# Total Synthesis of (15*R*)- and (15*S*)-$F_{2t}$-Isoprostanes by a Biomimetic Process Using the Cyclization of Acyclic Dihydroxylated Octa-5,7-dienyl Radicals

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We report a new route to $F_{2t}$-IsoP (formerly named 8-*epi*-$PGF_{2\alpha}$) using a biomimetic radical cyclization of a highly functionalized C20 precursor. The strategy employed gives a $\beta$-hydroxy free radical followed by molecular oxygen trapping, which is an unusual method for quenching carbon free radicals. We observed the formation of unique diastereoisomers (15*R*)- and (15*S*)-$F_{2t}$-IsoP. This result is consistent with a strong stereoelectronic control associated with a steric effect initiated by the side chains $\alpha$ and $\omega$ on the cyclopentane ring.

## Introduction

The synthesis of prostaglandins (PGs) has been a subject of chemical interest for the last 40 years[1] with the successful strategy developed by Corey and coworkers via a formyl lactone[2] in the *trans*-PG series, derived from the action of cyclooxygenases (COXs). The putative nonenzymatic metabolic scheme of arachidonic acid (AA) synthesis, as a free-radical-catalyzed mechanism,[3] has introduced new data concerning the reactivity of the arachidonyl radical in the absence of COXs and also a growing interest in the total synthesis of isoprostane (IsoPs) compounds.[4]

Our approach is based on two relevant observations.[5] The first observation concerns the stereochemical autoxidation of poly-unsaturated fatty acids (PUFAs) or lipid hydroperoxides[6−11] with the following: (i) the first report concerning the formation of PG compounds by a nonenzymatic mechanism by Unilever workers,[6] (ii) the course of mercuric ion-catalyzed cyclization of lipid hydroperoxides,[9] giving the major *cis*-cyclic endoperoxide, and (iii) the high selectivity[10] favoring the formation of the *cis*-PG structures in the absence of COXs. The second observation was the result of the homolitic demercuration according to Corey et al.,[11] giving preferentially the *cis*-bicyclic endoperoxide, which upon reduction affords (15*R*)- and (15*S*)-$F_{2t}$-IsoP.[12] The common characteristic was the formation of the very close $\beta$ free-radical generated and its implication as intermediate in biosynthesis of *trans*-PGs.[13] Our strategy is based on the regio- and stereoselectivities of the octa-5,7-dienyl radical[14] cyclization in accordance with Beckwith,[15] as expected from Balwin's rules.[16] This methodology has been used for the

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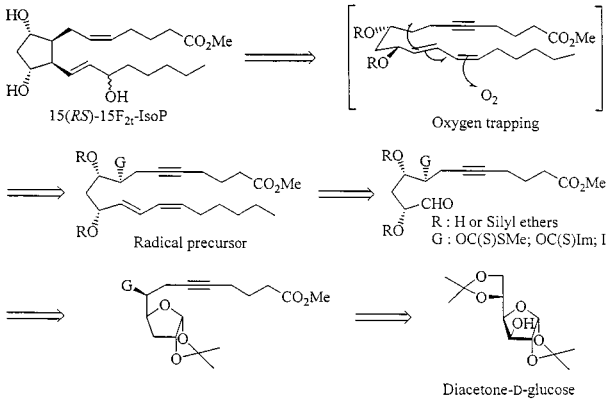
**Scheme 1. Retrosynthetic Analysis**




synthesis of preferentially *cis*-disubstituted cyclopentane derivatives.[17]

We present here our results on the use of highly functionalized free-radical precursor with 20 carbon atoms during biomimetic radical cyclization. Our aim was to investigate the reactivity of different radical precursors in terms of stereoselectivity induced by the side chains during the synthesis of isoprostanoid compounds. The retrosynthetic analysis (Scheme 1) points out two main steps from diacetone-D-glucose, i.e., (i) transformation into a radical precursor from the unstable aldehyde and (ii) cyclization reaction via a $\beta$-hydroxy free-radical as a faintly reminiscent natural radical postulated during the AA cascade, followed by molecular oxygen trapping.

**Synthesis of Radical Generators 9 and 11.** The synthesis of precursors **9** and **11** is outlined in Scheme 2. The commercially available diacetone-D-glucose is a good candidate as starting material. The absolute configuration of chiral centers (9*S*) and (11*R*) in compound **26** is the same as those of C4 and C2 positions in glucose derivative **1**. Moreover, radical precursors **9** and **11** contain three chiral centers, and if we control the stereochemical course of the ring closure between the C-8 and C-12 positions, the biomimetic radical cyclization pathway brings a real advantage in the IsoP synthesis.

The first five steps[18] are the tranformation to the known deoxyepoxyglucose and its alkylation by dilithium acetylide salt of 5-hexynoic acid in HMPA (57% yield), giving the acetylenic methyl ester **2** with a 17% overall yield. Because of the toxicity of *n*-$Bu_3SnH$, used during the Barton−McCombie reaction,[19,20] deoxyepoxyglucose could be prepared in good yield (75%) with tris(trimethylsilyl)silane[21] as reducing agent. Then propargylic alcohol **2** was transformed into its triflate[22] derivative **3** (85% yield), which in the presence of *n*-$Bu_4NI$[23] in benzene yielded the expected iodo compound **4** (75% yield). The observed chemical shifts of H-5 ($\delta$: 3.89; 5.08 and 4.13) and C-5 signals (70.0; 85.7 and 34.8, respectively) in the $^1H$ and $^{13}C$ NMR spectra of compounds **2**, **3**, and **4** clearly indicated their structures.

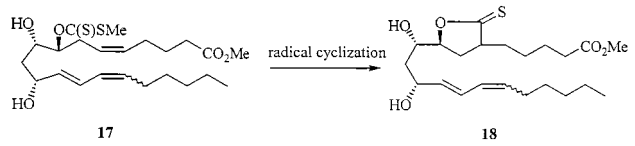
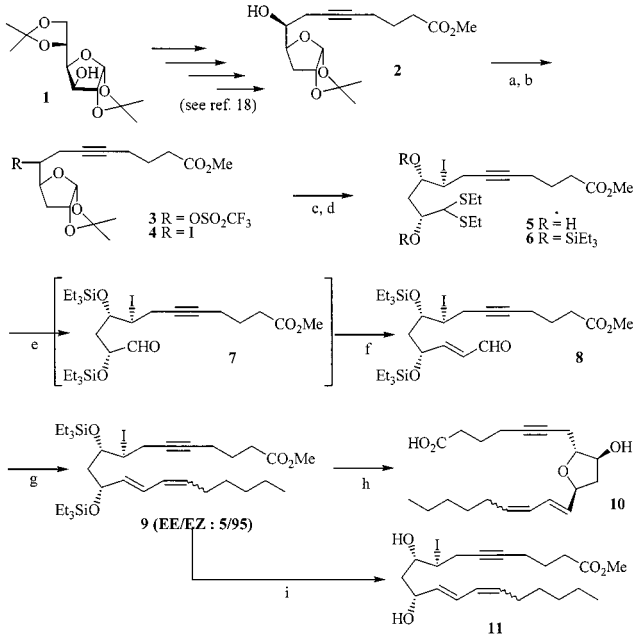



**Figure 1.** Oxacyclopenta-2-thione **18** from *S*-methyl dithionocarbonate **17**.

**Scheme 2. Synthesis of Radical Generators 9 and 11**[a]




[a] Reagents and conditions: (a) $(CF_3SO_2)_2O$, pyridine, $CH_2Cl_2$, −15 °C, 30 min, 85%; (b) *n*-$Bu_4NI$, benzene, reflux, 1.5 h, 75%; (c) $ZnCl_2$, EtSH, −15 °C, 1 h, 89%; (d) $Et_3SiCl$, pyridine, rt, 1 d, 89%; (e) HgO, $HgCl_2$, aqueous acetone, rt, 8 h; (f) $PPh_3$=CHCHO, DMF, 1 d, 67%; (g) *n*-hexyltriphenylphosphonium bromide, *n*-BuLi, THF, −78 to −10 °C, 10 min, 90%; (h) *n*-$Bu_4NF$, THF, rt, 2 h, 89%; (i) HCl (1 N), THF, rt, 3 h, 90%.

Treament of compound **4** with ethanethiol and $ZnCl_2$ at −15 °C gave diol−dithioacetal **5** (89% yield), which was converted to the disilyl ether **6** (89% yield) using $Et_3SiCl$ in dry pyridine. Hydrolysis under neutral conditions transformed the disilyl ether **6** into the corresponding unstable aldehyde **7**, which was immediately used in the next step without any purification. In an initial Wittig reaction, in the presence of (formylmethylene)triphenylphosphorane in dry DMF, compound **7** was converted to the fairly unstable $\alpha,\beta$-unsaturated aldehyde **8** in 67% overall yield, for these two steps. The E-double bond was confirmed by $^1H$ NMR spectroscopy ($J_{12,13}$ = 15.7 Hz). The next Wittig reaction, using *n*-hexyl triphenylphosphorane in dry THF, gave two isomeric olefins **9** (EE/EZ in a ratio of 5:95, with a 90% yield) as established by NMR

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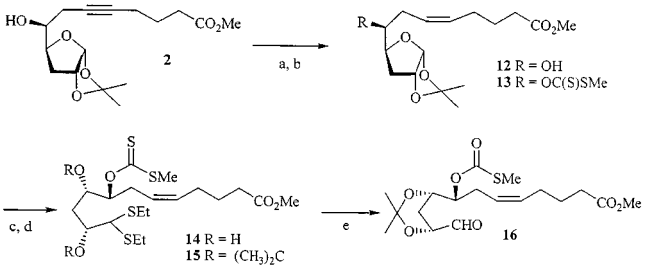
**Scheme 3. Transformation of Compound 15 to Thionocarbonate 16**[a]




[a] Reagents and conditions: (a) Ni "$P_2$", $H_2$, EtOH, rt, 2 h, 83%; (b) NaH, $CS_2$, MeI, THF, rt, 30 min, 72%; (c) $ZnCl_2$, EtSH, −10 °C, 20 min, 79%; (d) DMP, TsOH cat., rt, 1 h, 76%; (e) HgO, $HgCl_2$, acetone/water, rt, 5 h, 81%.

