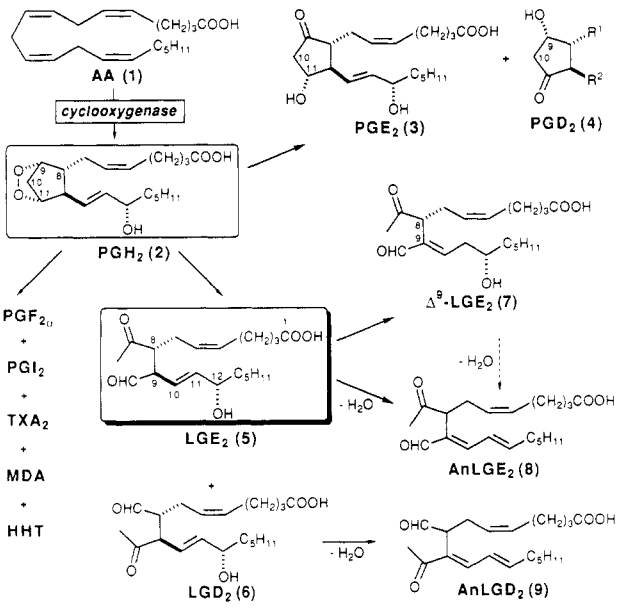
Diastereoselective 1,4-addition of a vinyl cuprate to a γ-chiral α,β-unsaturated ketone intermediate provides an efficient asymmetric total synthesis of levuglandin E_2. While resolution of a racemic precursor provided the second chiral center, preferential generation of the required configuration at the third center of this acyclic synthetic target involved a remarkably stereoselective epimerization.

Introduction

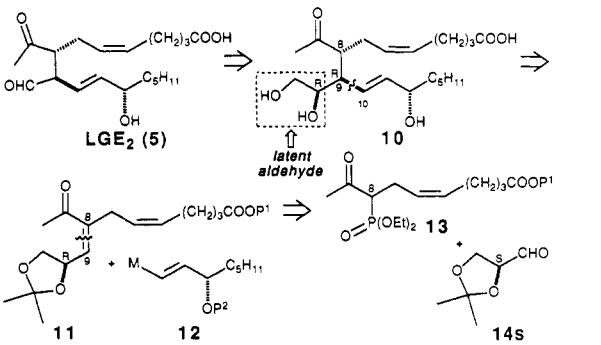
The prostaglandin endoperoxide PGH_2 (**2**) is a pivotal intermediate in the oxidative bioconversion of arachidonic acid (**1**) into a structurally diverse family of biologically active derivatives (Scheme I). PGH_2 is an extraordinarily unstable bicyclic dialkyl peroxide, rearranging in the aqueous environment of its biosynthesis with $t_{1/2} = 5$ min.[2] Our studies[3] of this water-induced rearrangement demonstrated that, besides the previously recognized[4] products PGE_2 (**3**) and PGD_2 (**4**), levulinaldehyde derivatives are formed (e.g. 22% yield at pH 7.9). We named these new eicosanoids levuglandins since they are seco-prostaglandins which are related *formally* to the corresponding prostaglandins by aldol condensation. Thus, the 10,11-seco acid is levuglandin E_2 (LGE_2, **5**) while the 9,10-seco acid is levuglandin D_2 (LGD_2, **6**). Mechanistic studies[5] on the 2,3-dioxabicyclo[2.2.1]heptane nucleus of PGH_2 indicated that LGE_2 is formed by an intramolecular *hydride* migration from the 9- to the 10-position in PGH_2, accompanied by cleavage of the 10,11 C–C and the peroxide O–O bonds while LGD_2 is formed by intramolecular *hydride* migration from the 11- to the 10-position in PGH_2, accompanied by cleavage of the 9,10 C–C and the peroxide O–O bonds. Mechanistic model studies[6] also revealed that the same products can be generated in base-catalyzed rearrangements of the 2,3-dioxabicyclo[2.2.1]heptane nucleus of PGH_2 involving *proton* abstraction from the bridgehead 9- or 11-positions, leading to LGE_2 or LGD_2, respectively.

Both of these new primary products from PGH_2 are chemically sensitive vinylogous β-hydroxycarbonyl compounds which readily lose water to produce anhydro levuglandins $AnLGE_2$ (**8**) and $AnLGD_2$ (**9**) and undergo allylic rearrangement to produce Δ^9 isomers, e.g. Δ^9-LGE_2 (**7**), at physiological pH and temperature (Scheme I).[7]

Scheme I



Scheme II



Isolation of the primary levuglandins from the mixture produced by rearrangement of PGH_2 is hampered by their instability. Although one of the primary levuglandins was isolated by HPLC, neither mass spectral nor nuclear magnetic resonance data[8] were deemed adequate for a choice between structures **5** and **6** for this keto aldehyde. Owing to the limited availability of PGH_2, we turned to total synthesis as a practical alternative source of levuglandins to facilitate thorough chemical characterization and biological evaluation.[9] We now report an efficient asymmetric synthesis of LGE_2 (**5**) [8(*R*)-acetyl-9(*R*)-

(1) Paper 25 in the series Prostaglandin Endoperoxides. For paper 24, see: Jirousek, M.; Salomon, R. G. *J. Liq. Chrom.* **1988**. For a review of earlier work see: Salomon, R. G. *Acc. Chem. Res.* **1985**, *18*, 294.

(2) (a) Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. U.S.A.* **1973**, *70*, 899. (b) Hamberg, M.; Svensson, J.; Wakabayashi, T.; Samuelsson, B. *Ibid.* **1974**, *71*, 345. (c) Nugteren, D. H.; Hazelhof, E. *Biochim. Biophys. Acta* **1973**, *326*, 488. (d) Raz, A.; Kenig-Wakshal, R.; Schwartzman, M. *Ibid.* **1977**, *488*, 322. (e) Nugteren, D. H.; Christ-Hazelhof, E. *Adv. Prostaglandin Thromboxane Res.* **1980**, *6*, 129.

(3) Zagorski, M. G.; Salomon, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 3498.

(4) At pH 8, products which were isolated from rearrangements of [1-^{14}C]PGH_2 by extraction of the acidified solution with diethyl ether, separated and identified by TLC, and quantified by liquid scintillation counting included PGE_2 (71%) and PGD_2 (20%).[2c] It is important to note that these are distributions of radioactive *products isolated* and not absolute yields.

(5) Salomon, R. G.; Miller, D. B.; Zagorski, M. G.; Coughlin, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 6049.

(6) (a) Zagorski, M. G.; Salomon, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 3498. (b) Zagorski, M. G.; Salomon, R. G. *J. Am. Chem. Soc.* **1984**, *106*, 1750.

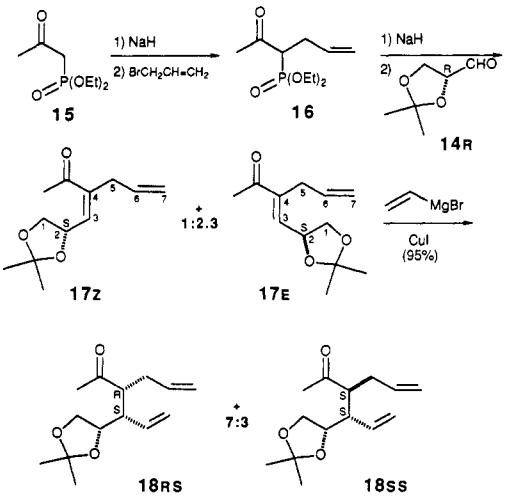
(7) This proclivity toward dehydration and allylic rearrangement is thoroughly delineated for LGE_2 in the accompanying article: Iyer, R. S.; Miller, D. B.; Salomon, R. G. *J. Org. Chem.*, following paper in this issue.

(8) Salomon, R. G.; Miller, D. B. *Adv. Prostaglandin Thrombox. Leuko. Res.* **1985**, *15*, 323.

(9) A preliminary account of this work was reported previously: Salomon, R. G.; Miller, D. B.; Raychaudhuri, S. R.; Avasthi, K.; Lal, K.; Levison, B. S. *J. Am. Chem. Soc.* **1984**, *106*, 8296.

0022-3263/90/1955-3164$02.50/0

Scheme III



formyl-12(*S*)-hydroxy-5(*Z*),10(*E*)-heptadecadienoic acid].

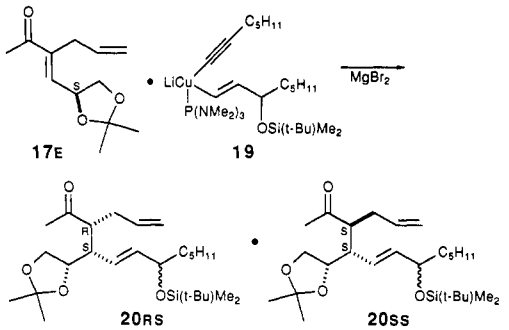
Results and Discussion

The Synthetic Design. Dominant considerations in planning a total synthesis of LGE_2 are its proclivity toward dehydration and allylic rearrangement as well as possible epimerization α to the acyl substituents at positions 8 and 9. Many of these difficulties are circumvented by replacing the aldehyde carbonyl with a latent equivalent, a vicinal diol as in **10** (Scheme II). This key feature of our synthetic strategy, generation of the sensitive vinylogous β-hydroxycarbonyl array in the last step of the synthesis, depends on the feasibility of achieving the **10** to **5** conversion under mild conditions by oxidative cleavage with periodate.[10] In analogy with a strategy for the total synthesis of prostaglandins,[11] a convergent construction of the levuglandin skeleton is achieved by Michael addition of a vinyl nucleophile **12** to enone **11**. Stereocontrol is a more difficult challenge in the synthesis of LGE_2 than it was for the total synthesis of PGE_2 since LGE_2 is acyclic and therefore more conformationally mobile than PGE_2, which has three of its four stereocenters arranged in the thermodynamically preferred all-trans configuration around a relatively rigid cyclopentanone ring.

The tactic of using a vicinal diol as a latent aldehyde group apparently complicates rather than simplifies the synthetic target by adding a fourth stereocenter. On the contrary, this additional center of chirality, which will not be incorporated in the final product, serves as a chiral auxilary directing enantioselective creation of the correct absolute configuration at position 9 during reaction of a vinyl nucleophile **12** with enone **11**. The neighboring alkoxy substituent in **11** is expected to foster generation of only the requisite absolute configuration at position 9 during 1,4-addition of a vinyl cuprate nucleophile.[12] The asymmetry of **11** is provided by L-glyceraldehyde acetonide (**14**),[13] which affords enone **11** upon olefination with phosphonate **13**. Furthermore, the correct configuration at position 8 should be available by epimerization of any 8-epi-**10** which might be generated.

The Effect of Magnesium Bromide on the 1,4-Addition. The synthetic strategy was first explored in model studies (Scheme III) which revealed important requirements for successful 1,4-addition of vinyl cuprate nucleophiles to enones like **11**. Thus, the β-keto phosphonate **16** is readily available by allylation[14] of diethylphosphonoacetone (**15**). Horner–Emmons reaction with isopropylidene-D-glyceraldehyde (**14R**)[15] provides a separable mixture of enones **17Z** and **17E**. ^1H NMR spectral analysis allows structural characterization of these isomeric alkenes. The C-3 vinyl methine hydrogen resonance of **17E** is shifted downfield approximately 0.6 ppm compared to the C-3 vinyl methine hydrogen resonance of **17Z**. Downfield shifts of similar magnitude for trans versus cis α,β-unsaturated carbonyl compounds are well documented.[16] Additional support for the above geometric assignments is provided by the hyperfine splitting patterns of the C-5 methylene hydrogen resonances. For **17Z** the C-5 methylene hydrogen resonances appear as a doublet (d) as expected for vicinal coupling with the C-6 vinylic methine hydrogen. In contrast, for **17E** the C-5 methylene signals appear as a doublet of doublet of doublets (ddd), owing to geminal nonequivalence amplified by spatial proximity to the chiral center at C-2.

1,4-Addition of magnesium bromide divinyl cuprate to **17E** cleanly delivered a readily separable pair of diastereomers **18RS** and **18SS** in 95% yield. Since only two of four possible diastereomeric products were generated, the conjugate addition was entirely stereoselective, generating only the *S* configuration at the 3-position as expected.[12a] Unexpectedly, however, 1,4-addition of the mixed cuprate **19** to enone **17E** afforded only a low yield (20–30%) of products **20SS** and **20RS**. Addition of a THF solution of $MgBr_2$ to the reaction mixture improved the yield of these adducts to 100%. THF alone had no beneficial effect on yield. Presumably $MgBr_2$ serves as a Lewis acid catalyst in this reaction.[17]



Methyl Ester of Levuglandin E_2. Acidic deketalization of **18RS** in acetic acid–water (2:1) at 40 °C afforded the deprotected diol. Upon complete removal of solvents and dissolution of the residue in $CDCl_3$, the diol underwent quantitative intramolecular hemiketalization as evidenced by an upfield shift of the acetyl methyl hydrogen resonance in the ^1H NMR spectrum. In **18RS** the acetyl methyl hydrogen resonance occurred at δ 2.20. For the hemi-

(10) An early application of a vicinal diol as a latent carbonyl appears in a synthesis of lysergic acid: Kornfeld, E. C.; Fornefeld, E. J.; Klein, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087.

(11) Sih, C. J.; Salomon, R. G.; Price, P.; Sood, R.; Peruzzotti, G. *J. Am. Chem. Soc.* **1975**, *97*, 857.

(12) (a) Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231. (b) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, 2327; *J. Am. Chem. Soc.* **1981**, *103*, 1224; **1982**, *104*, 2027. (c) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, 3465; **1980**, *21*, 4727. (d) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Ibid.* **1980**, *21*, 2840. (e) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Ibid.* **1981**, *22*, 3997. (f) Ziegler, F. E.; Gilligan, P. J. *J. Org. Chem.* **1981**, *46*, 3874. (g) Fuganti, C.; Graselli, P.; Pedrocchi-Fantoni, G. *Tetrahedron Lett.* **1981**, *22*, 4017.