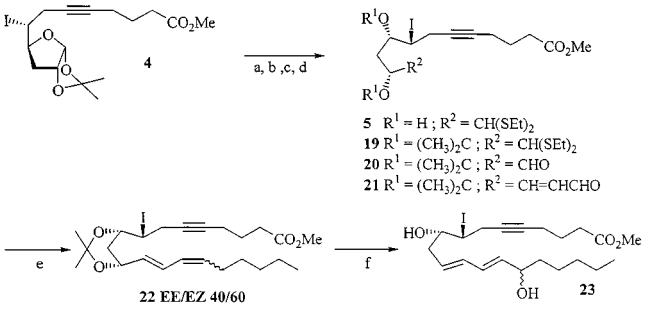
spectroscopy. The last step was the deprotection of the bis-silyl groups in compound **9**. Our first attempt was carried out using 1 equiv of *n*-$Bu_4NF$ for 1 equiv of compound **9** in dry THF, yielding (89%) the unexpected *C*-furanoside **10** via an intramolecular cyclization reaction between the allylic alkoxide in C-11 position and the C-8 center. This reaction has already been observed in a related compound.[20d] We have confirmed the structure of **10** by NMR studies in 1D ($^1H/^{13}C$) and 2D (HMQC/HMBC) as well as by elemental analysis. Finally, we have also desmonstrated the absolute configuration (8*R*,9*S*,11*S*) on compound **10** by steady-state NOE difference spectroscopy (DNOES) experiments (vide infra), which have been previously employed by our group[20b] with compounds such as shown in Figure 2. At least compound **11** was obtained in 90% yield under acidic conditions (HCl).

The validity of our strategy depicted in Scheme 2 was demonstrated by several difficulties encountered during the course of the work:

(i) In Scheme 3, several unexpected side reactions are summarized. First, direct substitution of the homoallylic alcohol **12** by an iodide derivative using to our procedure[24] did not give the expected product, nor did the route via the corresponding triflate.[22] Another difficulty was the transformation of the *S*-methyl dithiocarbonate **15** by action of mercuric salts (Scheme 3) to the *S*-methyl thiocarbonate **16**. Identical observations have appeared in the literature.[25−28]

(ii) The second difficulty was the formation of oxacyclopenta-2-thione methyl ester **18** from *S*-methyl dithiocarbonate **17** during the cyclization reaction (Figure 1). This observation was an another example proving the validity of Barton's mechanism.[29] The structural assignments by $^1H$ and $^{13}C$ NMR spectroscopy of compounds **17** and **18** were based on disappearance of the $SCH_3$ ($^1H$ $\delta$: 2.55 and $^{13}C$ $\delta$: 19.1) and the 5,6-ethylenic protons ($^1H$ $\delta$: 5.43 and $^{13}C$ $\delta$: 124.5 and 132) and the chemical shifts of H-8 ($\delta$: 5.65 and 4.59) and C-8 (85.5 and 53.7) signals, which were the proof of the cyclization reaction giving the thiolactone **18** (data not shown).

**Scheme 4. Acidic Rearrangement of Compound 22**[a]




[a] Reagents and conditions: (a) 4.0 equiv $ZnCl_2$, EtSH, −15 °C, 1 h, 89%; (b) 10.0 equiv DMP, TsOH cat., acetone, rt, 30 min, 89%; (c) 8.1 equiv of HgO, 3.1 equiv of $HgCl_2$, aqueous acetone, rt, 8 h; (d) 1.5 equiv of $Ph_3P$=CHCHO, DMF, rt, 1 d, 62%; (e) 2.2 equiv *n*-hexyltriphenylphosphonium bromide, 2.0 equiv of *n*-BuLi (2.5 M in hexane), THF, −78 to −10 °C, 20 min, 86%; (f) 50% v/v aqueous acetic acid, rt, 3 d, 38%.

(iii) Finally, the third difficulty (Scheme 4) was the unexpected rearrangement during the acidic deprotection step of compound **22** giving the iodo diol **23**. An attractive explanation of this reaction was an acidic activation of 11-allylic alcohol giving, after elimination reaction, the delocalized carbocation. This intermediate can react with water as nucleophile. Identical reactivity was observed during the nonenzymatic opening of leukotriene $LTA_4$.[30] This observation is also consistent with the great reactivity of C-11 allylic alcohol under acidic or basic elimination conditions.[31]

The structural assignments ($^1H/^{13}C$ NMR) of compound **23** compared with its precursor **22** are shown for the observed H-15 and C-15 signals (see the Experimental Section).

**Cyclization Reaction of Radical Precursors 9 and 11.** Basically, the radical cyclization reaction is a well-known procedure for carbon−carbon bond formation as well as for the synthesis of cyclic and polycyclic compounds[32] with good stereo- and regioselectivity. As in the case of the biosynthetic pathway,[9c] the formation of isoprostanoid compounds involves two consecutive radical cyclizations giving *cis*-1,2-dioxolane by ring closure of the appropriately constituted alkylperoxy radical (step 1), a second cyclization (step 2) leading to the formation of the bicyclic endoperoxide structure, followed by a *cis* stereoselective transfer of molecular oxygen (step 3) on a conjugated free radical. During this process, two molecules of molecular oxygen are trapped.[33] We now report our results on the cyclization, oxygenation, and reduction reactions concerning the carbon free redical **A** (Scheme 5). It can be assumed that this intermediate was very close to the expected radical species in the PG biosynthesis.

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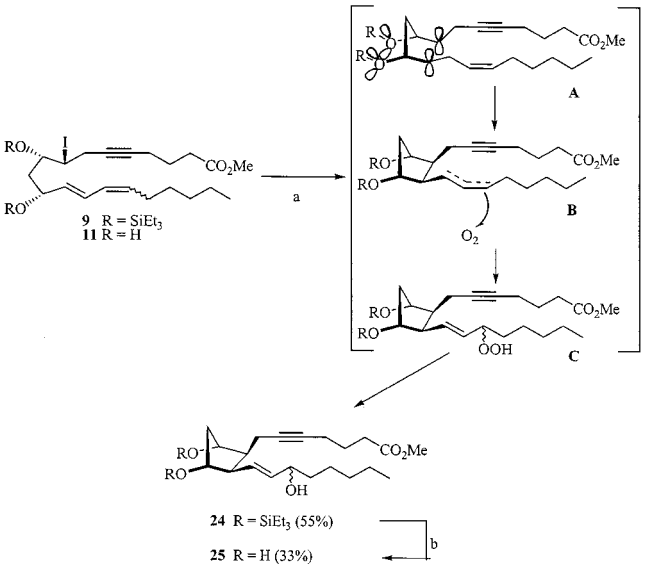
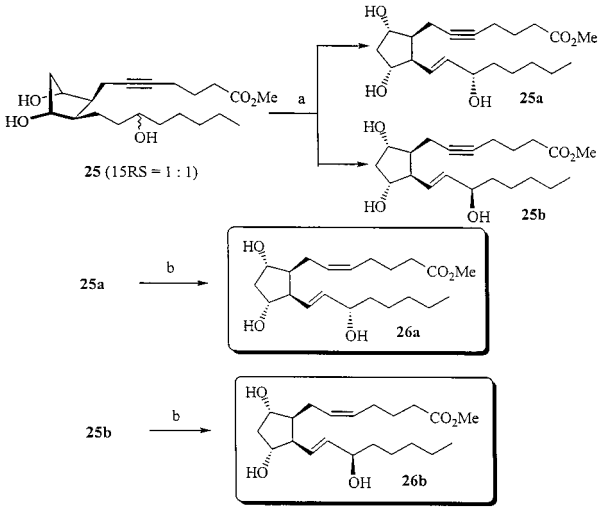
**Scheme 5. Cyclization Reactions of Radical Precursors 9 and 11**[a]




[a] Reagents and conditions: (a) 1.4 equiv of *n*-$Bu_3SnH$, 2.0 equiv of $BEt_3$, dry air, xylene, rt, 20 min, then below 2.1 equiv of $PPh_3$, rt, 2 h; (b) *n*-$Bu_4NF$, THF, rt, 1 h, 90%.

During the ring closure (Scheme 5), the last step was the hydrogen atom transfer. Although the reduction and also the synthetic applications of radical oxygenation are well documented,[36] there are very few data in the literature concerning radical trapping by molecular oxygen quench after radical cyclization.[9a,11,14,35] The singlet molecular oxygen trapping[17c] during prostanoid biosynthesis and also during lipid autoxidation gives bicycloendoperoxides under enzymatic[13] or by free-radical-catalyzed mechanisms.[3] From Scheme 5, it can be anticipated that the partitioning of carbon radical **A** between the expected cyclized compound **B** and the likely byproduct resulting from the $O_2$-trapping in the C-8 position will depend on the oxygen and hydride donor concentrations. It is noteworthy that the direct oxygenation of the hex-5-enyl radical to give 5-hexenol has been reported[36] to proceed with a 64% yield and with less than 1% of cyclized compound. This result, which is different from ours, is probably closely associated with the difference between the very fast direct oxygen transfer probably diffusion-controlled ($k = 10^8-10^9$ $M^{-1}$ $s^{-1}$, refs 37 and 38) and the rate constant of the fast cyclization reaction ($k = 2.5\ 10^5$ $M^{-1}$ $s^{-1}$) for the hex-5-enyl radical.[17]

**Scheme 6. Synthesis of (15*R*)- and (15*S*)-$F_{2t}$-IsoP 26a and 26b**[a]




[a] Reagents and conditions: (a) separation by HPLC, Zorbax ODS column 4 × 250 mm, eluent: MeOH/$H_2O$ (60:40), AcOH 1%, pH = 5.8, flow rate 0.6 mL/min, retention time 30.6 and 27.3 min for **25a** and **25b**, respectively; (b) Ni "P2", $H_2$, EtOH, 1 d, 90%.

The cyclization reactions of iodo-radical generators **9** and **11** were carried out under conditions we previously described.[20b,39] In our case and after several experiments, the following conditions gave the following results:[40] 2 equiv of 1 N $Et_3B$ in hexane was added in 0.1 equiv portions in order to maintain a low concentration of *n*-$Bu_3Sn^{\bullet}$, and then dry air was bubbled into the flask. As observed in TLC, three major compounds appeared ($R_f$ 0.54 and 0.47/0.44 in $C_6H_{12}$/AcOEt 70:30; $R_f$ 0.55 and 0.22/0.20 in $CH_2Cl_2$/MeOH 95:5 from compounds **9** and **11**, respectively). Two equivalents of $Ph_3P$ was added, and the solution was stirred for 2 h at rt. The least polar spot disappeared to the advantage of two unseparable epimeric mixtures **24** and **25** in a yield of 55% and 33%, respectively. The reaction was very clean (checked by TLC), especially when the iodo bis-silyl ether **9** was used. With the unprotected iodo precursor **11**, the modest yield (33%) of compound **25** was most likely the result of the decomposition of the expected compound **C** (Scheme 5) during workup. The complete structural assignments of (15*RS*)-5,6-dehydro $F_{2t}$-IsoP were established by $^1H$ and $^{13}C$ NMR spectroscopy (1D/2D and DNOES, vide infra). Finally, deprotection of the bis-silyl groups in **24** was carried out using *n*-$Bu_4NF$[41] to afford **25** in 90% yield, and the two C15 epimers of **25** were separated by HPLC (Scheme 6).

Then, **25a** was transformed by specific reduction of the triple bond in the presence of Ni "P2"[42] in ethanol into the pure (15*R*)-$F_{2t}$-IsoPs **26a** in 90% yield. In a similar fashion, **25b** was converted into the pure (15*S*)-$F_{2t}$-IsoPs **26b** in 90% yield (Scheme 6). On the other hand, the 5,6-dehydro compound **25** afforded the labeled (5,6-$^2H$ and

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(40) When the addition of 2.0 equiv of $Et_3B$ was achieved at once, we have always observed an incomplete reaction and a very poor yield in cyclized product (less than 15%).