(13) Baker, S. R. *J. Am. Chem. Soc.* **1952**, *74*, 827.

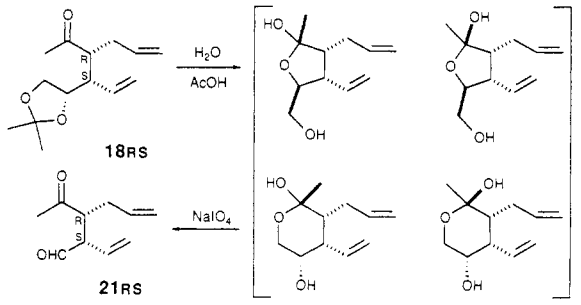
(14) Clark, R. D.; Kozar, L. G.; Heathcock, C. H. *Synthesis* **1975**, 635.

(15) Baer, E.; Fischer, H. O. L. *J. Biol. Chem.* **1939**, *128*, 463.

(16) Martin, G. J.; Martin, M. L. *Prog. Nuc. Mag. Reson. Spect.* **1972**, *8(e)* (The Stereochemistry of Double Bonds), 174.

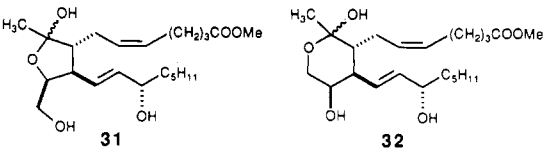
(17) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119 and references cited therein.

ketalized product, four upfield methyl hydrogen singlets were observed. This may indicate that two anomers of each of the two possible lactol products are formed. However, epimerization α to the carbonyl substituents cannot be ruled out. Nevertheless, it was especially interesting that one of the lactol isomers accounted for more than 85% of the mixture. Its methyl hydrogen resonance occurred at δ 1.50. Oxidative cleavage of this mixture of lactols with sodium metaperiodate in aqueous solution produced a single aldehyde, presumably **21RS**, in 70% yield. The acetyl methyl hydrogen resonance for this levulinaldehyde derivative occurred at δ 2.25.



The LGE_2 carbon skeleton was assembled as outlined in Scheme IV. Allylation of **15** with methyl (*Z*)-7-bromohept-5-enoate (**22**)[18] provided ketophosphonate **23**. The sodium salt of **23** undergoes Horner–Emmons condensation with isopropylidene-L-glyceraldehyde (**14S**) to give chiral nonracemic enones **24E** and **24Z** (2:1) in 75% yield. Configurational assignments for these isomers were made by ^{1}H NMR as described above for the model enones **17E** and **17Z**. Magnesium bromide catalyzed 1,4-addition of mixed cuprate **19S** to *either* geometrically isomeric enone **24E** and **24Z** *delivered an identical mixture* (3:7) of epimeric adducts **25SR** and **25RR**, respectively, in 95% yield. Assignment of the configuration at C-8 for these epimers was based upon an analysis of their ^{1}H NMR spectra and comparison with that of LGE_2. Thus, the ^{1}H NMR spectrum of **25RR** exhibits a downfield vinyl resonance at δ 5.49 (dd, J = 15.4, 5.9 Hz), which corresponds to the C-11 vinyl methine hydrogen. The ^{1}H NMR spectrum of LGE_2 (**5**), displays a very similar multiplet at δ 5.75 (dd, J = 15.6, 5.1 Hz). However, the ^{1}H NMR spectrum of **25SR** does not show a similar multiplet. That **25RR** and **25SR** are epimeric at C-8 is confirmed by the observation that saponification of either ester is accompanied by epimerization to afford identical equilibrium 3:7 mixtures of epimeric acids **26SR** and **26RR**.

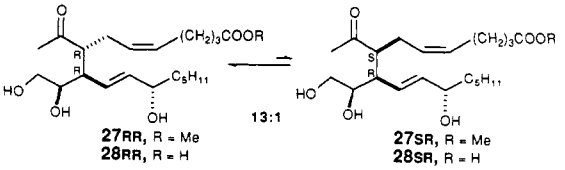
Deprotection of the three hydroxyl groups in ketal silyl ether **25RR** could be accomplished by treatment with acetic acid–water (2:1 v/v) at 40 °C for 3.5 h. Removal of the solvents by lyophilization (sublimation from the frozen solution) gave a crude oily product which tenaciously retained acetic acid. After dissolution in ethanol/*n*-heptane (1:5 v/v), the *n*-heptane–acetic acid azeotrope[18] was removed by rotary evaporation under water aspirator reduced pressure. The ^{1}H and ^{13}C NMR spectra of the product (99% yield) indicated that the intermediate triol **27** had undergone quantitative intramolecular hemiketalization to give a single product. This behavior is similar to that of the diol from **18RS** discussed above. Thus, the ^{1}H NMR spectrum of the product exhibited a single anomeric methyl singlet at δ 1.44, which is upfield from the position expected for the methyl ketone **27** (vide infra). In addition, the ^{13}C NMR spectrum of the putative hemiketal exhibited 22 resonances, including a single peak for the anomeric hemiketal carbon at δ 104.6, as expected for a single anomeric hemiketal. Since cyclization of **27** could have produced four isomeric lactol products (eight if epimerization occurs α to the ketone), *the hemiketalization proceeds with remarkably high regio- and stereoselectivity*. The NMR data are not sufficient for unambiguous assignment of a specific anomer of a 5-membered lactol **31** or a 6-membered lactol **32**.[19]



That lactol formation does not occur under the conditions of the acidic deprotection of **25RR** was demonstrated by characterizing the products in the reaction mixture. Thus, **25RR** was dissolved in 1:2 (v/v) D_2O–CD_3COOD, and the hydrolysis was monitored by ^{1}H NMR spectroscopy at 40 °C. That hydrolysis was occurring was evident by the collapse of the pair of singlets at δ 0.01 and −0.01, corresponding to the diastereotopic silyl methyls, to a singlet, and by the slower disappearance of the isopropylidene methyl singlets at δ 1.34 and 1.29. The hydrolysis was complete after 3 h. Most importantly, the spectrum after completion of the hydrolysis showed a characteristic singlet at δ 2.19, corresponding to the methyl ketone group in **27**. No upfield methyl singlet attributable to a lactol was present.

Oxidative cleavage of triol **27** by addition of $NaIO_4$ to the hydrolysis reaction mixture delivered LGE_2 methyl ester (**29RR**) together with its C-8 epimer **29SR** in a 13:1 ratio (see Scheme IV) as judged by the relative integral areas of ^{1}H NMR singlet resonances at δ 9.46 and 9.56, respectively. The structural assignments are discussed further below. The lactol derived from triol **27** also delivered **29RR** upon treatment with $NaIO_4$ in aqueous acetic acid.

Surprisingly, deprotection of the three hydroxyl groups in ketal silyl ether **25SR** by treatment with aqueous acetic acid and complete removal of the solvents delivered the exact same lactol as had been obtained from **25RR**, the C-8 epimer of **25SR**. Thus, *hydrolysis of **25SR** is accompanied by a remarkable stereoselective epimerization at C-8*. Oxidative cleavage with periodate of either the hydrolysis reaction mixture from **25SR** or a solution of the purified lactol redissolved in aqueous acetic acid delivered the same 13:1 mixture of aldehydes **29RR** and **29SR** as obtained above from **25RR**. This ratio apparently reflects the equilibrium ratio between **27RR** and **27SR**. The high,

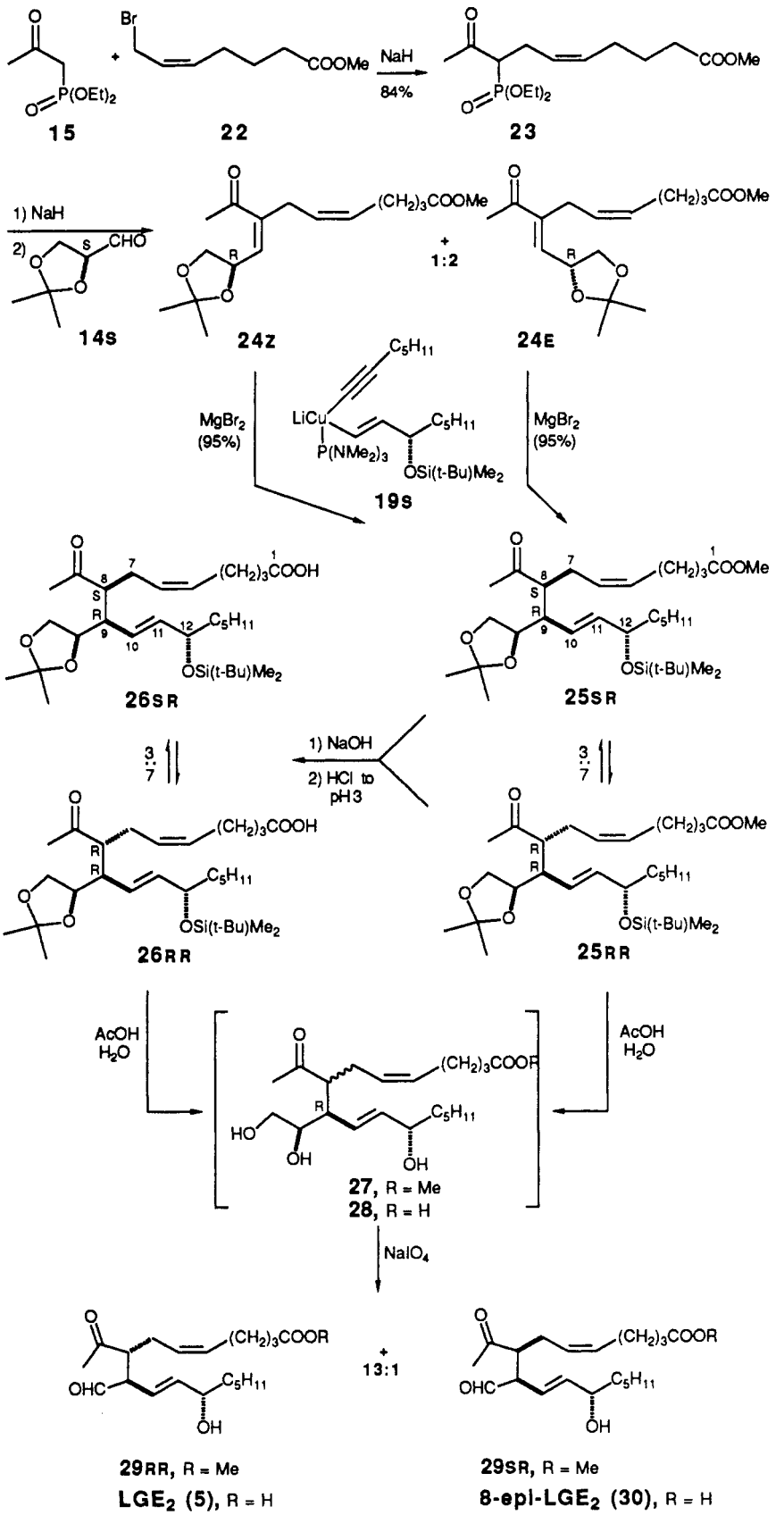


i.e. 13:1, preference for the 8*R*,9*R* over the 8*S*,9*R* configuration in **27** contrasts with the moderate preference observed with the corresponding C-8 epimers of **25** and **26**. While not anticipated, this preference is the final key to an efficient stereoselective total synthesis of LGE_2 (vide infra) since separation of mixtures of isomeric interme-

(18) Crould, R. F., Ed. *Advances in Chemistry Series* **1973**, *116* (Azeotropic Data III), 113.

(19) The difficulty in distinguishing the pyranose from the furanose form of reducing sugars has been discussed, see: (a) Angyal, S. J.; Pickles, V. A. *Carbohydr. Res.* **1967**, *4*, 269. (b) *Aust. J. Chem.* **1972**, *25*, 1695.

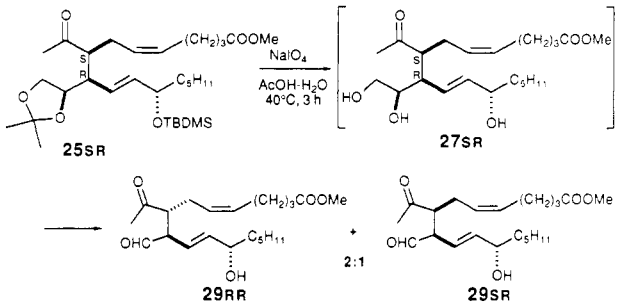
Scheme IV



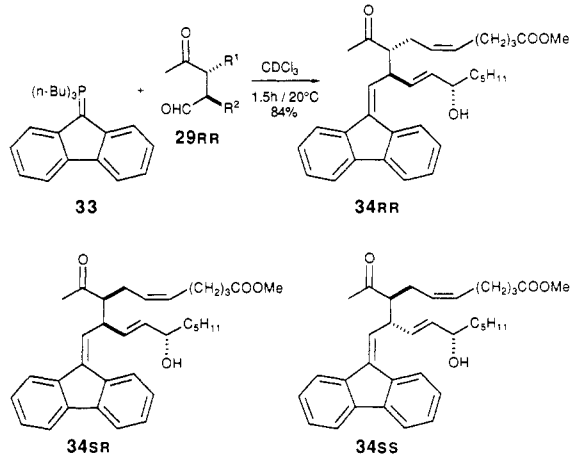
diates is unnecessary. The exclusive formation of an 8*R* epimer of the lactol **31** or **32** is a reasonable consequence of the preference for a trans relationship between the C-8 and C-9 substituents.

That the stereoselective epimerization of **27SR** occurs prior to generation of LGE_2 methyl ester (**5**) was shown by partial interception of this intermediate before complete equilibration. Thus, treatment of **25SR** with aqueous acetic acid *in the presence of* $NaIO_4$ delivered a 2:1 mixture of **29RR** and **29SR**.