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5,6-$^3$H) biologically and specifically active compounds (15*R*)- and (15*S*)-$F_{2t}$-isoPs.[43]

## Results and Discussion

The main goals of our study were focused on three points: (i) the proof that a $\beta$-hydroxy carbon free radical can react in a similar way but without the *cis*-1,2-dioxolane formation, (ii) the stereochemical preference in the cyclization reaction, and (iii) the role in the stereocontrol of two appendages or the stereoelectronic effects in transition state **A** (Scheme 5) during this crucial step.

Concerning the first point, the biomimetic cyclization of precursors **9** and **11** gives the isoP-structures. This point corroborates the biosynthetic pathway where cyclization and oxygen trapping by a conjugated carbon free-radical **B** are concomitant (Scheme 5). Starting from O-unprotected or O-protected precursors **9** or **11**, we synthesized and stereochemically characterized of the 1:1 15*R*/15*S* epimeric mixture **25** as only a single compound, indicating the remarkable stereoselection in the three steps. Our data, which differ radically from enzyme-mediated cyclization, indicate also that the diastereoisomer mixture **25** is single whose C-15 epimers are chromatographically separated from them. The proton assignments and DNOES (Figure 2) confirmed the assigned regiochemistry of oxygenation by the conjugated allylic carbon free radical. We found no evidence for oxygenation at the C-13 position, although very low levels of such compounds could have escaped detection. This oxygenation step selectively occurs at the C-15 position, and the overall yield from precursors **9** and **11** were 55% and 33%, respectively,[44] after three steps (cyclization, $O_2$-trapping, and reduction).

The second point is more surprising with respect to our former study.[39] Indeed, we have shown that acyclic 1-substituted 2,4-dihydroxylated hex-5-enyl radicals can take on "chairlike" or folded envelope conformations in the transition state. Our results show that the stereoselection in acyclic dihydroxylated octa-5,7-dienyl radicals is very complex. According to the Beckwith−Houk model,[45] the stereocontrol could be successfully explained by several factors: the strong hydrogen bonds between free hydroxylic functions in unprotected derivatives or drastic 1,3-diaxial interactions with introduction of bulky protecting groups and the pivotal role of the oxygen atom bordering on the radical center could be the main factors.

The last point is an explanation for the high diastereoselectivity leading to epimeric (15*RS*)-$F_{2t}$-IsoP **25**: (i) the remarkable electronic stabilization of the carbon free radical by the p-orbital of C-11 $\pi$-bond and the pairs of n-electrons from the oxygen atoms, which is consistent with a strong stereoelectronic control (very close to the cyclic ketals[46]) associated with a steric effect due to $\alpha$ and $\omega$ side chains in the transition state and (ii) the strong influence of the two side chains $\alpha$ and $\omega$ in the choice of the transition-state conformation. During the radical cyclization step, and according to our observed results, the ring closure requires a disrotatory motion leading to exo,exo-oriented appendage. In this case and for a complete understanding of the stereocontrol in radical cyclizations, ab initio calculations are necessary.

**Structural Determination of Compounds 10 and 25a.** We have shown that the NOE $^1$H NMR experiment is a simple and efficient method for the determination a priori of the relative functional configuration of the tetrasubstituted cyclopentane. Applied to the isoP-structures, this method is a method of choice for solving the problem of configuration determinations.[19b,38] Thus, the relative configuration in compound **10** between the acetylenic chain situated in C-7 and the hydroxyl group in C-9 is demonstrated by irradiation of 10-H and the observed enhancemant in the NOE (3.5%) on 11-H and (3.0%) on 8-H. The irradiation of 10′-H showed an NOE of 5.2% on 11-H, 2.8% on 9-H, and 1.7% on 7-H. These results are in agreement with a relative *trans* configuration between protons 8-H and 9-H.

In the same manner, the irradiation of 12-H induces a NOE of 4.4% on 11-H, 2.0% on 10-H, and 4.5% on 8-H. These observations allow one to check the relative *trans* configuration of protons 11-H and 8-H and the absolute configuration (8*R*,9*S*,11*S*).

The irradiation of 10-H in compound **25a** resulted in a NOE signal enhancement (1.8%) for protons 9-H and 11-H, whereas irradiation of 10′-H induced no NOE. The 1,3-triethylsilyl ethers are therefore in a *cis* configuration with respect to each other, which is consistent with the synthesis and a *cis* configuration when compared with the 10′-H proton.

Concerning the relative configuration of the chain situated in C8 and the silyl ether in C9, the irradiation of 7-H induces a NOE of 1.4% on 9-H and 11-H. These results are in agreement with a relative *trans* configuration between protons 8-H and 9-H.

Similarly, the relative configuration of the side chain situated on C12 and the silyl ether on C11 is determined by irradiation of 13-H, NOE of 0.9% induced on 9-H and 11-H allows one to check the relative *trans* configuration of protons 11-H and 12-H and the final configuration (8*S*,9*S*,11*R*,12*R*). In Figure 2, the observed enhancement NOE for compounds **10** and **25a** after irradiation of different protons are illustrated.

## Conclusion

In summary, we have described a biomimetic route to (15*R*)- and (15*S*)-$F_{2t}$-isoprostanes in 15 steps from commercially available starting materials. One of the goals of this approach is the successful synthesis of (15*R*)- and (15*S*)-$F_{2t}$-isoprostanes labeled in positions 5 and 6 from the acetylenic precursors. We can draw two main conclusions from this study. The first, based on evidence that continues to accumulate, shows that this mechanism is operating, is general, and can be applied to all essential PUFAs bearing three or more *cis* double bonds.[33] The second is that the cyclization reaction of highly functionalized C-20 radical deviates from the COX enzyme-controlled reaction in a dramatic way: we only obtained an epimeric mixture of (15*RS*)-5,6-dehydro-$F_{2t}$-IsoP. This result shows, once again, high selectivity in favor of the formation of *cis*-iso-P. The main function of COX-enzymes is not only the formation of the $\beta$-peroxy radical, but also

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(44) The modest yields of pure compounds **25a** and **25b** are most likely the result of side reactions (see on TLC) during the reduction of the **C** intermediate (Scheme 6) or during the workup.

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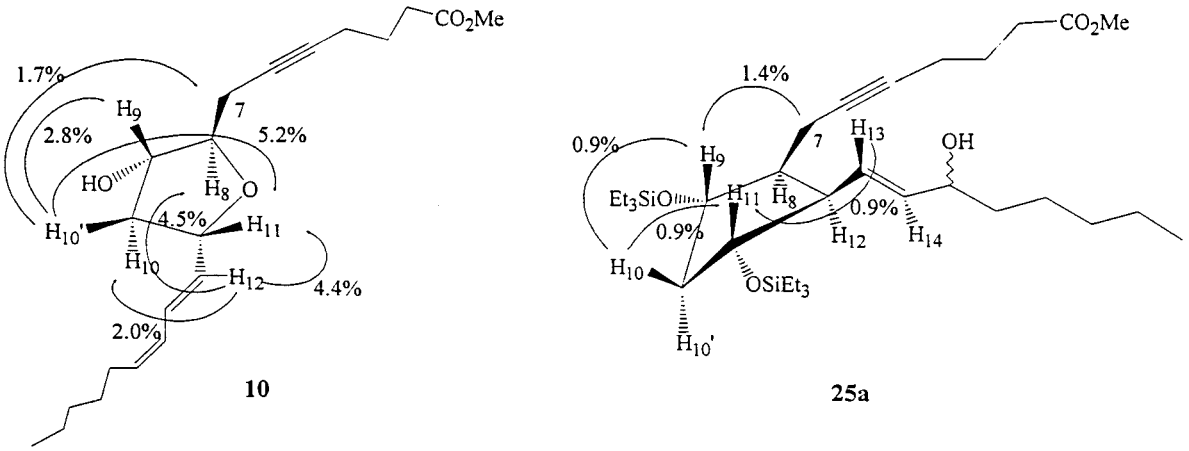


**Figure 2.** Relative configuration observed by steady-state NOE difference spectroscopy of compounds **10** and **25a**.

the maintenance of a proper orientation of the side chains for the ring closure in a *trans* fashion after a conrotatory motion.

## Experimental Section

**General Methods.** Reagents and solvents were obtained from commercial suppliers and were used as received, unless otherwise noted. All reactions were conducted under nitrogen in distilled and dry solvents. The reactions were monitored by thin-layer chromatography (TLC) and judged complete when the starting material was no longer visible in the reaction mixture. Analytical TLC was performed using precoated silica gel plates (0.25 mm, $60_{254}$) with *p*-anisaldehyde in ethanol as indicator, and UV (254 nm) absorption. The extracts were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography with the eluting solvent indicated. For unstable products, the NMR spectra were obtained on a Bruker AMX-3GO. Elemental analyses were performed by the "Centre National de la Recherche Scientifique, Service d'Analyses, Vernaison, France".

**(5*S*)-3,6-Dideoxy-1,2-*O*-isopropylidene-5-hydroxy-6-(methylhex-1-ynoate)-α-D-*ribo*-hexofuranose (2).** To 5-hexynoic acid (1.8 g, 16.2 mmol) in 15 mL of dry HMPA at 5 °C was added dropwise *n*-BuLi (13 mL, 32.5 mmol). The colorless solution became orange. The dianion was stirred at 0 °C for 1 h. The 5,6-anhydro-3-deoxy-1,2-*O*-isopropylidene-α-D-ribohexofuranose (1.5 g, 8.06 mmol) in 15 mL of HMPA was added dropwise. The solution was stirred at rt overnight. A 100 mL portion of 1 N HCl solution and 200 mL of ethyl acetate were added. The acid phase was extracted with 3 × 100 mL of ethyl acetate. The organic layers were washed with 100 mL of 1 N HCl solution and 3 × 100 mL of brine, dried, and evaporated. The residue was methylated with etheral diazomethane. The ether was removed, and the residual oil was purified by flash chromatography (5−30% ethyl acetate in cyclohexane) to yield 1.35 g (54%) of solid **2**. Mp: 40−42 °C. TLC (cyclohexane/ethyl acetate, 1:1): $R_f$ = 0.34. IR (film) $\nu$: 3480 (OH), 1720 $cm^{-1}$ (C=O). $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ 1.30 (s, 3H, C($CH_3$)$_2$), 1.49 (s, 3H, C($CH_3$)$_2$), 1.78 (m, 2H, $H_{10}$), 1.82 (m, 1H, $H_3$), 2.06 (dd, $J_{3-2}$ = 4.5 Hz, $J_{3-3'}$ = 13.5 Hz, 1H, $H_{3'}$), 2.21 (m, 2H, $H_9$), 2.37 (m, 2H, $H_6$), 2.40 (t, $J_{11-10}$ = 7.2 Hz, 2H, $H_{11}$), 3.65 (s, 3H, $OCH_3$), 3.89 (q, $J_{5-6}$ = 4.5 Hz, 1H, $H_5$), 4.26 (dt, $J_{4-5}$ = 4.5 Hz, $J_{4-3}$ = 11.2 Hz, 1H, $H_4$), 4.72 (t, $J_{2-3}$ = 4.0 Hz, 1H, $H_2$), 5.78 (d, $J_{1-2}$ =4.0 Hz, 1H, $H_1$). $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$: 18.2 ($C_9$), 23.7 ($C_6$), 24.0 ($C_{10}$), 26.2 (C($CH_3$)$_2$), 26.8 (C($CH_3$)$_2$), 32.8 ($C_3$), 32.9 ($C_{11}$), 51.5 ($OCH_3$), 70.0 ($C_5$), 76.2 ($C_8$), 79.9 ($C_4$), 80.6 ($C_2$), 81.7 ($C_7$), 105.4 ($C_1$), 111.3 ($C$(CH$_3$)$_2$), 173.6 ($C_{12}$). Anal. Calcd for $C_{16}H_{24}O_6$ (312.36): C, 61.52; H, 7.74. Found: C, 61.48; H, 7.70.