Stereochemical Correlation with Naturally Derived LGE_2: Flourenylidene Derivatives. Chromato-



graphic analysis and purification of LGE_2 is hampered by chemical instability. LGE_2 readily eliminates water and undergoes allylic rearrangement of the 10,11-C=C bond into conjugation with the formyl substituent.[7] Therefore, a method was sought for a mild and high-yielding chemical derivatization. It was reasoned that a reaction which selectively modified the sensitive vinylogous β-hydroxy aldehyde functional array might provide a more stable material since the chemical instability of LGE_2 appeared to be associated with this portion of the molecule. Successful derivatization of LGE_2 methyl ester (**29RR**) was achieved by chemoselective Wittig olefination of the aldehyde carbonyl with flourenylidene(tri-*n*-butyl)-phosphorane (**33**),[20] which delivers **34RR**. The progress of the derivatization in $CDCl_3$ was conveniently monitored by ^1H NMR spectroscopy. Concomitant with the disappearance of the aldehydic resonance at δ 9.47 there appeared a new downfield olefinic doublet (δ 6.56, d, J = 10.0 Hz) owing to **34RR**. In contrast with LGE_2 methyl ester (**29RR**), pure **34RR** was *readily isolated quantitatively* by HPLC on silica gel. The Wittig adduct **34RR** shows intense UV absorptions (ϵ_{max} = 40000; hexane) at both 258 and 229 nm.



Reaction of ylide **33** with the 2:1 mixture of **29RR** and **29SR** obtained by treatment of **25SR** with a solution of $NaIO_4$ in aqueous acetic acid delivered a 2:1 mixture of **34RR** and **34SR**, which are readily separable by HPLC showing relative retention times of 1:1.47 respectively on Partisil with 20% ethyl acetate in hexane (v/v). The fluorenylidene derivatization allowed quantitative confirmation of the degree of stereoselection provided by epimerization at position 8 during acidic deprotection of **25SR** and **25RR**. The fluorenylidene adduct mixtures obtained from either epimeric precursor by hydrolysis with aqueous acetic acid, followed by oxidative cleavage with $NaIO_4$, and treatment of the crude aldehyde product mixture with ylide **33** were identical 13:1 mixtures of **34RR** and **34SR**, respectively.

(20) Johnson, A. W.; La Count, R. B. *Tetrahedron* **1969**, *9*, 130.

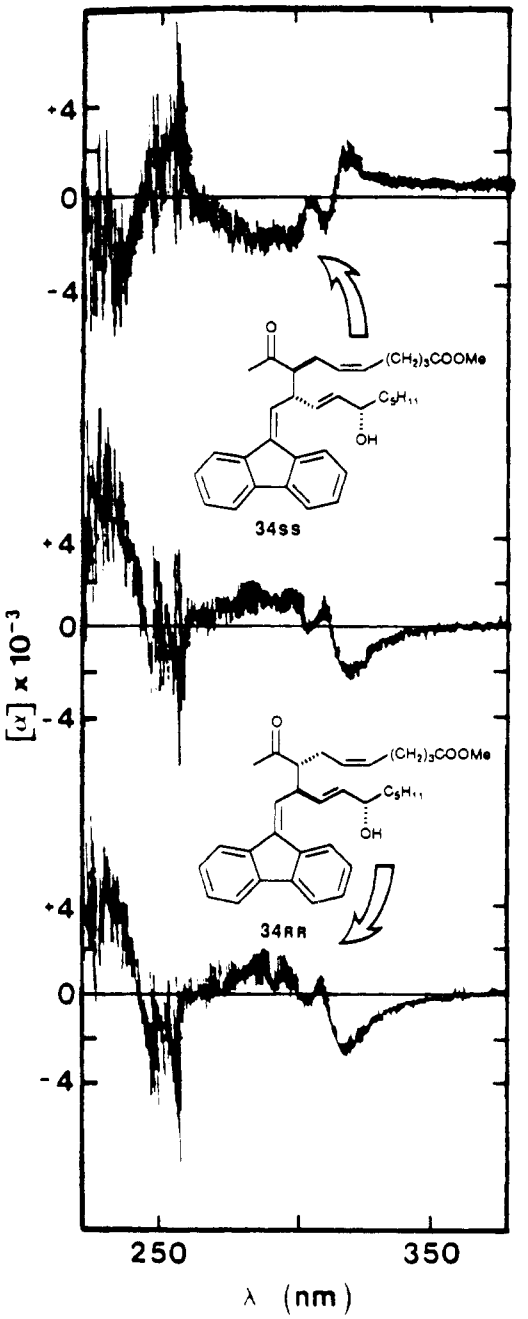


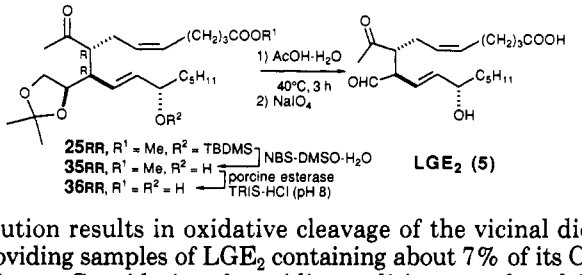
Figure 1. ORD spectra of fluorenylidene derivatives: top, **34SS**; middle, fluorenylidene derivative of LGE_2-methyl ester obtained from PGH_2; bottom, **34RR**.

For comparison with synthetic levuglandins, LGE_2 obtained by rearrangement of PGH_2 was methylated with CH_2N_2 (a low-yielding reaction owing to appreciable destruction of the aldehyde group). The resulting sample of LGE_2 methyl ester was derivatized with ylide **33**. The 8-epi-9-epi isomer **34SS** was also prepared for comparison. The 8-epi-9-epi isomer **25SS** of **25RR** was prepared by substituting isopropylidene-D-glyceraldehyde (**14R**) for the L isomer (**14S**) in Scheme IV. Derivatization of **25SS** with ylide **33** delivered **34SS**. Although the ^1H and ^{13}C NMR spectra of **25SS** and **25RR** are almost identical, the fluorenylidene derivatives **34RR** and **34SS** were readily distinguished by their almost mirror image ORD spectra (Figure 1). As expected, the fluorenylidene derivative obtained from the LGE_2 methyl ester sample prepared from PGH_2 exhibited an ORD spectrum identical with that of **34RR**. This clearly shows that LGE_2 does not interconvert with its 8-epi-9-epi isomer through enolization of

the carbonyl substituents at positions 8 and 9, and **25RR** is not interconverted with **25SS** by such epimerization during the total synthesis of Scheme IV.

Levuglandin E_2. Before the favorable equilibrium between the esters **27RR** and **27SR** (and the corresponding acids **28RR** and **28SR**) was discovered, a route to LGE_2 (**5**) from **25RR** was sought which scrupulously avoided epimerization at C-8. The diastereomers **25RR** and **25SR** are readily separated chromatographically. Treatment of pure **25RR** with 1.1 equiv of *N*-bromosuccinimide (NBS) in wet DMSO[21] removed the TBDMS protecting group to afford the allylic alcohol **35RR** in 75% yield. Removal of the TBDMS group was also accomplished quantitatively with fluoride ion,[22] but this was accompanied by extensive epimerization at C-8. Ester hydrolysis of **35RR** was accomplished using porcine liver esterase,[23] which cleanly afforded the carboxylic acid **36RR** in 93% yield. Hydrolysis of the ketal in **36RR** was achieved upon treatment with 2:1 acetic acid–water at 40 °C for 3.5 h. Removal of the solvents by freezing at −20 °C and sublimation at 0.05 Torr delivered a lactol, which exhibited a single upfield methyl singlet at δ 1.44 and a ^{13}C NMR spectrum showing 21 resonances including a single resonance for the anomeric hemiketal carbon at δ 104.9. As for the triol ester **27RR**, the triol acid **28RR** underwent quantitative intramolecular hemiketalization to produce a single isomeric lactol. Hydrolysis of **36RR** in deuterated aqueous acetic acid provided a solution containing uncyclized triol acid **28RR** as evidenced by a characteristic methyl ketone singlet at δ 2.22. Oxidative cleavage of this intermediate delivered a sample of LGE_2 (**5**) showing only 18% of one hydrogen at C-8 (the resonance at δ 2.94), indicating extensive deuterium incorporation through enolization at this chiral center, presumably enolization of **28RR**.

The novel stereoselective epimerization of triol acid **28** which favors the 8*R* over the 8*S* configuration by 13:1 serendipitously allows synthesis of the requisite C-8 configuration for LGE_2 without the need to separate epimeric intermediates. Thus, the 7:3 mixture of **25RR** and **25SR** obtained by addition of vinyl cuprate **19S** to a 1:2 mixture of enones **24Z** and **24E** (Scheme IV) cleanly affords a 7:3 mixture of **36RR** and its C-8 epimer, respectively, upon desilylation with fluoride and saponification with hydroxide. Deketalization of this epimeric mixture with aqueous acetic acid results in predominate formation of triol **28RR**, which possesses the stereochemistry at C-8 required for LGE_2. Addition of sodium periodate to this



solution results in oxidative cleavage of the vicinal diol, providing samples of LGE_2 containing about 7% of its C-8 epimer. Considering the acidic conditions employed for the oxidative cleavage of **28RR** and the potential for acid to catalyze ionization of the allylic alcohol and enolization of the aldehyde group in LGE_2, it is remarkable that dehydration of LGE_2 to give $AnLGE_2$ (**8**) was not observed under these conditions. The success of this last crucial step of the total synthesis depends upon the fact that the rate of dehydration actually *decreases* as pH decreases.[7] The abundant supply of LGE_2 provided by this total synthesis is now being used to explore the biological activities[24] and biochemistry[25] of this new rearrangement product from the pivotal prostaglandin endoperoxide intermediate in the cyclooxygenase pathway for arachidonic acid metabolism.

Experimental Section

General. All proton nuclear magnetic resonance (NMR) spectra were recorded at 200.06 MHz on a Varian XL-200 spectrometer. Proton chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane (δ 0.00). Tetramethylsilane or chloroform (δ 7.24) were used as internal standard. Significant ^1H NMR spectral data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constant(s) in hertz, and positional assignment if established. All NMR samples were analyzed as solutions in $CDCl_3$.

^{13}C NMR spectra were recorded on a Varian XL-200 spectrometer at 50.31 MHz. ^{13}C NMR are reported in parts per million on the δ scale relative to chloroform-*d* (δ 77.0). Attached proton test (APT)[26] spectra for ^{13}C were obtained using a Varian XL-200 spectrometer operating with the pulse sequence [D1–(90° pulse)–D2–(180° pulse)–(D2 + D3)–(180° pulse)–D3–data acquisition], where D1, D2, and D3 are delays equal to 7 s, 7 ms, and 40 μs, respectively. The high-power electron decoupler was gated off during the first D2 delay and was on during the remainder of the pulse sequence. Under these conditions quaternary and methylene carbons exhibit phases opposite to those displayed by methine and methyl carbons. APT spectral phasing was adjusted such that quaternary and methylene carbons showed positive absorptions while methine and methyl carbons showed negative absorptions. The results from APT spectra are shown by placing a plus (+) sign; indicating a quaternary or methylene carbon, or a minus (−) sign; indicating a methine or methyl carbon, after the chemical shift position of the carbon resonance. Assignments of carbon resonances were made on the basis of results from APT spectra and by comparison with published chemical shift data for similar structures.[27]

High-resolution mass spectra were recorded on a Kratos/AEI MS-30 dual beam, double-focusing magnetic sector mass spectrometer interfaced to a DS-50S Nova-3 computer. Unless otherwise stated, samples were run at 70 eV, 4 kV, 3000 resolution at 3 s per decade. Samples were introduced to the ionization chamber by direct probe insertion. Elemental analysis was performed by Spang Microanalytical Laboratory, Eagle Harbor, MI; no special purifications were used to prepare analytical samples. UV spectra were recorded on a Perkin-Elmer Model lambda-3 spectrophotometer. Optical rotations were measured at the sodium D line (589 nm) using a Perkin-Elmer Model 141 polarimeter. Optical rotatory dispersion (ORD) spectra were recorded on a Cary 60 spectrophotometer.

Thin-layer chromatography (TLC) was performed on glass plates precoated with silica gel (Kieselgel 60 F_{254}, E. Merck, Darmstadt, West Germany), R_f values are quoted for plates of thickness 0.25 mm. Visualization was done by viewing the developed plates under short-wavelength UV light and by heating the plates after spraying with vanillin–sulfuric acid. Flash column chromatography was performed on 230–400-mesh silica gel supplied by E. Merck. Preparative high-pressure liquid chromatography (HPLC) was performed using a Waters Associates system consisting of a Waters M-6000A solvent delivery system and a Waters U6K injector. The eluate was monitored with a Waters

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R 401 differential refractometer or an Instrumentation Specialties Company Model 1840 UV absorbance detector.

Materials. All reactions were performed in an inert moisture-free atmosphere under a positive pressure of nitrogen or argon except when working in aqueous media. Purification and handling of all solvents and reagents used in synthetic procedures were conducted under a nitrogen or argon atmosphere except for aqueous solutions. All solvents were reagent grade or purer. Thiophene-free benzene was boiled under reflux over potassium for several hours and distilled. Hexane and heptane were distilled, stirred over concentrated H_2SO_4 for 1 day, washed with water, saturated $NaHCO_3$, and water, dried over anhydrous $CaCl_2$, boiled under reflux over potassium 1 day, and redistilled. Tetrahydrofuran (THF) was boiled under reflux over potassium benzophenone ketal and distilled. Diethyl ether was boiled under reflux over $LiAlH_4$ and distilled. Ethyl acetate, hexane, and diethyl ether used for extractions or chromatography were distilled to remove nonvolatile impurities prior to use. The term "reduced pressure" refers to solvent removal via a Büchi rotavapor under water aspirator reduced pressure, followed by evacuation of the flask through a dry ice cooled vacuum trap at 0.1 mm for several hours. Water used in reactions was purified by passage through a reverse osmosis membrane to remove organic and particulate matter followed by distillation under nitrogen with partial condensation. Lead tetraacetate was obtained from Eastman Kodak Co. and was twice recrystallized from acetic acid prior to use. Anhydrous $MgBr_2$ was prepared by the reaction of 1,2-dibromoethane with excess magnesium turnings in THF. Porcine type II esterase and TRIS [2-amino-2-(hydroxymethyl)-1,3-propanediol] was obtained from Sigma Chemical Co.

Methyl 8-(Diethylphosphono)-9-oxodec-5(*Z*)-enoate (23). To a magnetically stirred suspension of sodium hydride (853 mg, 35.5 mmol, 1.2 equiv) in anhydrous THF (50 mL) was added (diethylphosphono)acetate (**15**) (5.75 g, 29.6 mmol) at room temperature. Stirring was continued for 2 h, and then methyl 7-bromohept-5(*Z*)-enoate (**22**)[28] (6.18 g, 28.1 mmol) was added in the dark at room temperature. The reaction mixture was stirred in the dark for 12 h. The solvent was then removed by rotary evaporation, and water (40 mL) was added to the resulting dark yellow residue. The aqueous mixture was extracted with ethyl acetate (5 × 50 mL), and the combined ethyl acetate extracts were washed once with brine (40 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to furnish 9.02 g of a clear oil. This oil was flash chromatographed on a 13-cm column packed with a 15-cm bed of silica gel employing ethyl acetate/hexane (3:1, v/v) as the mobile phase. The pooled product fractions were concentrated under reduced pressure, and the product was further purified by preparative HPLC on a Whatman M20 column (20 mm i.d. × 50 cm), employing a mobile phase of ethyl acetate/hexane (2:1, v/v) at a flow rate of 14 mL/min to remove a dialkylation product which was slightly less polar. The yield of **23**, homogeneous by TLC (R_f 0.3, 100% ethyl acetate, was 7.93 g (84% based on allylic bromide **22**): ^{1}H NMR δ 5.42–5.16 (2 H, C-4, C-5 H's), 4.07 (apparent quintet, 4 H, J = 8.3 Hz, OCH_2CH_3), 3.61 (s, 3 H, OCH_3), 3.11 (ddd, H, J = 23.8, 10.6, 3.8 Hz, C-8 H), 2.82–2.58 (br m, H, C-7 H_a), 2.54–2.34 (br m, H, C-7 H_b), 2.25 (t, 2 H, J = 7.6 Hz, C-2 H), 2.23 (s, 3 H, C-10 H), 2.05 (apparent q, 2 H, J = 6.8 Hz, C-4 H), 1.62 (apparent quintet, 2 H, J = 7.2 Hz, C-3 H), 1.27 (t, 6 H, J = 7.3 Hz, OCH_2CH_3); ^{13}C NMR δ 203.05 and 202.97 (C-9, +), 173.76 (C-1, +), 131.15 (C-5, –), 126.73 and 126.43 (C-6, –), 62.68 and 62.54 and 62.47 and 62.33 (2 OCH_2CH_3's, +), 53.31 (d, J = 124.2 Hz, C-8 split by ^{31}P, –), 51.33 (OCH_3, –), 33.25 (C-2, +), 31.36 (C-10, –), 26.38 (C-3, +), 24.47 (C-4, +), 24.22 and 24.13 (C-7, +), 16.28 and 16.16 (OCH_2CH_3, –). Anal. Calcd for $C_{15}H_{27}O_6P$: C, 53.88; H, 8.14; P, 9.26. Found: C, 52.70; H, 8.05; P, 9.48.

The dialkylation product gave the following physical data: ^{1}H NMR δ 5.48–5.21 (4 H, olefinic H), 4.03 (apparent quintet, 4 H, J = 7.6 Hz, OCH_2CH_3), 3.56 (s, 6 H, OCH_3), 2.57 (apparent dd, 4 H, J = 5.0, 15.4 Hz), 2.21 (s, 3 H, acetyl methyl), 2.19 (t, 4 H, J = 7.5 Hz), 2.00 (apparent q, 4 H, J = 7.7 Hz), 1.60 (apparent quintet, 4 H, J = 7.3 Hz), 1.22 (t, 6 H, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR δ 205.0 (+), 173.5 (+), 131.2 (–), 124.5 (d, J = 9.2 Hz, –), 62.3 (d, J = 7.1 Hz, +), 57.7 (d, J = 128.4 Hz, +), 41.1 (–), 33.1 (+), 28.1 (+), 28.0 (–), 26.4 (+), 24.3 (+), 16.1 (d, J = 5.7 Hz, –). Anal. Calcd for $C_{23}H_{40}O_8P$: C, 58.09; H, 8.48; P, 6.51. Found: C, 57.78; H, 8.31; P, 6.63.

Isopropylidene-L-glyceraldehyde (14S). The procedure of Baker[13] was modified. Thus, 4,5-isopropylidene-L-arabinose dibenzyl thioacetal (12.14 g, 28.9 mmol) was dissolved in anhydrous benzene (300 mL). While stirring vigorously, finely powdered lead tetraacetate (12.8 g, 28.9 mmol) was added in one portion at room temperature. Stirring was continued for 1.5 h and then stopped to allow the fine white crystals of lead diacetate to settle. The benzene solution was filtered, and the filtrate was transferred to a distillation flask. The benzene was distilled under reduced pressure through an efficient fractionating column at 28 °C (110 mm). When only 20 mL of liquid remained in the pot, the distillation was stopped, the contents of the pot were transferred to a smaller distillation flask, and *n*-heptane (20 mL) was added. The *n*-heptane/acetic acid azeotrope[18] was distilled at 18 °C (40 mm). After adding and distilling 3 × 20-mL portions of *n*-heptane from the flask, the product was fractionally distilled at 36 °C (9 mm) to furnish 1.57 g of **14S** as a clear oil, 90% pure by ^{1}H NMR spectroscopy and essentially free of acetic acid. Its ^{1}H NMR spectrum agreed with that reported for the D-glyceraldehyde enantiomer.[29]

Isopropylidene-D-glyceraldehyde (14R). The procedure was identical with that used to produce the L-glyceraldehyde derivative **14S** except the oxidative cleavage was performed on 4,5-isopropylidene-D-arabinose dibenzyl thioacetal[13] or 1,2,5,6-diisopropylidene-D-mannitol.[15]

Methyl 8-Acetyl-10(*R*),11-(isopropylidenedioxy)-5(*Z*),8-undecadienoates [(10*R*)-24]. A magnetically stirred suspension of sodium hydride (302 mg, 12.58 mmol, 1.25 equiv) in anhydrous THF (20 mL) was cooled to –5 °C. The β-keto phosphonate (**23**) (3.38 g, 10.11 mmol) in anhydrous tetrahydrofuran (20 mL) was added via a dropping funnel over 10 min. Stirring was continued at this temperature for 4 h. Then isopropylidene-L-glyceraldehyde (**14S**) (1.67 g, 11.12 mmol, 1.1 equiv, 88% purity) in anhydrous THF (5 mL) was added over 5 min. The solution was allowed to warm to room temperature and stirring was continued for 12 h. The solvent was then removed by rotary evaporation, and water (50 mL) was added to the resulting brown oily residue. The aqueous mixture was extracted with diethyl ether (5 × 50 mL), and the combined organic extracts were washed once with water (20 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure to afford 2.93 g of a clear yellow oil. This oil was flash chromatographed in three runs, each of approximately 1 g, on a 5-cm column packed with a 15-cm bed of silica gel. The column was eluted with ethyl acetate/hexane (1:3, v/v). Thirty 50-mL fractions were collected from each run. The mixed **24Z** and **24E** isomers eluted in fractions 13–22 and gave 2.32 g, from the three runs combined, of a clear oil (75% based on β-keto phosphonate **23**). The **24Z** and **24E** isomers (1:2.3, respectively) need not be separated for the next reaction; however, these geometrical isomers were separated for thorough characterization using the "shave-recycle" HPLC technique. Thus, a solution containing 150 mg of the mixture of **24Z** and **24E** in 0.6 mL of ethyl acetate/hexane (1:3, v/v) was injected onto a Whatman M9 column (9.4 mm i.d. × 50 cm) and eluted with this same solvent mixture at a flow of 2.2 mL/min. The eluate was monitored by UV absorption at 274 nm and, after removal of a forerun, was recycled through the column five times. Separate fractions were collected from the late-eluting portion of the product peaks (first through fifth passes) and from the early eluting portion of the product peaks (third through fifth passes). Complete chromatographic resolution of the geometrical isomers was achieved after the fifth passage through the column. This afforded, after complete removal of solvents under reduced pressure, 45 mg of the less polar **methyl 8-acetyl-10(*R*),11-(isopropylidenedioxy)-5(*Z*),8(*Z*)-undecadienoate (24Z)**: ^{1}H NMR δ 5.72 (dt, H, J = 7.2, 1.3 Hz, C-9 H), 5.59–5.41 (m, H, C-5 H), 5.40–5.22 (m, H, C-6 H), 4.84 (apparent q, H, J = 6.9 Hz, C-10 H), 4.25 (dd, H, J = 6.7, 8.2 Hz, C-11 H), 3.62 (s, 3 H, OCH_3), 3.50 (dd, H, J = 7.2,

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8.2 Hz, C-11 H), 2.99 (br d, 2 H, J = 6.8 Hz, C-7 H), 2.28 (t, 2 H, J = 7.4 Hz, C-2 H), 2.21 (s, 3 H, acetyl methyl), 2.05 (apparent q, 2 H, J = 7.2 Hz, C-4 H), 1.66 (apparent quintet, 2 H, J = 7.2 Hz, C-3 H), 1.38 (s, 3 H, isopropylidene methyl), 1.31 (s, 3 H, isopropylidene methyl); ^{13}C NMR δ 201.9 (acetyl carbonyl, +), 173.8 (C-1, +), 140.8 (C-8, +), 137.2 (–), 131.6 (–), 126.1 (–), 109.4 (isopropylidene ketal carbon, +), 73.9 (C-10, –), 69.7 (C-11, +), 51.5 (OCH_3, –), 33.3 (+), 31.4 (+), 29.1 (acetyl methyl, –), 26.5 (2 C, coincident resonances, isopropylidene methyl and C-4, + and –), 25.4 (isopropylidene methyl, –), 24.5 (C-3, +); $[\alpha]^{25}_D$ –114.9° (c 0.166, $CHCl_3$): ORD (c 7.3 × 10^{-2}, n-heptane), at 25 °C $[\alpha]_{600}$ –164°, $[\alpha]_{589}$ –172°, $[\alpha]_{361}$ –726° (broad peak), $[\alpha]_{298}$ +218°, $[\alpha]_{270}$ +109°, $[\alpha]_{255}$ +355°; high-resolution mass spectrum, m/e calculated for $C_{17}H_{26}O_5$ 310.1780, found m/e (rel intensity) 310.1740 (0.2), 252 (8), 235 (22), 222 (10), 121 (13), 43 (100). There was also obtained 105 mg of the more polar **methyl 8-acetyl-10(*R*),11-(isopropylidenedioxy)-5(*Z*),8(*E*)-undecadienoate (24E)**: ^{1}H NMR δ 6.49 (d, H, J = 8.0 Hz, C-9 H), 5.41–5.21 (m, H, C-5 H), 5.19–5.01 (m, H, C-6 H), 4.89 (apparent q, H, J = 6.4 Hz, C-10 H), 4.16 (dd, H, J = 8.2, 6.4 Hz, C-11 H), 3.64 (s, 3 H, OCH_3), 3.61 (dd, H, J = 8.2, 6.4 Hz), 3.08 (dd, H, J = 6.6, 14.9 Hz, C-7 H_a), 2.97 (dd, H, J = 6.7, 14.7 Hz, C-7 H_b), 2.31 (t, 2 H, J = 7.5 Hz, C-2 H), 2.30 (s, 3 H, acetyl methyl), 2.14 (apparent q, 2 H, J = 6.9 Hz, C-4 H), 1.69 (apparent quintet, 2 H, J = 7.3 Hz, C-3 H), 1.44 (s, 3 H, isopropylidene methyl), 1.38 (s, 3 H, isopropylidene methyl); ^{13}C NMR δ 198.4 (acetyl carbonyl, +), 173.8 (C-1, +), 142.5 (C-8, +), 139.8 (–), 129.6 (–), 127.4 (–), 109.8 (isopropylidene ketal carbon, +), 72.7 (C-10, –), 68.8 (C-11, +), 51.3 (OCH_3, –), 33.3 (C-7, +), 26.5 (2 C, coincident resonances, + and –), 25.6 (–), 25.5 (–), 24.5 (+), 24.1 (+); $[\alpha]^{25}_D$ –23.5° (c 0.43, $CHCl_3$); ORD (2.6 × 10^{-2}, n-heptane), at 25 °C, $[\alpha]_{600}$ –27°, $[\alpha]_{589}$ –27°, $[\alpha]_{396}$ –58°, $[\alpha]_{377}$ –41°, $[\alpha]_{368}$ –51°, $[\alpha]_{361}$ –44°, $[\alpha]_{348\text{–}343}$ –97° (shoulder), $[\alpha]_{335}$ –155°, $[\alpha]_{330}$ –145°, $[\alpha]_{324}$ –167°, $[\alpha]_{316}$ –142° (shoulder), $[\alpha]_{275}$ +204°; high-resolution mass spectrum, m/e calculated for $C_{17}H_{26}O_5$ 310.1780, found m/e (rel intensity) 310.1793 (6.7), 293 (16), 253 (63), 252 (29), 235 (75), 222 (57), 121 (27), 43 (100).

Methyl 8-Acetyl-10(*S*),11-(isopropylidenedioxy)-5(*Z*),8-undecadienoates [(10*S*)-24]. The procedure was identical with that used to prepare the C-10(R) compounds (i.e., **24Z** and **24E** except that isopropylidene-D-glyceraldehyde (**14R**) was substituted for the L enantiomer (**14S**). The ^{1}H and ^{13}C NMR spectra of the products were identical in all respects to the C-10(R) enantiomers. Optical rotary dispersion spectra were of equal but opposite intensity. The following optical rotations were found. **Methyl 8-acetyl-10(*S*),11-(isopropylidenedioxy)-5(*Z*),8(*Z*)-undecadienoate**: $[\alpha]^{25}_D$ +113.8° (c 0.087, $CDCl_3$). **Methyl 8-acetyl-10(*S*),11-(isopropylidenedioxy)-5(*Z*),8(*E*)-undecadienoate**: $[\alpha]^{25}_D$ +23.1° (c 0.342, $CDCl_3$).