**(5*S*)-3,6-Deoxy-1,2-isopropylidene-6-(methylhex-1-ynoate)-5-*O*-trifluorosulfonyl-α-D-ribohexofuranose (3).** In a flask with two addition funnels were added pyridine (2.36 mL, 26.03 mmol) and 90 mL of methylene chloride. A solution of trifluorosulfonyl anhydride (2.92 mL, 17.35 mmol) dissolved in 45 mL of methylene chloride was added dropwise at −15 °C. A thick white precipitate began to form during the addition. After addition was complete, the suspension was stirred for 15 min. The solution of **2** (2.70 g, 8.68 mmol) in 45 mL of methylene chloride was added dropwise, and stirring was continued for 30 min. A 100 mL portion of saturated salt solution was added at 0 °C. The aqueous layer was extracted with 2 × 100 mL of methylene chloride. The combined extracts were dried and removed. The crude residue was subjected to flash chromatography (0−5% ethyl ether in methylene chloride) to give 3.27 g (85%) of **3** as a colorless oil. This product was immediately used in the next step. TLC (cyclohexane/ethyl acetate, 1:1): $R_f$ = 0.75. IR (film) $\nu$: 1725 $cm^{-1}$ (C=O). $^1$H NMR (100 MHz, $CDCl_3$) $\delta$: 1.30 (s, 3H, C($CH_3$)$_2$), 1.46 (s, 3H, C($CH_3$)$_2$), 1.71−2.00 (m, 4H, $H_3$, $H_{10}$), 2.15 (m, 2H, $H_9$), 2.43 (m, 2H, $H_{11}$), 2.66 (m, 2H, $H_6$), 3.65 (s, 3H, $OCH_3$), 4.48 (m, 1H, $H_4$), 4.65 (t, $J_{2-1,2-3}$ = 3.7 Hz, 1H, $H_2$), 5.08 (m, 1H, $H_5$), 5.81 (d, $J_{1-2}$ = 3.7 Hz, 1H, $H_1$). $^{13}$C NMR (25 MHz, $CDCl_3$) $\delta$: 18.0 ($C_9$), 22.3 ($C_6$), 23.6 ($C_{10}$), 26.1 (C($CH_3$)$_2$), 26.6 (C($CH_3$)$_2$), 32.7 ($C_3$), 33.6 ($C_{11}$), 51.5 ($OCH_3$), 73.0 ($CF_3$), 77.1 ($C_4$), 78.5 ($C_7$), 80.1 ($C_2$), 80.5 ($C_8$), 85.7 ($C_5$), 105.3 ($C_1$), 111.6 ($C$(CH$_3$)$_2$), 173.6 ($C_{12}$).

**3,5,6-Deoxy-1,2-isopropylidene-5-iodo-6-(methylhex-1-ynoate)-α-D-*ribo*-hexofuranose (4).** The triflate ester **3** (3.08 g, 6.95 mmol) and tetrabutylammonium iodide (5.13 g, 13.9 mmol) in 70 mL of benzene was refluxed for 90 min. The mixture was removed by chromatography (0−3% ethyl ether in methylene chloride) to give 2.19 g (75%) of **4**. TLC (cyclohexane/ethyl acetate, 7:3): $R_f$ = 0.50. IR (film) $\nu$: 1722 $cm^{-1}$ (C=O). $^1$H NMR (360 MHz, $CDCl_3$) $\delta$: 1.31 (s, 3H, C($CH_3$)$_2$), 1.49 (s, 3H, C($CH_3$)$_2$), 1.77 (m, 3H, $H_3$, $H_{10}$), 2.20 (m, 3H, $H_{3'}$, $H_9$), 2.43 (t, $J_{11-10}$ = 7.4 Hz, 2H, $H_{11}$), 2.87 (m, 2H, $H_6$), 3.65 (S, 3H, $OCH_3$), 3.93 (m, 1H, $H_4$), 4.13 (dt, $J$ = 3.6 Hz, $J$ = 7.1 Hz, 1H, $H_5$), 4.74 (t, $J_{2-1,2-3}$ = 4.2 Hz, 1H, $H_2$), 5.83 (d, $J_{1-2}$ = 3.6 Hz, 1H, $H_1$). $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$: 18.2 ($C_9$), 23.9 ($C_{10}$), 26.4 (C($CH_3$)$_2$), 26.9 (C($CH_3$)$_2$), 28.3 ($C_6$), 32.9 ($C_{11}$), 34.8 ($C_5$), 38.8 ($C_3$), 51.5 ($OCH_3$), 78.2 ($C_4$), 78.8 ($C_7$), 80.5 ($C_2$), 81.8 ($C_8$), 105.6 ($C_1$), 111.6 ($C$(CH$_3$)$_2$), 173.6 ($C_{12}$). Anal. Calcd for $C_{16}H_{23}O_5I$ (422.26): C, 45.51; H, 5.49. Found: C, 45.53; H, 5.44.

**(8*R*,9*S*,11*R*)-Methyl-8-iodo-12,12-di(ethylthio)-9,11-dihydroxydodec-5-ynoate (5).** To the iodo derivative **4** (2 g, 4.74 mmol) in 5 mL of ethanethiol was added anhydrous zinc chloride (2.58 g, 18.9 mmol) at −15 °C. The solution became purple. After 1 h, the excess ethanethiol was removed at −10 °C in vacuo. The foamy residue was placed on a flash chromatography column with a few milliliters of methylene chloride, and water and was eluted (3−15% ethyl acetate in cyclohexane). A 2.05 g (89%) yield of **5** was obtained. TLC (cyclohexane/ethyl acetate, 7:3): $R_f$ = 0.36. IR (film) $\nu$: 3490 (OH), 1722 $cm^{-1}$ (C=O). $^1$H NMR (360 MHz, $CDCl_3$) $\delta$: 1.27

(t, $J$ = 7.2 Hz, 6H, SCH$_2$*CH*$_3$), 1.71 (m, 3H, H$_3$, H$_{10}$), 2.05 (m, 1H, H$_{10'}$), 2.21 (m, 2H, H$_4$), 2.43 (t, $J_{2-3}$ = 14.8 Hz, 2H, H$_2$), 2.67 (m, 4H, S*CH*$_2$CH$_3$), 2.66−2.99 (m, 2H, H$_7$), 3.39 (m, 1H, H$_9$), 3.66 (s, 3H, OCH$_3$), 3.77 (d, $J_{12-11}$ = 7.0 Hz, 1H, H$_{12}$), 3.87 (m, 1H, H$_{11}$), 4.14 (dt, $J_{8-9}$ = 2.7 Hz, $J_{8-7}$ = 7.3 Hz, 1H, H$_8$). $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$: 14.5 (SCH$_2$*CH*$_3$), 14.6 (SCH$_2$*CH*$_3$), 18.2 (C$_4$), 23.9 (C$_3$), 24.5 (S*CH*$_2$CH$_3$), 25.7 (S*CH*$_2$CH$_3$), 28.1 (C$_7$), 32.9 (C$_2$), 40.9 (C$_8$), 41.3 (C$_{10}$), 51.5 (OCH$_3$), 58.7 (C$_{12}$), 71.8 (C$_9$), 73.9 (C$_{11}$), 79.1 (C$_6$), 81.7 (C$_5$), 173.7 (C$_1$). Anal. Calcd for C$_{17}$H$_{29}$O$_4$IS$_2$ (488.43): C, 41.80; H, 5.98. Found: C, 41.84; H, 5.97.

**(8*S*,9*S*,11*R*)-Methyl-8-iodo-9,11-di(triethylsilyloxy)-12,12-di(ethylthio)dodec-5-ynoate (6).** To the diol **5** (1.16 g, 2.38 mmol) in 18 mL of dry pyridine was added chrorotriethylsilane (3.2 mL, 19 mmol). The reaction mixture was stirred at rt for 1 d. A 50 mL portion of brine was added, and the product was extracted with 3 × 50 mL of ether. The organic layers were washed with 3 × 50 mL of saturated hydrogenocarbonate solution, dried, and evaporated. The residue was purified by chromatography (0−2% ethyl acetate in cyclohexane) to give 1.52 g (89%) of **6**. TLC (cyclohexane/ethyl acetate, 7:3): $R_f$ = 0.82. IR (film) $\nu$: 1733 cm$^{-1}$ (C=O). $^1$H NMR (360 MHz, CDCl$_3$) $\delta$: 0.64 (m, 12H, Si*CH*$_2$CH$_3$), 0.97 (t, $J$ = 7.9 Hz, 18H, SiCH$_2$*CH*$_3$), 1.25 (t, $J$ = 7.3 Hz, 6H, SCH$_2$*CH*$_3$), 1.80 (m, 2H, H$_3$), 1.89 (m, 1H, H$_{10}$), 2.13 (m, 1H, H$_{10'}$), 2.20 (m, 2H, H$_4$), 2.44 (t, $J_{2-3}$ = 7.4 Hz, 2H, H$_2$), 2.69 (m, 4H, S*CH*$_2$CH$_3$), 2.85 (m, 2H, H$_7$), 3.36 (m, 1H, H$_9$), 3.65 (s, 3H, OCH$_3$), 3.78 (d, $J_{12-11}$ = 3.0 Hz, 1H, H$_{12}$), 4.01 (dt, $J_{11-12}$ = 3.0 Hz, $J_{11-10}$ = 4.5 Hz, 1H, H$_{11}$), 4.14 (dt, $J_{8-9}$ = 2.3 Hz, $J_{8-7}$ = 7.4 Hz, 1H, H$_8$). $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$: 5.3 (Si*CH*$_2$CH$_3$), 6.9 (SiCH$_2$*CH*$_3$), 7.0 (SiCH$_2$*CH*$_3$), 14.5 (SCH$_2$*CH*$_3$), 14.7 (SCH$_2$*CH*$_3$), 18.3 (C$_4$), 23.9 (C$_3$), 25.7 (C$_7$), 26.0 (S*CH*$_2$CH$_3$), 27.5 (S*CH*$_2$CH$_3$), 32.8 (C$_2$), 39.8 (C$_8$), 42.1 (C$_{10}$), 51.5 (OCH$_3$), 57.6 (C$_{12}$), 70.4 (C$_9$), 73.0 (C$_{11}$), 79.5 (C$_6$), 81.2 (C$_5$), 173.8 (C$_1$). Anal. Calcd for C$_{29}$H$_{57}$O$_4$Si$_2$IS$_2$ (716.96): C, 48.58; H, 8.01. Found: C, 48.51; H, 7.97.