Methyl 8-Acetyl-9(*R*)-[1(*R*),2-(isopropylidenedioxy)-ethyl]-12(*S*)-(*tert*-butyldimethylsiloxy)-5(*Z*),10(*E*)-heptadecadienoates [(9*R*)-25]. The mixed cuprate **19S** from 1-iodo-3(S)-(*tert*-butyldimethylsiloxy)-1(E)-octene[30] (2.2 g, 5.74 mmol, 1.15 equiv) was prepared by the method of Corey and Beames.[31] To this was added anhydrous magnesium dibromide as a 0.2 M solution in THF[33] (28.6 mL, 5.7 mmol, 1.15 equiv) dropwise over 15 min at –78 °C. Upon completing the addition, a mixture of C-8(Z),C-10(R) and C-8(E),C-10(R) enones **24** (1.55 g, 5.00 mmol, 1 equiv) was added dropwise as a 1.5 M solution in anhydrous diethyl ether. The temperature was kept at –78 °C for 1 h, and then the reaction mixture was allowed to slowly warm to 0 °C over 1 h and quenched by addition of saturated aqueous ammonium chloride (5 mL). The reaction mixture was diluted with water (50 mL), and the aqueous layer was extracted with diethyl ether (3 × 75 mL). The combined ether extracts were washed with ice-cold 2% aqueous sulfuric acid (4 × 15 mL). The aqueous washes were reextracted with ether (2 × 50 mL). The combined ether extracts were filtered, and the filtrate was washed with saturated aqueous sodium bicarbonate (20 mL). The extract was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 3.08 g of a clear yellow oil. This oil was flash chromatographed on an 8-cm i.d. column packed with a 15-cm bed of silica gel. The column was eluted with ethyl acetate/hexane (1:4, v/v), and 40 50-mL fractions were collected. Fractions 11–20 contained the C-8(S) and C-8(R) 1,4-addition products **25** (2.12 g). Fractions 21–25 contained the C-8(R) epimer **25RR**, along with a more polar byproduct in a 60/40 ratio (192 mg). Fractions 31–40 contained recovered starting enones **24Z** and **24E** (187 mg). Thus, the overall yield for this conjugate addition was 92% based on enones **24** consumed with an 88% conversion.

The C-8(S) and C-8(R) epimers of **25** were separated by HPLC on a Whatman Partisil Magnum 20 preparative LC column (20 mm i.d. × 50 cm) employing a mobile phase of *tert*-butyl methyl ether/ethyl acetate/heptane (10/7/83, v/v/v) at a flow of 14 mL/min. Under these conditions, the retention times for the C-8(S) and C-8(R) epimers were 39 and 43 min, respectively. After HPLC there was obtained 567 mg of the minor C-8(S) epimer **25SR** and 1.374 g of the major C-8(R) epimer **25RR**. Thus, the combined overall isolated yield and pure epimers of (9R)-**25** was 80%.

Methyl 8(*S*)-acetyl-9(*R*)-[1(*R*),2-(isopropylidenedioxy)-ethyl]-12(*S*)-(*tert*-butyldimethylsiloxy)-5(*Z*),10(*E*)-heptadecadienoate (25*SR*): R_f = 0.50, 50% ethyl acetate/heptane (v/v); ^{1}H NMR δ 5.48–5.36 (2 H, C-10, C-11 H's), 5.41–5.18 (2 H, C-5, C-6 H's), 4.07–3.94 (m, H, C-12 H), 3.94–3.80 (2 H), 3.63 (s, 3 H, OCH_3), 3.57–3.46 (m, H), 3.07–2.97 (m, H, C-8 H), 2.38–2.18 (2 H, C-9 H, C-7 H_a), 2.26 (t, 2 H, J = 7.8 Hz, C-2 H), 2.16 (s, 3 H, acetyl methyl), 2.07–1.90 (3 H, C-4 H, C-7 H_b), 1.64 (apparent quintet, 2 H, J = 7.3 Hz, C-3 H), 1.46–1.28 (2 H, C-13 H), 1.38 (s, 3 H, isopropylidene methyl), 1.30 (s, 3 H, isopropylidene methyl), 1.23 (br s, 6 H, C-14, C-15, C-16 H's), 0.85 (s, 9 H, *tert*-butyl silyl), 0.84 (t, 3 H, J = 5.9 Hz, C-17 H), 0.00 (s, 6 H, dimethyl silyl); ^{13}C NMR δ 211.95 (+), 173.97 (C-1, +), 138.62 (–), 130.63 (–), 127.59 (–), 125.09 (–), 109.37 (+), 76.13 (–), 73.05 (C-12, –), 69.11 (+), 52.13 (C-8, –), 51.48 (OCH3, –), 49.96 (C-9, –), 38.46 (+), 33.46 (+), 32.45 (–), 31.81 (+), 28.22 (+), 26.95 (–), 26.67 (+), 25.83 (3 C, *tert*-butyl methyls, –), 25.58 (–), 24.84 (+), 24.72 (+), 22.64 (+), 18.21 (+), 14.03 (C-17, –), –4.44 (–), –4.85 (–); high-resolution mass spectra (8 eV), m/e calculated for (M – 15) 537.3611, found m/e (rel intensity) 537.3593 (6.3), 495 (100), 437 (21), 421 (17), 345 (12), 255 (29), 101 (23).

Methyl 8(*R*)-acetyl-9(*R*)-[1(*R*),2-(isopropylidenedioxy)-ethyl]-12(*S*)-(*tert*-butyldimethylsiloxy)-5(*Z*),10(*E*)-heptadecadienoate (25RR): R_f = 0.48, 50% ethyl acetate/heptane (v/v); ^{1}H NMR δ 5.49 (dd, H, J = 15.4, 5.9 Hz, C-11 H), 5.40–5.15 (2 H, C-5, C-6 H's), 5.18 (ddd, H, J = 15.5, 8.8, 0.9 Hz, C-10 H), 4.02 (apparent q, H, J = 6.7 Hz, C-12 H), 3.99–3.86 (2 H), 3.63 (s, 3 H, OCH_3), 3.64–3.49 (m, H), 2.77–2.62 (m, H, C-8 H), 2.58–2.39 (m, H, C-9 H), 2.29–2.02 (2 H, C-7 H), 2.27 (t, 2 H, J = 7.8 Hz, C-2 H), 2.10 (s, 3 H, acetyl methyl), 2.01 (apparent q, 2 H, J = 7.8 Hz, C-4 H), 1.63 (apparent quintet, 2 H, J = 7.3 Hz, C-3 H), 1.48–1.28 (2 H, C-13 H), 1.33 (s, 3 H, isopropylidene methyl), 1.29 (s, 3 H, isopropylidene methyl), 1.23 (br s, 6 H, C-14, C-15, C-16 H's), 0.85 (s, 9 H, *tert*-butylsilyl), 0.84 (t, 3 H, J = 6.1 Hz, C-17 H), 0.00 (s, 3 H, methyl silyl), –0.02 (s, 3 H, methylsilyl); ^{13}C NMR δ 210.61 (+), 174.01 (C-1, +), 138.59 (C-11, –), 130.44 (–), 127.61 (–), 125.04 (–), 109.57 (+), 77.17 (–), 72.76 (C-12, –), 68.79 (+), 54.43 (C-8, –), 51.44 (OCH_3, –), 49.58 (C-9, –), 38.31 (+), 33.50 (+), 31.78 (+), 30.80 (–), 26.66 (+), 26.51 (+), 26.42 (–), 25.80 (3 C, *tert*-butyl methyls, –), 25.58 (–), 24.73 (+), 24.70 (+), 22.60 (+), 18.20 (+), 14.01 (C-17, –), –4.45 (–), –4.78 (–); high-resolution mass spectrum (8 eV), m/e calculated for $C_{31}H_{56}O_6Si$: 552.3846, found m/e (rel intensity) 552.3766 (1), 537 (6), 495 (79), 432 (23), 421

(30) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827.

(31) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

(32) The purity of the diastereomers of LGE_2-methyl ester (**29**) obtained after periodate oxidations was determined by dividing the intergral height of the aldehydic resonances by the intergral height corresponding to one proton of the terminal methyl resonance (δ 0.85, t, 3 H) and multiplying by 100. Since the maternal balance from these reactions was often nearly quantitative, this value also corresponds to the percent yield. To insure quantitative intergration of the aldehyde resonance, the T_1 relaxation of this resonance was determined by the inversion–recovery technique. Data analysis was performed using the standard Varian XL-200 T_1 software program. For LGE_2-methyl ester (**29RR**) in $CDCl_3$ at 20 °C the T_1 relaxation of the aldehyde signal (s, δ 9.46) is 2.2 s. A pulse sequence delay of at least five times the calculated T_1 for a particular pulse width was used during data acquisition of spectra used for yield determinations.

(33) This solution, prepared from 1,2-dibromoethane and excess magnesium turnings in THF, is supersaturated. It must be used immediately after preparation. Once the bromide crystallizes from the solution, it cannot be redissolved.

(28), 395 (54), 345 (20), 337 (26), 255 (49), 101 (100).

Methyl 8-Acetyl-9(*S*)-[1(*S*),2-(isopropylidenedioxy)-ethyl]-12(*S*)-(*tert*-butyldimethylsiloxy)-5(*Z*),10(*E*)-heptadecadienoates [(9*S*)-25]. The procedure was identical with that used to prepare the C-9(*R*) 1,4-addition products [i.e., (9*R*)-**25**] except to the mixed cuprate **19S** was added a mixture of C-8(*Z*),C-10(*S*), and C-8(*E*),C-10(*S*) enones [i.e., (10*S*)-**24**] derived from isopropylidene-D-glyceraldehyde (**14R**). Thus, to the vinyl cuprate from 1-iodo-3(*S*)-(*tert*-butyldimethylsiloxy)-1(*E*)-octene[30] (1.213 g, 3.29 mmol, 1.05 equiv) containing magnesium dibromide (60.76 mg, 3.30 mmol, 1.05 equiv) was added a mixture of the C-8(*Z*) and C-8(*E*) enones 10*S*-**24** (973 mg, 3.13 mmol, 1 equiv). After aqueous quench and extractive workup as described above, there was obtained 1.78 g of product as a yellow oil. Purification by flash chromatography and HPLC in an analogous manner to that used to obtain **25SR** and **25RR** afforded the minor, less polar C-8(*R*) epimer **25RS** (293 mg), the major, more polar C-8(*S*) epimer **25SS** (918 mg), and recovered starting enones (10*S*)-**24** (42 mg). Thus, the combined overall isolated yield of pure epimers of (9*S*)-**25** was 74% with a 96% conversion for this conjugate addition reaction.

Methyl 8(*R*)-acetyl-9(*S*)-[1(*S*),2-(isopropylidenedioxy)-ethyl]-12(*S*)-(*tert*-butyldimethylsiloxy)-5(*Z*),10(*E*)-heptadecadienoate (25RS): R_f = 0.50, 50% ethyl acetate/heptane (v/v); ^{1}H NMR δ 5.48–5.39 (2 H, C-10, C-11 H's), 5.39–5.10 (2 H, C-5, C-6 H's), 4.04–3.92 (m, H, C-12 H), 3.92–3.76 (2 H), 3.63 (s, 3 H, OCH_3), 3.52–3.40 (m, H), 3.03–2.89 (m, H, C-8 H), 2.46–2.18 (2 H, C-9 H, C-7 H_a), 2.27 (t, 2 H, J = 7.8 Hz, C-2 H), 2.15 (s, 3 H, acetyl methyl), 2.11–1.94 (3 H, C-4 H, C-7 H_b), 1.64 (apparent quintet, 2 H, J = 7.3 Hz, C-3 H), 1.46–1.26 (2 H, C-13 H), 1.37 (s, 3 H, isopropylidene methyl), 1.30 (s, 3 H, isopropylidene methyl), 1.22 (br s, 6 H, C-14, C-15, C-16 H's), 0.85 (s, 9 H, *tert*-butylsilyl), 0.84 (t, 3 H, J = 5.9 Hz, C-17 H), 0.02 (s, 3 H, methylsilyl), −0.01 (s, 3 H, methylsilyl); ^{13}C NMR δ 211.66 (+), 173.98 (C-1, +), 138.55 (C-11, −), 130.60 (−), 127.72 (−), 125.49 (−), 109.42 (+), 76.16 (−), 73.03 (C-12, −), 68.96 (+), 52.65 (C-8, −), 51.42 (OCH_3, −), 49.79 (C-9, −), 38.41 (+), 33.50 (+), 32.22 (−), 31.78 (+), 28.18 (+), 26.90 (−), 26.68 (+), 25.85 (3 C, *tert*-butyl methyls, −), 25.62 (−), 24.89 (+), 24.77 (+), 22.63 (+), 18.19 (+), 14.00 (C-17, −), −4.34 (−), −4.81 (−); high-resolution mass spectrum, m/e calculated for (M − 15) 537.3611, found m/e (rel intensity) 537.3602 (4.5), 495 (84), 437 (100), 421 (13), 345 (15), 225 (36), 43 (16).

Methyl 8(*S*)-acetyl-9(*S*)-[1(*S*),2-(isopropylidenedioxy)-ethyl]-12(*S*)-(*tert*-butyldimethylsiloxy)-5(*Z*),10(*E*)-heptadecadienoate (25SS): R_f = 0.48, 50% ethyl acetate/heptane (v/v); ^{1}H NMR δ 5.51 (dd, H, J = 15.4, 5.7 Hz, C-11 H), 5.40–5.19 (2 H, C-5, C-6 H's), 5.18 (ddd, H, J = 15.6, 9.7, 0.9 Hz, C-10 H), 4.07–3.96 (m, H, C-12 H), 3.96–3.83 (2 H), 3.63 (s, 3 H, OCH_3), 3.61–3.49 (m, H), 2.74–2.60 (m, H, C-8 H), 2.51 (apparent q, H, J = 8.2 Hz, C-9 H), 2.26 (t, 2 H, J = 7.8 Hz, C-2 H), 2.25–2.00 (2 H, C-7 H_a, C-7 H_b), 2.10 (s, 3 H, acetyl methyl), 1.99 (apparent q, 2 H, J = 6.0 Hz, C-4 H), 1.71–1.53 (2 H, C-3 H), 1.46–1.30 (2 H, C-13 H), 1.31 (s, 3 H, isopropylidene methyl), 1.28 (s, 3 H, isopropylidene methyl), 1.22 (br s, 6 H, C-14, C-15, C-16 H's), 0.85 (s, 9 H, *tert*-butyl silyl), 0.83 (t, 3 H, J = 5.7 Hz, C-17 H), 0.00 (s, 3 H, methyl silyl), −0.03 (s, 3 H, methyl silyl); ^{13}C NMR δ 210.73 (+), 173.93 (C-1, +), 138.51 (C-11, −), 130.47 (−), 127.58 (−), 125.21 (−), 109.58 (+), 77.34 (−), 72.67 (C-12, −), 68.71 (+), 54.60 (C-8, −), 51.38 (OCH_3, −), 49.58 (C-9, −), 38.36 (+), 33.51 (+), 31.77 (+), 30.84 (−), 27.19 (+), 26.52 (−), 26.33 (−), 25.80 (3 C, *tert*-butyl methyls, −), 25.60 (−), 24.79 (+), 24.76 (+), 22.59 (+), 18.18 (+), 13.96 (C-17, −), −4.47 (−), −4.83 (−); high-resolution mass spectrum, m/e calculated for (M − 15) 537.3611, found m/e (rel intensity) 537.3642 (4.8), 495 (100), 437 (7), 421 (6), 345 (7), 255 (44), 101 (33), 43 (10).

Hemiketalization of Methyl 8(*R*)-Acetyl-9(*R*)-[1(*R*)-[1-(*R*),2-dihydroxyethyl]-12(*S*)-hydroxy-5(*Z*),10(*E*)-heptadecadienoate (27RR). A magnetically stirred solution of **25RR** (44.8 mg, 0.081 mmol) in 1.8 mL of acetic acid/water (2:1, v/v) was warmed to 40 °C for 3.2 h. The reaction flask was then cooled to −25 °C, and the solvents were removed by sublimation into a trap cooled to −78 °C. The residual oily product, which tenaciously retained acetic acid, was dissolved in anhydrous ethanol (2 mL), and dry *n*-heptane (10 mL) was added. The solvents were removed by rotary evaporation, and this process of solvent addition and evaporative removal was repeated three times. After complete removal of solvents under high vacuum, there was obtained 32.4 mg (99% yield) of a clear viscous oil completely free of contaminating acetic acid. NMR spectral analysis indicated that the product had undergone quantitative stereoselective and regioselective intramolecular hemiketalization as evidenced by the upfield shift of the acetyl methyl resonance from δ 2.10 to δ 1.44 in the ^{1}H NMR spectrum and the absence of an acetyl carbonyl resonance in the ^{13}C NMR spectrum. It could not be ascertained if it was the hydroxyl group γ or δ to the carbonyl group which was involved in the cyclization;[19] however, the expected number of 22 resonances in the ^{13}C NMR spectrum indicated that a single anomer predominated: ^{1}H NMR δ 5.62–5.23 (4 H, C-5, C-6, C-10, C-11 H's), 4.04 (apparent q, H, J = 6.3 Hz, C-12 H), 3.90–3.10 (br, 3 H, OH), 3.89–3.79 (m, H), 3.71 (dd, H, J = 11.4, 2.4 Hz), 3.64 (s, 3 H, OCH_3), 3.47 (dd, H, J = 11.7, 2.8 Hz), 2.66 (ddd, H, J = 11.3, 8.4, 8.3 Hz, C-9 H), 2.28 (t, 2 H, J = 7.3 Hz, C-2 H), 2.27–1.85 (4 H, C-7, C-4 H's), 1.78–1.61 (m, H, C-8 H), 1.65 (apparent quintet, 2 H, J = 7.2 Hz, C-3 H), 1.54–1.32 (2 H, C-13 H), 1.45 (s, 3 H, anomeric methyl), 1.26 (br s, 6 H, C-14, C-15, C-16 H's), 0.85 (t, 3 H, J = 6.7 Hz, C-17 H); ^{13}C NMR δ 174.31 (+), 136.77 (−), 130.32 (−), 129.39 (−), 128.82 (−), 104.65 (anomeric C, +), 82.85 (−), 72.51 (−), 61.64 (+), 54.45 (−), 51.54 (−), 47.68 (−), 37.14 (+), 33.36 (+), 31.65 (+), 26.43 (+), 25.95 (−), 25.76 (+), 25.06 (+), 24.57 (+), 22.54 (+), 13.98 (−).

When the above procedure was carried out on the C-8(*S*) epimer (**25SR**) (40.1 mg, 0.073 mmol) there was afforded 28.8 mg (98% yield) of a clear viscous oil which exhibited completely identical ^{1}H and ^{13}C NMR spectra as the hemiketal arising from the C-8(*R*) epimer (**25RR**) described above.

8-Acetyl-9(*R*)-[1(*R*),2-(isopropylidenedioxy)ethyl]-12-(*S*)-(*tert*-butyldimethylsiloxy)-5(*Z*),10(*E*)-heptadecadienoic Acids (26). A 7:3 mixture of the epimeric esters **25RR** and **25SR** (100 mg, 0.181 mmol) was stirred with 4.5 mL of water/methanol/tetrahydrofuran (2:5:3, v/v/v) containing sodium hydroxide (36 mg, 0.904 mmol, 5 equiv) at room temperature. After 1.5 h, the reaction mixture was acidified to pH 3 with 2 N HCl and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed once with water (10 mL), and this aqueous wash was reextracted once with ethyl acetate (15 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 96 mg (98% yield) of the epimeric carboxylic acids. The C-8(*R*) and C-8(*S*) epimers were separated by preparative HPLC on a Whatman Partisil Magnum 9 column (9.4 i.d. × 50 cm), employing acetic acid/ethyl acetate/*n*-heptane (2/20/78, v/v/v) as the mobile phase at a flow of 2.0 mL/min. Under these conditions, the retention times for the epimeric products **26SR** and **26RR** were 23 and 27 min, respectively. HPLC purification afforded 28 mg (29%) of **8(*S*)-acetyl-9(*R*)-[1(*R*),2-(isopropylidenedioxy)ethyl]-12(*S*)-(*tert*-butyldimethylsiloxy)-5(*Z*),10(*E*)-heptadecadienoic acid (26SR):** ^{1}H NMR δ 5.47–5.39 (2 H, C-10, C-11 H's), 5.38–5.22 (2 H, C-5, C-6 H's), 4.08–3.97 (m, H, C-12 H), 3.96–3.83 (2 H), 3.59–3.46 (m, H), 3.10–2.96 (m, H, C-8 H), 2.41–2.19 (2 H, C-9 H, C-7 H_a), 2.31 (t, 2 H, J = 7.8 Hz, C-2 H), 2.16 (s, 3 H, acetyl methyl), 2.11–1.92 (3 H, C-4 H, C-7 H_b), 1.65 (apparent quintet, 2 H, J = 7.3 Hz, C-3 H), 1.53–1.38 (2 H, C-13 H), 1.39 (s, 3 H, isopropylidene methyl), 1.31 (s, 3 H, isopropylidene methyl), 1.24 (br s, 6 H, C-14, C-15, C-16 H's), 0.86 (s, 9 H, *tert*-butylsilyl), 0.85 (t, 3 H, J = 5.6 Hz, C-17 H), 0.01 (s, 6 H, dimethylsilyl); ^{13}C NMR δ 210.78 (+), 173.92 (C-1, +), 138.59 (C-11, −), 130.46 (−), 127.73 (−), 125.05 (−), 109.39 (isopropylidene ketal carbon, +), 76.11 (−), 73.05 (C-12, −), 69.09 (+), 52.11 (C-8, −), 49.96 (C-9, −), 38.41 (+), 33.35 (+), 32.45 (+), 31.29 (−), 28.21 (+), 26.92 (−), 26.54 (+), 25.82 (3 C, *tert*-butyl methyls, −), 25.56 (−), 24.83 (+), 24.42 (+), 22.62 (+), 18.21 (+), 14.01 (C-17, −), −4.47 (−), −4.86 (−). There was also obtained 67 mg (70%) of **8(*R*)-acetyl-9(*R*)-[1(*R*),2-(isopropylidenedioxy)ethyl]-12(*S*)-(*tert*-butyldimethylsiloxy)-5(*Z*),10(*E*)-heptadecadienoic acid (26RR):** ^{1}H NMR δ 5.50 (dd, H, J = 15.4, 5.9 Hz, C-11 H), 5.43–5.19 (2 H, C-5, C-6 H's), 5.17 (dd, H, J = 15.4, 9.8, 1.0 Hz, C-10 H), 4.02 (apparent q, H, J = 5.0 Hz, C-12 H), 3.99–3.89 (2 H), 3.65–3.53 (m, H), 2.78–2.66 (m, H, C-8 H), 2.61–2.44 (m, H, C-9 H), 2.31 (t, 2 H, J = 7.6 Hz, C-2 H), 2.30–2.01 (2 H, C-7 H), 2.11 (s, 3 H, acetyl methyl), 2.04 (apparent q, 2 H, J = 7.3 Hz, C-4 H), 1.65 (apparent quintet, 2 H, J = 7.3 Hz, C-3 H), 1.47–1.31 (2 H, C-13 H), 1.34

(s, 3 H, isopropylidene methyl), 1.29 (s, 3 H, isopropylidene methyl), 1.23 (br s, 6 H, C-14, C-15, C-16 H's), 0.86 (s, 9 H, *tert*-butylsilyl), 0.84 (t, 3 H, J = 5.3 Hz, C-17 H), 0.01 (s, 3 H, methylsilyl), −0.01 (s, 3 H, methylsilyl); ^{13}C NMR δ 210.86 (+), 179.31 (C-1, +), 138.57 (C-11, −), 130.27 (−), 127.69 (−), 124.93 (−), 109.58 (isopropylidene ketal carbon, +), 77.11 (−), 72.71 (C-12, −), 68.71 (+), 54.36 (C-8, −), 49.67 (C-9, −), 38.23 (+), 33.39 (+), 31.73 (+), 30.79 (−), 26.61 (+), 26.36 (2 C, coincident resonances, + and −), 25.76 (3 C, *tert*-butyl methyls, −), 25.53 (−), 24.66 (+), 24.41 (+), 22.57 (+), 18.16 (+), 13.97 (C-17, −), −4.53 (−), −4.85 (−).

Methyl 8(*R*)-Acetyl-9(*R*)-[1(*R*),2-(isopropylidenedioxy)-ethyl]-12(*S*)-hydroxy-5(*Z*),10(*E*)-heptadecadienoate (35RR). To a magnetically stirred solution of *N*-bromosuccinimide (88.2 mg, 0.496 mmol, 1.1 equiv) in dimethyl sulfoxide (1.8 mL) containing water (100 μL) was added **25RR** (250 mg, 0.45 mmol, 1 equiv) at room temperature.[21] After 3 h, the reaction mixture was diluted with diethyl ether (30 mL) and the organic phase was washed with brine (2 × 10 mL). The aqueous washes were reextracted with diethyl ether (1 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 233 mg (116% material balance) of a pale yellow oil. This oil was purified by HPLC on a Whatman Magnum 9 column (9.4 mm i.d. × 50 cm) employing ethyl acetate/hexane (3:7, v/v) as the mobile phase at a flow of 2 mL/min. Under these conditions, the deprotected alcohol **35RR** exhibited a retention time of 62 min: ^{1}H NMR δ 5.58 (dd, H, J = 16.2, 5.6 Hz, C-11 H), 5.44–5.20 (3 H, C-5, C-6, C-10 H's), 4.06 (apparent q, H, J = 7.2 Hz, C-12 H), 4.00–3.87 (2 H), 3.64 (s, 3 H, OCH_3), 3.64–3.52 (m, H), 2.74 (apparent q, H, J = 7.32 Hz, C-8 H), 2.62–2.44 (m, H, C-9 H), 2.28 (t, 2 H, J = 7.3 Hz, C-2 H), 2.22–1.98 (2 H, C-7 H), 2.12 (s, 3 H, acetyl methyl), 2.10–1.80 (br, H, OH), 2.01 (apparent q, 2 H, J = 7.5 Hz, C-4 H), 1.62 (apparent quintet, 2 H, J = 7.3 Hz, C-3 H), 1.53–1.37 (2 H, C-13 H), 1.33 (s, 3 H, isopropylidene methyl), 1.28 (s, 3 H, isopropylidene methyl), 1.26 (br s, 6 H, C-14, C-15, C-16 H's), 0.85 (t, 3 H, J = 6.3 Hz, C-17 H); ^{13}C NMR δ 211.07 (+), 174.23 (C-1, +), 137.98 (C-11, −), 130.50 (−), 127.53 (−), 126.03 (−), 109.60 (isopropylidene ketal carbon, +), 77.10 (−), 71.93 (−), 68.51 (+), 54.34 (−), 51.56 (OCH_3, −), 49.55 (−), 37.19 (+), 33.31 (+), 31.69 (+), 30.95 (−), 26.88 (+), 26.44 (+), 26.38 (−), 25.55 (−), 24.98 (+), 24.62 (+), 22.58 (+), 14.00 (C-17, −).