**(8*S*,9*S*,11*R*)-Methyl-8(*S*)-iodo-9(*S*),11(*R*)-di(triethylsilyloxy)-12-oxododec-5-ynoate (7).** To the thiocetal **6** (1.44 g, 2 mmol) in 85/8.5 mL of acetone/water were added mercuric oxide (3.79 g, 17.5 mmol) and mercuric chloride (1.63 g, 6 mmol). The heterogeneous mixture was stirred at rt for 8 h. A 60 mL portion of saturated hydrogenocarbonate solution was added. The mixture was filtered through Celite and extracted with 3 × 50 mL of methylene chloride. The organic layers were washed with 3 × 50 mL of potassium iodide solution and with 2 × 50 mL of brine. The extracts were dried and evaporated. The aldehyde **7** was purified futher and was used directly. TLC (cyclohexane/ethyl acetate, 7:3): $R_f$ = 0.75. $^1$H NMR (100 MHz, CDCl$_3$): $\delta$ 0.65 (m, 12H, Si*CH*$_2$CH$_3$), 0.99 (m, 18H, SiCH$_2$*CH*$_3$), 1.27 (m, 2H, H$_{10}$), 1.82 (m, 2H, H$_3$), 2.37 (m, 4H, H$_2$, H$_4$), 2.83 (m, 2H, H$_7$), 3.65 (s, 3H, OCH$_3$), 4.04 (m, 3H, H$_8$, H$_9$, H$_{11}$), 9.61 (s, 1H, H$_{12}$). $^{13}$C NMR (25 MHz, CDCl$_3$): $\delta$ 4.6 (Si*CH*$_2$CH$_3$), 5.1 (Si*CH*$_2$CH$_3$), 6.6 (SiCH$_2$*CH*$_3$), 6.7 (SiCH$_2$*CH*$_3$), 18.2 (C$_4$), 23.9 (C$_3$), 25.7 (C$_7$), 32.7 (C$_2$), 37.6 (C$_{10}$), 38.1 (C$_8$), 51.5 (OCH$_3$), 69.9 (C$_9$), 74.4 (C$_{11}$), 79.1 (C$_6$), 81.3 (C$_5$), 173.6 (C$_1$), 203.3 (C$_{12}$).

**(8*R*,9*S*,11*R*,)-Methyl-8-iodo-9,11-di(triethylsilyloxy)-14-oxotetradec-12*E*-en-5-ynoate (8).** To the aldehyde **7** (1.22 g, 2 mmol) in 8 mL of dimethyl formamide was added (triphenylphosphoranyliden)acetaldehyde (9.15 mg, 3 mmol). After the mixture was stirred for 1 d at rt, 50 mL of saturated hydrogenocarbonate solution was added to the reaction mixture, which was then extracted with 4 × 50 mL of ethyl acetate. The organic extracts were washed with 3 × 50 mL of hydrogenocarbonate solution, dried, and evaporated. The residue was subjected to flash chromatography (0−4% ethyl acetate in cyclohexane) to give 852 mg (67%) of colorless oil **8**. TLC (cyclohexane/ethyl acetate, 7:3): $R_f$ = 0.80. IR (film) $\nu$: 1720 (C=O), 1690 cm$^{-1}$ (C=O). $^1$H NMR (360 MHz, CDCl$_3$): $\delta$ 0.61 (m, 12H, Si*CH*$_2$CH$_3$), 0.94 (m, 18H, SiCH$_2$*CH*$_3$), 1.71 (m, 3H, H$_3$, H$_{10}$), 2.05 (ddd, $J_{10'-11}$ = 5.8 Hz, $J_{10'-9}$ = 6.5 Hz, $J_{10'-10}$ = 13.9 Hz, 1H, H$_{10'}$), 2.18 (m, 2H, H$_4$), 2.43 (t, $J_{2-3}$ = 7.4 Hz, 2H, H$_2$), 2.75 (ddt, $J_{7-4}$ = 2.3 Hz, $J_{7-8}$ = 7.4 Hz, $J_{7-7'}$ = 17.1 Hz, 1H, H$_7$), 2.97 (ddt, $J_{7'-4}$ = 2.1 Hz, $J_{7'-8}$ = 7.2 Hz, $J_{7'-7}$ = 17.1 Hz, 1H, H$_{7'}$), 3.47 (dt, $J_{9-8}$ = 2.3 Hz, $J_{9-10}$ = 6.5 Hz, 1H, H$_9$), 3.66 (s, 3H, OCH$_3$), 4.22 (dt, $J_{8-9}$ = 2.3 Hz, $J_{8-7}$ = 7.2 Hz, 1H, H$_8$), 4.47 (m, 1H, H$_{11}$), 6.25 (dd, $J_{13-14}$ = 7.8 Hz, $J_{13-12}$ = 15.7 Hz, 1H, H$_{13}$), 6.78 (dd, $J_{12-11}$ = 7.3 Hz, $J_{12-13}$ = 15.5 Hz, 1H, H$_{12}$), 9.57 (d, $J_{14-13}$ = 7.8 Hz, 1H, H$_{14}$). $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$: 4.8 (Si*CH*$_2$CH$_3$), 5.2 (Si*CH*$_2$CH$_3$), 6.7 (SiCH$_2$*CH*$_3$), 6.8 (SiCH$_2$*CH*$_3$), 18.2 (C$_4$), 24.0 (C$_3$), 27.7 (C$_7$), 32.9 (C$_2$), 39.7 (C$_8$), 43.8 (C$_{10}$), 51.5 (OCH$_3$), 68.9 (C$_{11}$), 69.8 (C$_9$), 79.2 (C$_6$), 81.4 (C$_5$), 131.0 (C$_{13}$), 158.6 (C$_{12}$), 173.8 (C$_1$), 193.2 (C$_{14}$). Anal. Calcd for C$_{27}$H$_{49}$O$_5$Si$_2$I (636.75): C, 50.93; H, 7.76. Found: C, 51.01; H, 7.74.

**(8*S*,9*S*,11*R*)-Methyl-8-iodo-9,11-di(triethylsilyloxy)-eicosa-12*E*,14*Z*-dien-5-ynoate (9).** To *n*-hexyltriphenylphosphonium bromide (1.08 g, 2.53 mmol) in 7.5 mL of dry THF was added 2.5 N *n*-BuLi (0.94 mL, 2.34 mmol) rapidly at rt. The ylide was stirred for 10 min and cooled to −78 °C. Then, the aldehyde **8** (730 mg, 1.14 mmol) in 7.5 mL of THF was added slowly. The mixture was stirred for 10 min at −10 °C, quenched with 30 mL of brine, and extracted with 3 × 30 mL of ethyl acetate. The organic layers were washed with 3 × 30 mL of saturated salt solution, dried, and evaporated. The residue was subjected to flash chromatography (0−10% ether in cyclohexane) to give 726 mg (90%) of colorless oil of a mixture of *E*/*Z*, *E*/*E* olefins **9** in a 95/5 ratio. TLC (cyclohexane/ethyl acetate, 7:3): $R_f$ = 0.90. IR (film) $\nu$: 1725 cm$^{-1}$ (C=O). $^1$H NMR (360 MHz, CDCl$_3$) $\delta$: 0.58 (m, 12H, Si*CH*$_2$CH$_3$), 0.86 (t, $J_{20-19}$ = 6.9 Hz, 3H, H$_{20}$), 0.94 (m, 18H, SiCH$_2$*CH*$_3$), 1.25 (m, 4H, H$_{18}$, H$_{19}$), 1.35 (m, 2H, H$_{17}$), 1.71 (m, 1H, H$_{10}$), 1.79 (t, $J_{3-2}$ = 7.2 Hz, 2H, H$_3$), 1.88 (m, 1H, H$_{10'}$), 2.16 (m, 4H, H$_4$, H$_{16}$), 2.43 (t, $J_{2-3}$ = 7.2 Hz, 2H, H$_2$), 2.75 (ddt, $J_{7-4}$ = 2.4 Hz, $J_{7-8}$ = 8.0 Hz, $J_{7-7'}$ = 17.1 Hz, 1H, H$_7$), 2.87 (ddt, $J_{7'-4}$ = 2.2 Hz, $J_{7'-8}$ = 6.7 Hz, $J_{7'-7}$ = 17.1 Hz, 1H, H$_{7'}$), 3.41 (dt, $J_{9-8}$ = 2.3 Hz, $J_{9-10}$ = 6.1 Hz, 1H, H$_9$), 3.65 (s, 3H, OCH$_3$), 4.21 (m, 2H, H$_8$, H$_{11}$), 5.43 (dt, $J_{15-16}$ = 7.4 Hz, $J_{15-14}$ = 10.7 Hz, 1H, H$_{15}$), 5.56 (dd, $J_{12-11}$ = 7.1 Hz, $J_{12-13}$ = 15.2 Hz, 1H, H$_{12}$), 5.94 (t, $J_{14-13,14-15}$ = 10.9 Hz, 1H, H$_{14}$), 6.41 (dd, $J_{13-14}$ = 10.9 Hz, $J_{13-12}$ = 15.2 Hz, 1H, H$_{13}$). $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$: 5.0 (Si*CH*$_2$CH$_3$), 5.3 (Si*CH*$_2$CH$_3$), 6.8 (SiCH$_2$*CH*$_3$), 6.9 (SiCH$_2$*CH*$_3$), 14.0 (C$_{20}$), 18.2 (C$_4$), 22.5 (C$_{19}$), 23.9 (C$_3$), 27.2 (C$_7$), 27.7 (C$_{16}$), 29.3 (C$_{17}$), 31.4 (C$_{18}$), 32.8 (C$_2$), 40.5 (C$_8$), 45.0 (C$_{10}$), 51.5 (OCH$_3$), 70.4 (C$_9$), 70.5 (C$_{11}$), 79.5 (C$_6$), 81.1 (C$_5$), 125.8 (C$_{13}$), 127.7 (C$_{14}$), 132.8 (C$_{15}$), 135.3 (C$_{12}$), 173.6 (C$_1$). Anal. Calcd for C$_{33}$H$_{61}$O$_4$Si$_2$I (704.92): C, 56.23; H, 8.72. Found: C, 56.19; H, 8.72.