Methyl 8(*S*)-Acetyl-9(*S*)-[1(*S*),2-(isopropylidenedioxy)-ethyl]-12(*S*)-hydroxy-5(*Z*),10(*E*)-heptadecadienoate (35SS). The procedure was identical with that used to produce the C-8(*R*), C-9(*R*) diastereomer **35RR**, except the deprotection was performed on **25SS** (38.6 mg, 0.070 mmol) and, after aqueous workup and chromatographic purification as described above, afforded 22.2 mg (66% yield) of **35SS**: ^{1}H NMR δ 5.57 (dd, H, J = 15.4, 6.5 Hz, C-11 H), 5.44–5.20 (2 H, C-5, C-6 H's), 5.26 (dd, H, J = 15.1, 10.3 Hz, C-10 H), 4.02 (apparent q, H, J = 6.0 Hz, C-12 H), 3.99–3.85 (2 H), 3.64 (s, 3 H, OCH_3), 3.63–3.50 (m, H), 2.78–2.62 (m, H, C-8 H), 2.60–2.42 (m, H, C-9 H), 2.28 (t, 2 H, J = 7.2 Hz, C-2 H), 2.26–2.00 (2 H, C-7 H), 2.12 (s, 3 H, acetyl methyl), 2.02 (apparent q, 2 H, J = 7.9 Hz, C-4 H), 1.76–1.62 (br, H, OH), 1.62 (apparent quintet, 2 H, J = 7.2 Hz, C-3 H), 1.54–1.37 (2 H, C-13 H), 1.33 (s, 3 H, isopropylidene methyl), 1.29 (s, 3 H, isopropylidene methyl), 1.25 (br s, 6-H, C-14, C-15, C-16 H's), 0.85 (t, 3 H, J = 6.5 Hz, C-17 H); ^{13}C NMR δ 211.04 (+), 174.27 (C-1, +), 138.20 (−), 130.52 (−), 127.56 (−), 126.71 (−), 109.66 (+), 77.36 (−), 72.45 (C-12, −), 68.55 (+), 54.54 (−), 51.60 (OCH_3, −), 49.68 (−), 37.15 (+), 33.23 (+), 31.68 (+), 30.89 (−), 27.01 (+), 26.41 (+), 26.38 (−), 25.58 (−), 25.08 (+), 24.57 (+), 22.60 (+), 14.01 (C-17, −).

8(*R*)-Acetyl-9(*R*)-[1(*R*),2-(isopropylidenedioxy)ethyl]-12(*S*)-hydroxy-5(*Z*),10(*E*)-heptadecadienoic Acid (36RR). A solution of **35RR** (148 mg, 0.34 mmol) in acetone (12 mL) was added to a magnetically stirred solution of 0.05 M pH 8.0 Tris-HCl buffer (700 mL) containing type II esterase from Porcine liver (5 mg protein, 500 units). The reaction mixture was stirred at room temperature for 4 h. The solution was then acidified to pH 3 with 6 N HCl and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed once with water (40 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 148 mg (103% material balance). The product was purified by HPLC on a Whatman Magnum 9 column (9.4 mm i.d. × 50 cm) employing ethyl acetate/hexane (1:1 v/v) as the mobile phase at a flow of 2 mL/min. The retention time of the product was 35 min. HPLC purification afforded 133 mg (93% yield) of the carboxylic acid **36RR**: ^{1}H NMR δ 6.45 (br, 2 H, OH, COOH), 5.61 (dd, H, J = 17.8, 5.0 Hz, C-11 H), 5.46–5.20 (3 H, C-5, C-6, C-10 H's), 4.13 (apparent q, H, J = 5.3 Hz, C-12 H), 4.02–3.86 (2 H), 3.63–3.50 (m, H), 2.76–2.61 (m, H, C-8 H), 2.50 (apparent q, H, J = 10.1 Hz, 1 Hz, C-9 H), 2.30 (t, 2 H, J = 6.8 Hz, C-2 H), 2.26–2.01 (2 H, C-7 H), 2.13 (s, 3 H, acetyl methyl), 2.05 (apparent q, 2 H, J = 8.2 Hz, C-4 H), 1.61 (apparent quintet, 2 H, J = 7.9 Hz, C-3 H), 1.54–1.38 (2 H, C-13 H), 1.32 (s, 3 H, isopropylidene methyl), 1.28 (s, 3 H, isopropylidene methyl), 1.25 (br s, 6 H, C-14, C-15, C-16 H's), 0.85 (t, 3 H, J = 6.7 Hz, C-17 H); ^{13}C NMR δ 211.59 (+), 177.52 (C-1, +), 137.16 (C-11, −), 130.45 (−), 127.61 (−), 125.91 (−), 109.61 (+), 77.10 (−), 71.81 (C-12, −), 68.49 (+), 54.53 (−), 49.73 (−), 36.93 (+), 32.79 (+), 31.66 (+), 31.12 (−), 27.22 (+), 26.33 (−), 26.18 (+), 25.54 (−), 24.89 (+), 24.35 (+), 22.56 (+), 14.00 (C-17, −).

Hemiketalization of 8(*R*)-Acetyl-9(*R*)-[1(*R*),2-dihydroxyethyl]-12(*S*)-hydroxy-5(*Z*),10(*E*)-heptadecadienoic Acid (28). A magnetically stirred solution of **36RR** (30 mg, 0.071 mmol) in 1 mL acetic acid/water (2:1, v/v) was warmed to 40 °C for 3 h. The reaction vessel was then cooled to −25 °C, and the solvents were removed by sublimation into a trap cooled to −78 °C. The residual oily product containing acetic acid was dissolved in anhydrous ethanol (2 mL), and dry *n*-heptane (10 mL) was added. The solvents were removed by rotary evaporation (20 mm, 20 °C), and this process of solvent addition and evaporative removal was repeated three times. After final concentration under high vacuum, there was obtained 26.5 mg (98% yield) of a clear oil which was completely free of contaminating acetic acid. NMR spectral analysis indicated that the product had undergone quantitative stereoselective and regioselective intramolecular hemiketalization as evidenced by the upfield shift of the acetyl methyl resonance from δ 2.13 to δ 1.45 in the ^{1}H NMR spectrum and the absence of an acetyl carbonyl resonance in the ^{13}C NMR spectrum: ^{1}H NMR δ 5.63–5.02 (8 H, 3 OH's, COOH, C-5, C-6, C-10, C-11 H's), 4.05 (apparent q, H, J = 6.2 Hz, C-12 H), 3.81 (ddd, H, J = 8.4, 2.8, 2.1 Hz), 3.69 (dd, H, J = 10.6, 2.1 Hz), 3.48 (dd, H, J = 10.6, 2.8 Hz), 2.62 (ddd, H, J = 10.6, 8.5, 8.4 Hz, C-9 H), 2.30 (t, 2 H, J = 6.6 Hz, C-2 H), 2.27–1.94 (4 H, C-7, C-4 H's), 1.84–1.66 (m, H, C-8 H) 1.66 (apparent quintet, 2 H, J = 7.0 Hz, C-3 H), 1.56–1.34 (2 H, C-13 H), 1.45 (s, 3 H, anomeric methyl), 1.27 (br s, 6 H, C-14, C-15, C-16 H's), 0.85 (t, 3 H, J = 5.8 Hz, C-17 H); ^{13}C NMR δ 177.59, 136.68, 130.12, 129.55, 128.95, 104.92 (anomeric carbon), 82.88, 72.52, 61.69, 54.53, 47.80, 36.98, 33.11, 26.26, 26.10, 25.69, 25.08, 24.29, 22.59, 14.02.

In a related experiment, **36RR** (20 mg, 0.047 mmoles) was dissolved in 0.5 mL of acetic acid-d_4/D_2O (2:1, v/v) and placed in an NMR tube. After taking an initial ^{1}H NMR spectrum, the NMR tube was placed in an oil bath and heated at 40 °C for 2.4 h. A new ^{1}H NMR spectrum of the sample was then obtained. The new spectrum revealed that quantitative removal of the isopropylidene protecting group had occurred, as evidenced by the disappearance of the isopropylidene methyl singlets at δ 1.40 and 1.37. In addition, this spectrum showed the characteristic upfield singlet due to the methyl ketone group at δ 2.22, indicating that, at least immediately after deprotection of the vicinal diol in acetic acid solution, the deprotected triol exists mainly in the open acyclic form.

Consecutive Hydrolysis and Oxidative Cleavage of 25RR. A solution of **25RR** (120 mg, 0.217 mmol) in 2.5 mL of acetic acid/water (2:1, v/v) was stirred magnetically and heated to 40 °C. After 4 h the resulting solution of triol **27**, R_f = 0.20, 2-propanol/hexane (1:4, v/v), was added to a solution of sodium metaperiodate (56 mg, 1.2 equiv) in 15 mL of 30% acetone/water (v/v). After 1.5 h the reaction was quenched by the addition of ethylene glycol (20 mg). After being stirred for an additional 15 min at room temperature, the solution was neutralized by the portionwise addition of sodium bicarbonate, diluted with water (20 mL), and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed once with water (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residual oily product containing acetic acid was dissolved in diethyl ether (2 mL), and dry *n*-heptane (10 mL) was added. The solvents were removed by rotary evaporation (20 mm, 20 °C),

and this process of solvent addition and evaporative removal was repeated three times. After final concentration under high vacuum, there was obtained 69 mg (90% material balance) of a clear oil which was completely free of contaminating acetic acid. Analysis by ^{1}H NMR spectroscopy indicated[32] that this product was a mixture containing at least 60% of **methyl 8(*R*)-formyl-12(*S*)-hydroxy-5(*Z*),10(*E*)-heptadecadienoate (LGE$_2$-methyl ester, 29RR)**: ^{1}H NMR δ 9.47 (s, H, CHO), 5.77 (dd, H, J = 15.6, 5.7 Hz, C-11 H), 5.57–5.16 (4 H, OH, C-5, C-6, C-10 H's), 4.10 (apparent q, H, J = 5.2 Hz, C-12 H), 3.63 (s, 3 H, OCH$_3$), 3.48 (apparent t, H, J = 9.5 Hz, C-9 H), 2.97 (ddd, H, J = 9.8, 8.1, 4.5 Hz, C-8 H), 2.35–1.96 (2 H, C-7 H), 2.26 (t, 2 H, J = 7.1 Hz, C-2 H), 2.22 (s, 3 H, acetyl methyl), 1.99 (apparent q, 2 H, J = 7.5 Hz, C-4 H), 1.65 (apparent quintet, 2 H, J = 7.9 Hz, C-3 H), 1.54–1.38 (2 H, C-13 H), 1.26 (br s, 6 H, C-14, C-15, C-16 H's), 0.84 (t, 3 H, J = 6.7 Hz, C-17 H) (a minor CHO resonance was observed at δ 9.56 which was tentatively assigned to the C-8 epimer **29SR**; this epimer accounted for less than 5% of the product mixture); ^{13}C NMR δ 210.96 (acetyl carbonyl), 199.78 (formyl carbonyl), 174.11 (ester carbonyl), 141.61 (C-11), 131.61, 125.64, 121.90, 71.96 (C-12), 57.05, 51.55, 51.07, 37.10, 33.22, 31.64, 30.93, 27.03, 26.49, 25.00, 24.51, 22.53, 13.97 (C-17).

This product mixture was further characterized by conversion of the aldehydes to stable adducts by reaction with 9-fluorenylidenetri-*n*-butylphosphorane (**33**).[20] Thus, to a solution of the aldehydes [2 mg (60% purity), 3 μmol] in 300 μL of dry CDCl$_3$ was added 20 μL of a 0.27 M solution of fluorenylidenetri-*n*-butylphosphorane in CDCl$_3$. The reaction was followed by the disappearance of the major aldehyde singlet (δ 9.47) in the ^{1}H NMR spectrum. After 1.5 h, the solvent was evaporated under a slow stream of nitrogen gas, the residue dissolved in a minimal amount of ethyl acetate/hexane (3:7, v/v) and eluted through a 5 mm i.d. pipet packed with a 6-cm bed of flash grade silica gel using this same solvent mixture at a flow of 0.5 mL/min. The eluate was monitored by UV absorbance at 275 nm. The major UV-active product eluted after 5.2 min. This product was further purified by HPLC on a Whatman Partisil column (4.6 mm i.d. × 25 cm) employing ethyl acetate/hexane (1:3, v/v) as the mobile phase at a flow rate of 2 mL/min. Under these conditions, the retention time of the major fluorenylidene Wittig adduct was 10 min. After HPLC there was obtained 1.3 mg (2.5 μmol, 87% yield) of **methyl 8(*R*)-acetyl-9(*S*)-(fluoren-9-ylidenemethyl)-12(*S*)-hydroxy-5(*Z*),10(*E*)-heptadecadienoate (34RR)**: ^{1}H NMR δ 7.87 (dd, H, J = 6.5, 1.6 Hz, aromatic), 7.73–7.60 (3 H, aromatic), 7.40–7.19 (4 H, aromatic), 6.56 (d, H, J = 10.0 Hz), 5.80–5.60 (2 H, C-10, C-11 H's), 5.46–5.20 (2 H, C-5, C-6 H's), 4.26–4.13 (m, H, C-9 H), 4.13–3.98 (m, H, C-12 H), 3.63 (s, 3 H, OCH$_3$), 2.82 (apparent q, H, J = 6.5 Hz, C-8 H), 2.40 (apparent t, 2 H, J = 6.2 Hz, C-7 H), 2.23 (t, 2 H, J = 7.3 Hz, C-2 H), 2.08 (s, 3 H, acetyl methyl), 1.99 (apparent q, 2 H, J = 8.0 Hz, C-4 H), 1.60 (apparent quintet, 2 H, J = 7.4 Hz, C-3 H), 1.56 (br, H, OH), 1.52–1.32 (2 H, C-13 H), 1.22 (br s, 6 H, C-14, C-15, C-16 H's), 0.82 (t, 3 H, J = 6.4 Hz, C-17 H); UV (c 5.06 × 10^{-5}, n-hexane) [$\lambda(\epsilon)$], 314 (13 600), 302 (13 300), 285 (15 300), 280 (shoulder) (14 600), 258 (40 000), 249 (31 100), 229 (39 700). Anal. Calcd for C$_{34}$H$_{42}$O$_4$: C, 79.34; H, 8.23. Found: C, 79.29; H, 8.17. Thorough characterization of the minor fluorenylidene adduct, i.e., that formed by reaction with the minor aldehydic product (**29SR**) is described subsequently.

Consecutive Hydrolysis and Oxidative Cleavage of 25SR. A solution of **25SR** (42.3 mg, 0.076 mmol) in acetic acid/water (2:1,v/v) was stirred magnetically and heated to 40 °C. After 3.5 h the resulting solution of the triol (**27**), R_f = 0.2, 20% 2-propanol/hexane (v/v), was added to a solution of sodium metaperiodate (19.8 mg, 1.2 equiv) in 6 mL of 30% acetone/water (v/v). After 1.2 h the reaction was quenched by the addition of ethylene glycol (10 mg). After an additional 10 min, the solution was diluted with water (15 mL), neutralized by the portionwise addition of sodium bicarbonate, and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed once with water (10 mL), dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residual oily product containing acetic acid was dissolved in diethyl ether (1 mL), and dry *n*-heptane (5 mL) was added. The solvents were removed by rotary evaporation (20 mm, 20 °C), and this process of solvent addition and evaporative removal was repeated three times. After final concentration under high vacuum, there was obtained 25.6 mg (91% material balance) of a clear oil which was completely free of contaminating acetic acid. The ^{1}H NMR spectrum of this material was essentially identical with the product obtained starting from **25RR**, i.e., at least 60% aldehyde product possessing a CHO resonance at δ 9.47 and a minor CHO resonance at δ 9.56. This product was characterized further by conversion of the aldehydes to stable fluorenylidene adducts as described above. The major fluorenylidene adduct obtained after chromatography, as described above, was identical in all respects to **34RR**.

Concomitant Hydrolysis and Oxidative Cleavage of 25SR. To a magnetically stirred solution of sodium metaperiodate (24.3 mg, 0.114 mmol, 1.5 equiv) in 2 mL of acetic acid/water (2:1, v/v) was added **25SR** (41.9 mg, 0.076 mmol), and the mixture was heated at 40 °C. After 3 h the reaction was quenched by the addition of ethylene glycol (15 mg). After an additional 10 min of stirring at room temperature the solution was neutralized by the portionwise addition of sodium bicarbonate, diluted with water, and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with water (1 × 5 mL), dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The resulting oily product containing residual acetic acid was dissolved in diethyl ether (2 mL), and dry *n*-heptane (10 mL) was added. The solvents were removed by rotary evaporation (20 mm, 20 °C), and this process of solvent addition and evaporative removal was repeated three times. After final concentration under high vacuum, there was obtained 26.1 mg (93% material balance) of a yellow oil. Analysis of this oil by ^{1}H NMR spectroscopy revealed three aldehydic resonances occurring at δ 9.56, 9.47, and 9.37 having approximate integration ratios of 1:2:1, respectively. The major aldehydic product, i.e., that giving rise to the resonance at δ 9.47, was assigned to the product having the C-8(*R*),C-9(*R*) configuration (**29RR**). The aldehyde resonance occurring at δ 9.37 was assigned to anhydro-LGE$_2$-methyl ester since the characteristic downfield olefinic resonances for this compound at δ 6.93 (d, 1 H) and δ 6.36 (m, 2 H) were also observable in the spectrum. The resonance at δ 9.56 was assigned to 8-epi-LGE$_2$-methyl ester (**29SR**) since partially purified samples of LGE$_2$ (**5**) derived from prostaglandin H$_2$ invariably show resonances in this region, presumed to be due to the C-8(*S*),C-9(*R*) and C-8(*R*),C-9(*S*) epimers of **5**. This mixture was subjected to fluorenylidene derivatization[20] for further characterization. Thus, the mixture of aldehydes (26.1 mg, 60% aldehydic products) was dissolved in CDCl$_3$ (400 μL) and placed in an NMR tube. A 200-MHz ^{1}H NMR spectrum was taken, and then 200 μL of a 0.32 M solution of fluorenylidenetri-*n*-butylphosphorane (**33**) in CDCl$_3$ was added. The reaction was monitored by ^{1}H NMR spectroscopy. Within 15 min after addition of the phosphonium ylide, the aldehydic resonances attributable to the methyl ester derivatives **29SR**, of 8-epi-LGE$_2$ and **29RR** of LGE$_2$ had disappeared while the aldehydic resonance of anhydro-LGE$_2$-methyl ester occurring at δ 9.37 remained unchanged. Analysis of this fluorenylidene derivatization mixture by TLC using a solvent system of ethyl acetate/hexane (2:3 v/v) revealed not only a material cochromatographing with the previously characterized C-8(*R*),C-9(*R*) fluorenylidene derivative **34RR** (R_f = 0.40) but also showed the presence of a second more polar material (R_f = 0.32) which exhibited similar fluorescence quenching and staining reactions on the TLC plates. Preliminary purification was accomplished by streaking the product mixture along the edge of a 0.25-mm TLC plate and eluting twice with ethyl acetate/hexane (35:55, v/v). Two well-resolved bands centered at R_f = 0.36 and R_f = 0.45 were each removed from the plate, and the products were eluted from the silica gel by trituration with ethyl acetate. After complete removal of the solvent under reduced pressure there was obtained 4.4 mg of the more polar product and 10.1 mg of the less polar product. The major, less polar product was identical by ^{1}H NMR spectroscopy and TLC analysis to the previously characterized fluorenylidene adduct **34RR** formed from the C-8(*R*),C-9(*R*) aldehyde product **29RR**. The minor, more polar product appeared by ^{1}H NMR spectroscopy and UV analysis to be the fluorenylidene adduct of 8-epi-LGE$_2$-methyl ester (**29SR**). This new derivative was further purified by HPLC on a Whatman Partisil column (4.6 mm i.d. × 20 cm) using ethyl acetate/hexane (3:7, v/v) at a flow of 0.8 mL/min. Its retention time under these conditions was 15.9 min. After HPLC there was obtained 4.0 mg of the new

fluorenylidene adduct **methyl 8(*S*)-acetyl-9(*S*)-(fluoren-9-ylidenemethyl)-12(*S*)-hydroxy-5(*Z*),10(*E*)-heptadecadienoate (34SR)**: ^{1}H NMR δ 7.91 (dd, H, *J* = 6.7, 1.6 Hz, aromatic), 7.76–7.60 (3 H, aromatic), 7.42–7.20 (4 H, aromatic), 6.46 (d, H, *J* = 10.2 Hz), 5.76–5.51 (2 H, C-10, C-11 H's), 5.42–5.20 (2 H, C-5, C-6 H's), 4.22 (ddd, H, *J* = 5.8, 9.6, 10.2 Hz, C-9 H), 4.02 (apparent q, H, *J* = 5.4 Hz, C-12 H), 3.58 (s, 3 H, OCH_3), 2.85 (ddd, H, *J* = 4.6, 9.3, 9.6 Hz, C-8 H), 2.47–2.18 (2 H, C-7 H), 2.17 (t, 2 H, *J* = 7.3 Hz, C-2 H), 2.15 (s, 3 H, acetyl methyl), 1.91 (apparent q, 2 H, *J* = 7.8 Hz, C-4 H), 1.54 (apparent quintet, 2 H, *J* = 7.2 Hz, C-3 H), 1.53 (br, H, OH), 1.48–1.30 (2 H, C-13 H), 1.22 (br s, 6 H, C-14, C-15, C-16 H's), 0.83 (t, 3 H, *J* = 6.4 Hz, C-17 H); UV (c 4.38 × 10^{-5}, n-hexane) [λ(ε)], 314 (13 200), 301 (12 900), 285 (15 000), 282 (shoulder) (13 700), 257 (40 000), 248 (30 300), 229 (39 300).

Consecutive Hydrolysis and Oxidative Cleavage of 25SS. The procedure was the same as that used for the C-8(*R*),C-9(*R*) diastereomer **25RR** described above, except the acidic deprotection and oxidative cleavage was performed on **25SS** (53.2 mg, 0.096 mmol) derived from isopropylidene-D-glyceraldehyde (**14R**). This afforded 34.5 mg (98% material balance) of a light yellow oil. Analysis of this oil by ^{1}H NMR spectroscopy indicated[32] that the product was a mixture containing at least 65% of **methyl 8-(*S*)-acetyl-9(*S*)-formyl-12(*S*)-hydroxy-5(*Z*),10(*E*)-heptadecadienoate (29SS)**: ^{1}H NMR δ 9.46 (s, H, CHO), 5.75 (dd, H, *J* = 15.5, 6.2 Hz, C-11 H), 5.59–5.17 (4 H, OH, C-5, C-6, C-10 H's), 4.09 (apparent q, H, *J* = 5.3 Hz, C-12 H), 3.63 (s, 3 H, OCH_3), 3.49 (dd, H, *J* = 9.5, 9.9 Hz, C-9 H), 2.95 (ddd, H, *J* = 10.0, 7.9, 4.4 Hz, C-8 H), 2.37–1.97 (2 H, C-7 H), 2.26 (t, 2 H, *J* = 7.1 Hz, C-2 H), 2.21 (s, 3 H, acetyl methyl), 2.02 (apparent q, 2 H, *J* = 7.5 Hz, C-4 H), 1.63 (apparent quintet, 2 H, *J* = 7.5 Hz, C-3 H), 1.52–1.34 (2 H, C-13 H), 1.25 (br s, 6 H, C-14, C-15, C-16 H's), 0.84 (t, 3 H, *J* = 6.7 Hz, C-17 H) (a minor aldehydic proton resonance was also observed at δ 9.55 which was tentatively assigned to the C-8 epimer **29RS**; this epimer accounted for less than 5% of the mixture); ^{13}C NMR δ 210.90 (acetyl carbonyl), 199.68 (formyl carbonyl), 174.17 (C-1), 141.80 (C-11), 131.58, 125.64, 122.02, 72.19 (C-12), 57.19, 51.55, 51.12, 37.10, 33.16, 31.61, 30.91, 27.04, 26.48, 25.02, 24.48, 22.51, 13.95 (C-17). This product mixture was further characterized by conversion of the aldehydes to stable adducts by reaction with 9-fluorenylidenetri-*n*-butylphosphorane (**33**).[20] Thus, to a solution of the aldehyde [2 mg (60% purity), 3 μmol] in 300 μL of dry $CDCl_3$ was added 200 μL of a 0.27 M solution of fluorenylidenetri-*n*-butylphosphorane (**33**) in $CDCl_3$. The reaction was followed by the disappearance of the major aldehyde signal (δ 9.46) in the ^{1}H NMR spectrum. The workup and purification of the major Wittig adduct **34SS** was performed exactly as described above for **34RR**. This afforded 1.1 mg (2 μmol, 70% yield) of **methyl 8(*S*)-acetyl-9(*R*)-(fluoren-9-ylidenemethyl)-12(*S*)-hydroxy-5,10-heptadecadienoate (34SS)**: ^{1}H NMR δ 7.89 (dd, H, *J* = 6.5, 1.7 Hz aromatic), 7.70–7.61 (3 H, aromatic), 7.40–7.20 (4 H, aromatic), 6.55 (d, H, *J* = 10.1 Hz), 5.81–5.59 (2 H, C-10, C-11 H's), 5.47–5.23 (2 H, C-5, C-6 H's), 4.23–4.12 (m, H, C-9 H), 4.08 (apparent q, H, *J* = 5.7 Hz, C-12 H), 3.64 (s, 3 H, OCH_3), 2.80 (dt, H, *J* = 8.7, 5.8 Hz, C-8 H), 2.47–2.35 (2 H, C-7 H), 2.24 (t, 2 H, *J* = 7.2 Hz, C-2 H), 2.07 (s, 3 H, acetyl methyl), 2.02 (apparent q, 2 H, *J* = 7.2 Hz, C-4 H), 1.60 (apparent quintet, 2 H, *J* = 7.4 Hz, C-3 H), 1.55 (br, H, OH), 1.53–1.36 (2 H, C-13 H), 1.19 (br s, 6 H, C-14, C-15, C-16 H's), 0.78 (t, 3 H, *J* = 5.3 Hz, C-17 H); UV (*c* 2.73 × 10^{-5}, *n*-hexane) [λ(ε)], 313 (12 600), 300 (12 200), 284 (14 000), 279 (shoulder) (13 300), 258 (40 700), 249 (28 700), 229 (37 000).

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Decomposition of Levuglandin E_2. Dehydration and Allylic Rearrangement Products[1]

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In aqueous solutions at 37 °C the β,γ-unsaturated δ-hydroxy aldehyde functional array in levuglandin E_2 (LGE_2) readily eliminates water to give an α,β,γ,δ-unsaturated aldehyde, anhydro levuglandin E_2 ($AnLGE_2$), in competition with allylic prototropic shift to give an α,β-unsaturated δ-hydroxy aldehyde, Δ^9-LGE_2. The allylic isomerization is catalyzed by $H_2PO_4^-$, perhaps by a bifunctional mechanism involving both proton acceptance by and donation from the catalyst. Thus, by appropriate adjustment of buffer *concentration*, the product distribution can be altered in a synthetically useful manner. Unexpectedly, the dehydration is *not* catalyzed by acid under the conditions examined (pH 2.8–8.0) and LGE_2 is *most* stable at pH 3–4.

Introduction

The complexity of the arachidonic acid (AA) cascade and of its myriad involvements in normal and pathophysiological processes is widely recognized. Recently we discovered a new branch in the cyclooxygenase pathway of the AA cascade, the formation of levuglandins.[2] Thus, decomposition of the prostaglandin endoperoxide PGH_2 under the aqueous conditions of its biosynthesis produces two levulinaldehyde derivatives, LGE_2 and LGD_2, concomitantly with the corresponding[3] prostaglandins PGE_2 and PGD_2. The fact that these primary levuglandins are themselves susceptible to facile molecular transformations, i.e. dehydration and rearrangement, further complicates studies of the cyclooxygenase pathway. As a foundation for investigations on the biochemistry of levuglandins, a thorough understanding of their chemical reactions is desirable especially in view of the biological activities of

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(3) *Formally*, PGE_2 and LGE_2 are interconvertable by aldol condensation as are PGD_2 and LGD_2. This interconversion has never been detected.

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