**(2*R*,3*S*,5*R*)-3-Hydroxy-2-(methylhept-2-ynoate)-5-(nona-1*E*,3*Z*-diene)tetrahydrofuran (10).** To a mixture of **9** (50 mg, 71 $\mu$mol) and 1 N tetrabutylammonium fluoride (71 $\mu$mol) was added 2 mL of THF at rt for 2 h. To the solution was added 2 mL of brine, and the mixture was extracted with 3 × 3 mL of ethyl acetate and washed with 2 × 2 mL of brine. The organic layers were dried and evaporated. The residue was subjected to flash chromatography (0−10% e**t**hyl acetate in cyclohexane) to give 22 mg (89%) of **10**. TLC (cyclohexane/ethyl acetate, 7:3): $R_f$ = 0.50. IR (film) $\nu$: 3510 (OH), 1720 cm$^{-1}$ (C=O). $^1$H NMR (360 MHz, CDCl$_3$) $\delta$: 0.86 (t, $J_{20-19}$ = 6.9 Hz, 3H, H$_{20}$), 1.27 (m, 4H, H$_{18}$, H$_{19}$), 1.36 (quint, $J_{17-16,17-18}$ = 6.7 Hz, 2H, H$_{17}$), 1.63−1.89 (m, 4H, H$_3$, H$_{10}$), 2.19 (m, 4H, H$_4$, H$_{16}$), 2.41 (t, $J_{2-3}$ = 7.5 Hz, 2H, H$_2$), 2.57 (m, 2H, H$_7$), 3.10 (m, 2H, H$_8$, H$_9$), 3.65 (s, 3H, OCH$_3$), 4.46 (q, $J_{10-11,\ 11-12}$ = 6.7 Hz, 1H, H$_{11}$), 5.45 (dt, $J_{15-16}$ = 7.6 Hz, $J_{15-14}$ = 10.7 Hz, 1H, H$_{15}$), 5.69 (dd, $J_{12-11}$ = 6.7 Hz, $J_{12-13}$ = 15.1 Hz, 1H, H$_{12}$), 5.95 (t, $J_{14-13,14-15}$ = 10.2 Hz, 1H, H$_{14}$), 6.54 (dd, $J_{13-14}$ = 10.7 Hz, $J_{13-12}$ = 15.2 Hz, 1H, H$_{13}$). $^{13}$C NMR (90 MHz, CDCl$_3$): $\delta$ = 14.0 (C$_{20}$), 18.2 (C$_4$), 18.9 C$_7$), 22.5 (C$_{19}$), 24.0 (C$_3$), 27.7 (C$_{16}$), 29.2 (C$_{17}$), 31.4 (C$_{18}$), 32.8 (C$_2$), 35.0 (C$_{10}$), 51.6 (OCH$_3$), 54.4 (C$_8$), 54.6 (C$_9$), 71.2 (C$_{11}$), 75.6 (C$_6$), 81.3 (C$_5$), 126.4 (C$_{13}$), 127.4 (C$_{14}$), 133.7 (C$_{15}$), 134.2 (C$_{12}$), 173.6 (C$_1$). Anal. Calcd for C$_{21}$H$_{32}$O$_4$ (348.48): C, 71.96; H, 9.78. Found: C, 72.02; H, 9.78.

**(8*R*,9*S*,11*R*)-Methyl-9,11-dihydroxy-8-iodoeicosa-12*E*,-14*Z*-dien-5-ynoate (11).** In 23 mL of THF were stirred **9** (227 mg, 320 $\mu$mol) and 1 N aqueous HCl (640 $\mu$l, 640 $\mu$mol) at rt for 3 h to effect complete hydrolysis. A 10 mL portion of brine was added, and the mixture was extracted with 4 × 10 mL of ethyl acetate. The organic layers were washed with 3 × 5 mL of brine, dried, and evaporated. The residue was followed by flash chromatography (10−30% ethyl acetate in cyclohexane) to give 138 mg (90%) of **11**. TLC (cyclohexane/ethyl acetate, 7:3): $R_f$ = 0.20. IR (film) $\nu$: 3490 (OH), 1725 cm$^{-1}$ (C=O). $^1$H

NMR (360 MHz, $CDCl_3$) $\delta$: 0.87 (t, $J_{20-19} = 6.8$ Hz, 3H, $H_{20}$), 1.28 (m, 4H, $H_{18}$, $H_{19}$), 1.35 (m, 2H, $H_{17}$), 1.70 (dt, $J = 3.0$ Hz, $J_{10-10'} = 14.1$ Hz, 1H, $H_{10}$), 1.81 (m, 3H, H3, $H_{10'}$), 2.18 (m, 4H, $H_4$, $H_{16}$), 2.44 (t, $J_{2-3} = 7.3$ Hz, 2H, $H_2$), 2.85 (ddt, $J_{7-4} = 2.4$ Hz, $J_{7-8} = 7.6$ Hz, $J_{7-7'} = 17.2$ Hz,1H, $H_7$), 2.95 (ddt, $J_{7'-4} = 2.3$ Hz, $J_{7'-8} = 6.3$ Hz, $J_{7'-7} = 17.2$ Hz, 1H, $H_{7'}$), 3.04 (d, $J = 4.8$ Hz, 1H, OH), 3.44 (m, 1H, $H_9$), 3.66 (s, 3H, $OCH_3$), 4.14 (dt, $J_{8-9} = 3.0$ Hz, $J_{8-7} = 7.6$ Hz, 1H, $H_8$), 4.47 (m, 1H, $H_{11}$), 5.47 (dt, $J_{15-16} = 7.7$ Hz, $J_{15-14} = 10.7$ Hz, 1H, $H_{15}$), 5.66 (dd, $J_{12-11} = 6.7$ Hz, $J_{12-13} = 15.2$ Hz, 1H, $H_{12}$), 5.94 (t, $J_{14-13,14-15} = 10.9$ Hz, 1H, $H_{14}$), 6.53 (dd, $J_{13-14} = 11.1$ Hz, $J_{13-12} = 15.2$ Hz, 1H, $H_{13}$). $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$: 14.0 ($C_{20}$), 18.2 ($C_4$), 22.5 ($C_{19}$), 23.9 ($C_3$), 27.7 ($C_{16}$), 28.0 ($C_7$), 29.3 ($C_{17}$), 31.5 ($C_{18}$), 32.9 ($C_2$), 41.2 ($C_8$), 43.9 ($C_{10}$), 51.6 ($OCH_3$), 72.1 ($C_{11}$), 72.3 ($C_9$), 78.9 ($C_6$), 81.9 ($C_5$), 126.2 ($C_{13}$), 127.3 ($C_{14}$), 133.9 ($C_{15}$), 134.3 ($C_{12}$), 173.6 ($C_1$). Anal. Calcd for $C_{21}H_{33}O_4I$ (476.39): C, 52.95; H, 6.98. Found: C, 52.91; H, 7.01.

**(5*S*)-3,6-Dideoxy-1,2-*O*-isopropylidene-5-hydroxy-6-(methylhex-1*Z*-enoate)-α-D-*ribo*-hexofuranose (12).** To nickel acetate (1.71 g, 1.64 mmol) in 20 mL of 95% ethanol was added 0.5 N sodium borohydride solution in ethanol (2.2 mL, 1.1 mmol). The flask was flushed with hydrogen. Ethylenediamine (171 $\mu$L) was added. Hydrogenation was then initiated by introducing **2** (1.9 g, 6.1 mmol) in 40 mL of ethanol. The mixture was stirred for 2 h with hydrogen at rt. The solution was filtered through Celite. A 200 mL portion of ether was added. The organic layer was washed with 3 × 100 mL of water, dried, and evaporated to give 1.53 g (83%) of **12**. TLC (cyclohexane/ethyl acetate, 1:1): $R_f = 0.34$. IR (film) $\nu$: 3480 (OH), 1745 $cm^{-1}$ (C=O). $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$: 1.29 (s, 3H, C($CH_3$)$_2$), 1.48 (s, 3H, C($CH_3$)), 1.68 (q, $J_{10-9,10-11} = 6.3$ Hz, 2H, $H_{10}$), 1.87 (ddd, $J_{3-2} = 3.9$ Hz, $J_{3-4} = 11.1$ Hz, $J_{3-3'} = 23.2$ Hz, 1H, $H_3$), 1.92 (ddd, $J_{3'-2} = 3.9$ Hz, $J_{3'-4} = 11.1$ Hz, $J_{3'-3} = 23.2$ Hz, 1H, $H_{3'}$), 2.07 (dt, $J_{9-8} = 5.3$ Hz, $J_{9-10} = 6$ Hz, 2H, $H_9$), 2.16 (t, $J_{6-5,6-7} = 5.1$ Hz, 2H, $H_6$), 2.29 (t, $J_{11-10} = 6.3$ Hz, 2H, $H_{11}$), 3.64 (s, 3H, $OCH_3$), 3.87 (m, 1H, $H_5$), 4.17 (dt, $J_{4-5} = 4.5$ Hz, $J_{4-3} = 11.1$ Hz, 1H, $H_4$), 4.72 (dd, $J_{2-1} = 3.1$ Hz, $J_{2-3} = 3.5$ Hz, 1H, $H_2$), 5.47 (m, 2H, $H_7$, $H_8$), 5.78 (d, $J_{1-2} = 3.1$ Hz, 1H, $H_1$). $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$: 24.7 ($C_{10}$), 26.2 (C($CH_3$)$_2$), 26.7 ($C_9$), 26.8 (C($CH_3$)$_2$), 30.9 ($C_6$), 32 ($C_3$), 33.4 ($C_{11}$), 51.5 ($OCH_3$), 70.6 ($C_5$), 80.6 ($C_4$, $C_2$), 105.3 ($C_1$), 111.2 (*C*($CH_3$)$_2$), 125.8 ($C_8$), 131.6 ($C_7$), 174.0 ($C_{12}$). Anal. Calcd for $C_{16}H_{26}O_6$ (314.38): C, 61.13; H, 8.34. Found: C, 61.07; H, 8.31.

**(5*S*)-3,6-Dideoxy-1,2-*O*-isopropylidene-6-(methylhex-1*Z*-enoate)-5-*O*-(*S*-methyldithiocarbonate)-α-D-ribohexofuranose (13).** To a solution of imidazole (1 mg, 0.015 mmol) and **12** (1 g, 3.18 mmol) in 10 mL of THF was added sodium hydride (60% in oil, 320 mg, 8 mmol). The mixture was stirred for 30 min, and $CS_2$ (770 $\mu$l, 12.8 mmol) was added. The solution turned orange. After 30 min, methyl iodide (1.6 mL, 25.8 mmol) was added. The agitation was continued for 30 min. The mixture was filtered and evaporated, and 100 mL of ethyl acetate was added. The organic layer was washed with 2 × 50 mL of brine, dried, and evaporated. The residue was followed by flash chromatography (3−5% ethyl acetate in cyclohexane) to give 930 mg (72%) of **13**. TLC (cyclohexane/ethyl acetate, 1:1): $R_f = 0.89$. IR (film) $\nu$: 1730 (C=O), 1140 $cm^{-1}$ (C=S). $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$: 1.29 (s, 3H, C($CH_3$)$_2$), 1.48 (s, 3H, C($CH_3$)), 1.67 (q, $J_{10-9,10-11} = 6.1$ Hz, 2H, $H_{10}$), 1.84 (m, 1H, $H_3$), 2.06 (m, 2H, $H_9$), 2.15 (m, 1H, $H_{3'}$), 2.29 (t, 2H, $H_{11}$), 2.52 (m, 2H, $H_6$), 2.53 (s, 3H, $SCH_3$), 3.64 (s, 3H, $OCH_3$), 4.37 (dt, $J_{4-5} = 3.9$ Hz, $J_{4-3} = 8.8$ Hz, 1H, $H_4$), 4.70 (t, $J_{2-3} = 3.5$ Hz, 1H, $H_2$), 5.44 (m, 2H, $H_7$, $H_8$), 5.77 (d, $J_{1-2} = 3.1$ Hz, 1H, $H_1$), 5.88 (m, 1H, $H_5$). $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$: 19.1 ($SCH_3$), 24.7 ($C_{10}$), 26.2 (C($CH_3$)$_2$), 26.8 ($C_9$), 26.9 (C($CH_3$)$_2$), 28.9 ($C_6$), 33.5 ($C_{11}$), 34.8 ($C_3$), 51.4 ($OCH_3$), 78.1 ($C_4$), 80.2 ($C_2$), 82.5 ($C_5$), 105.5 ($C_1$), 111.4 (*C*($CH_3$)$_2$), 123.9 ($C_8$), 132.3 ($C_7$), 173.9 ($C_{12}$), 215.9 (C=S). Anal. Calcd for $C_{16}H_{28}O_6S_2$ (404.53): C, 53.44; H, 6.98. Found: C, 53.34; H, 6.96.

**(8*S*,9*S*,11*R*)-Methyl 12,12′-Di(ethylthio)-9,11-dihydroxy-8-*O*-(*S*-methyldithiocarbonate)dodeca-5*Z*-enoate (14).** To the xanthate **13** (202 mg, 0.5 mmol) in 2 mL of ethanethiol was added anhydrous zinc chloride (288 mg, 2.11 mmol) at −10 °C. After 20 min, the excess ethanethiol was removed at −10 °C in vacuo. A 5 mL portion of $NaHCO_3$-saturated solution and 10 mL of ethyl acetate were added to the foamy residue. The mixture was extracted with 3 × 20 mL of ethyl acetate. The organic layers were washed with 2 × 10 mL of brine, dried, and deposited on a flash chromatography column (5−15% ethyl acetate in cyclohexane). A 185 mg (79%) portion of **14** was obtained. TLC (cyclohexane/ethyl acetate, 1:1): $R_f = 0.73$. IR (film) $\nu$: 3510 (OH), 1700 (C=O), 1130 $cm^{-1}$ (C=S). $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$: 1.30 (t, $J = 8$ Hz, 6H, $SCH_2CH_3$), 1.65 (m, 3H, $H_3$, $H_{10}$), 2.15 (m, 3H, $H_4$, $H_{10'}$), 2.40 (t, $J_{2-3} = 7$ Hz, 2H, $H_2$), 2.50 (m, 2H, $H_7$), 2.55 (s, 3H, $SCH_3$), 2.65 (q, $J = 8$ Hz, 4H, $SCH_2CH_3$), 3.50 (m, 1H, $H_9$), 3.65 (s, 3H, $OCH_3$), 3.75 (m, 1H, $H_{12}$), 4.10 (m, 1H, $H_{11}$), 5.45 (m, 2H, $H_5$, $H_6$), 5.65 (q, $J_{8-6,8-7} = 5.3$ Hz, 1H, $H_8$). $^{13}C$ NMR (25 MHz, $CDCl_3$) $\delta$: 14.6 ($CH_3$), 18.9 (SCH $SCH_{23}$), 24.6 ($SCH_2CH_3$), 25.7 ($C_3$), 26.6 ($C_4$), 30.9 ($C_7$), 33.4 ($C_2$), 35.9 ($C_{10}$), 51.5 ($OCH_3$), 58.4 ($C_{12}$), 71.9 ($C_9$), 73.3 ($C_{11}$), 85.3 ($C_8$), 124.5 ($C_5$), 131.9 ($C_6$), 173.2 ($C_1$), 218.2 (C=S).

**(8*S*,9*S*,11*R*)-Methyl-12,12-di(ethylthio)-8-*O*-(*S*-methyldithiocarbonate)-9,11-*O*-isopropylidenedodec-5*Z*-enoate (15).** To thiocetal **14** (127 mg, 0.27 mmol) in 7 mL of acetone were added dimethoxypropane (350 $\mu$l, 2.84 mmol) and *p*-toluenesulfonic acid (catalytic). After 1 h at rt, the acetone was removed in vacuo. A 10 mL portion of brine was added. The mixture was extracted with 3 × 20 mL of ethyl acetate, and the organic layers were washed with 3 × 5 mL of brine, dried, and evaporated. The residue was subjected to flash chromatography (3% of ethyl acetate in cyclohexane) to give 111 mg (76%) of **15**. TLC (cyclohexane/ethyl acetate, 8:2): $R_f = 0.70$. IR (film) $\nu$: 1740 $cm^{-1}$ (C=O). $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$: 1.25 (t, $J = 7.7$ Hz, 6H, $SCH_2CH_3$), 1.40 (s, 6H, C($CH_3$)$_2$), 1.65 (m, 3H, $H_3$, $H_{10}$), 2.10 (m, 3H, $H_4$, $H_{10'}$), 2.35 (t, $J_{2-3} = 6.9$ Hz, 2H, $H_2$), 2.50 (s, 3H, $SCH_3$), 2.55 (m, 2H, $H_7$), 2.65 (q, $J = 8$ Hz, 4H, $SCH_2CH_3$), 3.50 (m, 1H, $H_9$), 3.65 (s, 3H, $OCH_3$), 3.75 (m, 1H, $H_{12}$), 4.10 (m, 1H, $H_{11}$), 5.45 (m, 2H, $H_5$, $H_6$), 5.65 (q, $J_{8-6,8-7} = 5.3$ Hz, 1H, $H_8$). $^{13}C$ NMR (25 MHz, $CDCl_3$) $\delta$: 14.6 ($SCH_2CH_3$), 18.9 ($SCH_3$), 19.8 (C($CH_3$)$_2$), 24.6 ($SCH_2CH_3$), 25.7 ($C_3$), 26.6 ($C_4$), 26.9 (C($CH_3$)$_2$), 30.9 ($C_7$), 33.4 ($C_2$), 35.9 ($C_{10}$), 51.5 ($OCH_3$), 58.4 ($C_{12}$), 71.9 ($C_9$), 73.3 ($C_{11}$), 85.3 ($C_8$), 102.12 (*C*($CH_3$)$_2$), 124.5 ($C_5$), 131.9 ($C_6$), 173.2 ($C_1$), 218.2 (C=S).

**(8*S*,9*S*,11*R*)-Methyl-8-*O*-(*S*-methylthiocarbonate)-9,11-*O*-isopropylidene-12-oxododec-5*Z*-enoate (16).** To the thiocetal **15** (54 mg, 105 $\mu$mol) in 3.7/0.37 mL of acetone/water were added mercuric oxide (187 mg, 860 $\mu$mol) and mercuric chloride (78 mg, 280 $\mu$mol). The heterogeneous mixture was stirred at rt for 5 h. A 10 mL sample of saturated hydrogenocarbonate solution was added. The mixture was filtered through Celite and extracted with 3 × 10 mL of methylene chloride. The organic layers were washed with 3 × 10 mL of potassium iodide solution and with 3 × 10 mL of brine. The extracts were dried and evaporated. The aldehyde **16** was not purified further. TLC (cyclohexane/ethyl acetate, 9:1): $R_f = 0.32$. $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$: 1.42 (s, 6H, C($CH_3$)$_2$), 1.71 (m, 3H, $H_3$, $H_{10}$), 2.09 (m, 3H, $H_4$, $H_{10'}$), 2.25 (s, 3H, $SCH_3$), 2.38 (m, 2H, $H_2$), 2.50 (m, 2H, $H_7$), 3.67 (s, 3H, $OCH_3$), 3.82 (m, 1H, $H_9$), 4.21 (m, 1H, $H_{11}$), 4.88 (m, 1H, $H_8$), 5.47 (m, 2H, $H_5$, $H_6$), 9.52 (s, 1H, $H_{12}$).

**(8*S*,9*S*,11*R*)-Methyl-8-iodo-9,11-*O*-isopropylidene-12,12-di(ethylthio)dodec-5-ynoate (19).** To thiocetal **5** (0.5 g, 1.23 mmol) in 15 mL of acetone were added dimethoxypropane (1.26 mL, 12.3 mmol) and *p*-toluenesulfonic acid (catalytic). After 30 min at rt, the acetone was removed in vacuo. A 10 mL portion of brine was added. The mixture was extracted with 3 × 10 mL of ethyl acetate. The organic layers were washed with 3 × 5 mL of brine, dried, and evaporated. The residue was subjected to flash chromatography (0−5% ether in cyclohexane) to give 471 mg (89%) of **19**. TLC (cyclohexane/ethyl acetate, 7:3): $R_f = 0.63$. IR (film) $\nu$: 1715 $cm^{-1}$ (C=O). $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$: 1.26 (t, $J = 7.2$ Hz, 6H, $SCH_2CH_3$), 1.44 (s, 6H, C($CH_3$)$_2$), 1.59−1.88 (m, 4H, $H_3$, $H_{10}$), 2.23 (t, $J_{4-3} = 7.1$ Hz, 2H, $H_4$), 2.43−2.68 (m, 6H, $H_2$, $SCH_2CH_3$), 2.90 (m, 2H, $H_7$), 3.65 (s, 3H, $OCH_3$), 3.66 (m, 2H, $H_{12}$, $H_9$), 3.92−4.15 (m, 2H, $H_8$, $H_{11}$). $^{13}C$ NMR (25 MHz, $CDCl_3$) $\delta$: 14.5 ($SCH_2CH_3$), 18.1 ($C_4$), 19.8 (C($CH_3$)$_2$), 23.9 ($C_3$), 25.8 ($C_7$), 26.7 ($SCH_2CH_3$), 29.5 (C($CH_3$)$_2$), 32.7 ($C_2$), 33.1 ($C_{10}$), 35.4 ($C_8$),

51.4 ($OCH_3$), 55.3 ($C_{12}$), 70.2 ($C_9$), 72.9 ($C_{11}$), 78.8 ($C_6$), 81.5 ($C_5$), 99.5 ($C(CH_3)_2$), 173.3 ($C_1$). Anal. Calcd for $C_{20}H_{33}IO_4S_2$ (528.50): C, 45.45; H, 6.29. Found: C, 45.39; H, 6.27.

**(8*S*,9*S*,11*R*)-Methyl 8-Iodo-9,11-*O*-isopropylidene-12-oxododec-5-ynoate (20).** The thioacetal **19** (471 mg, 0.98 mmol) was subjected to oxidation by a method similar to that described for the preparation of **7**. The aldehyde **20** was used without further purification. TLC (cyclohexane/ethyl acetate, 9:1): $R_f = 0.26$. $^1$H NMR (100 MHz, $CDCl_3$) $\delta$: 1.35−2.60 (m, 14 H, C($CH_3$)$_2$, $H_2$, $H_3$, $H_4$, $H_{10}$), 2.90 (m, 2H, $H_7$), 3.65 (s, 3H, $OCH_3$), 3.80 (m, 1H, $H_9$), 4.05 (m, 1H, $H_8$), 4.65 (m, 1H, $H_{11}$), 9.65 (s, 1H, $H_{12}$). $^{13}$C NMR (25 MHz, $CDCl_3$) $\delta$: 18.3 ($C_4$), 20.3 (C($CH_3$)$_2$), 23.9 ($C_3$), 27.1 ($C_7$), 29.3 (C($CH_3$)$_2$), 30.3 ($C_2$), 33.1 ($C_{10}$), 34.9 ($C_8$), 52 ($OCH_3$), 69.3 ($C_9$), 73.7 ($C_{11}$), 78.6 ($C_6$), 81.9 ($C_5$), 100.2 ($C(CH_3)_2$), 173.3 ($C_1$), 201.5 ($C_{12}$).

**(8*S*,9*S*,11*R*)-Methyl 8-iodo-9,11-O-isopropylidene-14-oxotetradec-12*E*-en-5-ynoate (21).** The aldehyde **20** (376 mg, 0.89 mmol) was convert into 250 mg (62%) of **21** by the same method as that described for the preparation of **8**. TLC (cyclohexane/ethyl acetate, 7:3): $R_f = 0.34$. IR (film) $\nu$: 1715-(C═O), 1690 cm$^{-1}$ (C═O). $^1$H NMR (100 MHz, $CDCl_3$) $\delta$: 1.46 (s, 6H, C($CH_3$)$_2$), 1.61 (m, 3H, $H_3$, $H_{10}$), 1.82 (m, 1H, $H_{10'}$), 2.19 (t, $J_{4-3} = 7.4$ Hz, 2H, $H_4$), 2.45 (t, $J_{2-3} = 7.4$ Hz, 2H, $H_2$), 2.74−2.89 (m, 2H, $H_7$), 3.65 (s, 3H, $OCH_3$), 3.71 (m, 1H, $H_9$), 3.85 (m, 1H, $H_8$), 4.63 (m, 1H, $H_{11}$), 6.16 (dd, $J_{13-14} = 7.3$ Hz, $J_{13-12} = 15.5$ Hz, 1H, $H_{13}$), 6.65 (dd, $J_{12-11} = 4.1$ Hz, $J_{12-13} = 15.5$ Hz, 1H, $H_{12}$), 9.47 (d, $J_{14-13} = 7.3$ Hz 1H, $H_{14}$). $^{13}$C NMR (25 MHz, $CDCl_3$) $\delta$: 18.1 ($C_4$), 19.8 (C($CH_3$)$_2$), 23.8 ($C_3$), 26.7 ($C_7$), 29.5 (C($CH_3$)$_2$), 32.7 ($C_2$), 34.7 ($C_{10}$, $C_8$), 51.4 ($OCH_3$), 67.6 ($C_{11}$), 69.7 ($C_9$), 78.6 ($C_6$), 81.6 ($C_5$), 99.5 ($C(CH_3)_2$), 130.8 ($C_{13}$), 154.9 ($C_{12}$), 173.3 ($C_1$), 193.2 ($C_{14}$). Anal. Calcd for $C_{18}H_{25}IO_5$ (448.29): C, 48.23; H, 5.62. Found: C, 48.26; H, 5.59.

**(8*S*,9*S*,11*R*)-Methyl 8-Iodo-9,11-*O*-isopropylideneicosa-12*E*,14*Z*,*E*-dien-5-ynoate (22).** The aldehyde **21** (250 mg, 0.56 mmol) was converted to 247 mg (86%) of diene **22** by the same method as that described for the preparation of **9**. The presence of two isomers *EZ*/*EE* in a ratio of 60/40 is evident from the NMR spectra. TLC (cyclohexane/ethyl acetate, 7:3): $R_f = 0.76$. IR (film) $\nu$: 1720 cm$^{-1}$ (C═O). Anal. Calcd for $C_{24}H_{37}O_4$ (516.45): C, 55.82; H, 7.22. Found: C, 55.79; H, 7.17.

**Isomer (12*E*,14*Z*).** $^1$H NMR (360 MHz, $CDCl_3$) $\delta$: 0.87 (t, $J_{20-19} = 6.9$ Hz, 3H, $H_{20}$), 1.28 (m, 4H, $H_{19}$, $H_{18}$), 1.37 (m, 2H, $H_{17}$), 1.43 (s, 3H, C($CH_3$)$_2$), 1.44 (m, 1H, $H_{10}$), 1.47 (s, 3H, C($CH_3$)$_2$), 1.65 (m, 1H, $H_{10'}$), 1.81 (t, $J_{3-2} = 7.3$ Hz, 2H, $H_3$), 2.16 (m, 2H, $H_{16}$), 2.23 (m, 2H, $H_4$), 2.45 (t, $J_{2-3} = 7.3$ Hz, 2H, $H_2$), 2.75 (m, 1H, $H_7$), 2.92 (m, 1H, $H_{7'}$), 3.66 (s, 3H, $OCH_3$), 3.71 (m, 1H, $H_9$), 3.99 (m, 1H, $H_8$), 4.45 (m, 1H, $H_{11}$), 5.42 (dt, $J_{15-16} = 7.6$ Hz, $J_{15-14} = 10.9$ Hz, 1H, $H_{15}$), 5.58 (dd, $J_{12-11} = 6.8$ Hz, $J_{12-13} = 15.5$ Hz, 1H, $H_{12}$), 5.94 (t, $J_{14-13,14-15} = 10.9$ Hz, 1H, $H_{14}$), 6.51 (dd, $J_{13-14} = 10.9$ Hz, $J_{13-12} = 15.5$ Hz, 1H, $H_{13}$). $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$: 14 ($C_{20}$), 18.1 ($C_4$), 19.9 (C($CH_3$)$_2$), 22.4 ($C_{19}$), 23.9 ($C_3$), 26.7 ($C_7$), 27.7 ($C_{16}$), 29.1 ($C_{17}$), 29.8 (C($CH_3$)$_2$), 31.3 ($C_{18}$), 32.7 ($C_2$), 35.5 ($C_8$), 35.7 ($C_{10}$), 51.5 ($OCH_3$), 69.6 ($C_9$), 70 ($C_{11}$), 78.8 ($C_6$), 81.4 ($C_5$), 99.2 ($C(CH_3)_2$), 126.7 ($C_{13}$), 127.5 ($C_{14}$), 132.3 ($C_{12}$), 133.4 ($C_{15}$), 173.4 ($C_1$).

**Isomer (12*E*,14*E*).** $^1$H NMR (360 MHz, $CDCl_3$) $\delta$: 0.86 (t, $J_{20-19} = 6.9$ Hz, 3H, $H_{20}$), 1.28 (m, 4H, $H_{19}$, $H_{18}$), 1.37 (m, 2H, $H_{17}$), 1.43 (s, 3H, C($CH_3$)$_2$), 1.44 (m, 1H, $H_{10}$), 1.47 (s, 3H, C($CH_3$)$_2$), 1.65 (m, 1H, $H_{10'}$), 1.81 (t, $J_{3-2} = 7.3$ Hz, 2H, $H_3$), 2.05 (m, 2H, $H_{16}$), 2.23 (m, 2H, $H_4$), 2.45 (t, $J_{2-3} = 7.3$ Hz, 2H, $H_2$), 2.75 (m, 1H, $H_7$), 2.92 (m, 1H, $H_{7'}$), 3.66 (s, 3H, $OCH_3$), 3.71 (m, 1H, $H_9$), 3.99 (m, 1H, $H_8$), 4.40 (m, 1H, $H_{11}$), 5.51 (dd, $J_{12-11} = 6.5$ Hz, $J_{12-13} = 15.1$ Hz, 1H, $H_{12}$), 5.69 (dt, $J_{15-16} = 7.2$ Hz, $J_{15-14} = 15$ Hz, 1H, $H_{15}$), 5.98 (dd, $J_{14-13} = 10.4$ Hz, $J_{14-15} = 15$ Hz, 1H, $H_{14}$), 6.21 (dd, $J_{13-14} = 10.4$ Hz, $J_{13-12} = 15.1$ Hz, 1H, $H_{13}$). $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$: 14 ($C_{20}$), 18.1 ($C_4$), 19.9 (C($CH_3$)$_2$), 22.4 ($C_{19}$), 23.9 ($C_3$), 26.6 ($C_7$), 29.1 ($C_{17}$), 29.8 (C($CH_3$)$_2$), 31.3 ($C_{18}$), 32.4 ($C_{16}$), 32.7 ($C_2$), 35.5 ($C_8$), 35.7 ($C_{10}$), 51.5 ($OCH_3$), 69.3 ($C_{11}$), 69.6 ($C_9$), 78.8 ($C_6$), 81.4 ($C_5$), 99.2 ($C(CH_3)_2$), 129.3 ($C_{12}$), 130 ($C_{14}$), 131.6 ($C_{13}$), 136 ($C_{15}$), 173.4 ($C_1$).

**(8*S*,9*S*,15*RS*)-Methyl 9,15-Hydroxy-8-iodoeicosa-12*E*,13*E*-dien-5-ynoate (23).** To structure **22** (69 mg, 0.13 mmol) was added 10 mL of 50% v/v aqueous acetic acid in 5 mL of THF. The mixture was stirred for 3 d at rt. The solvents were removed, and the residue was subjected to flash chromatography (0−15% ethyl acetate in cyclohexane) to give 24 mg (38%) of **23**. TLC (cyclohexane/ethyl acetate, 7:3): $R_f = 0.50$. IR (film) $\nu$: 3490 (OH), 1720 cm$^{-1}$ (C═O). $^1$H NMR (360 MHz, $CDCl_3$) $\delta$: 0.87 (m, 3H, $H_{20}$), 1.24 (m, 4H, $H_{19}$, $H_{18}$), 1.28 (m, 4H, $H_{17}$), 1.55 (m, 2H, $H_{10}$), 1.78 (t, $J_{3-2} = 7.2$ Hz, 2H, $H_3$), 2.20 (m, 4H, $H_4$, $H_{16}$), 2.43 (t, $J_{2-3} = 7.2$ Hz, 2H, $H_2$), 2.91 (m, 2H, $H_7$), 3.07 (m, 1H, OH), 3.66 (s, 3H, $OCH_3$), 4.07 (m, 1H, $H_{15}$), 4.17 (m, 2H, $H_8$, $H_9$), 5.64 (m, 2H, $H_{11}$, $H_{14}$), 6.17 (m, 2H, $H_{12}$, $H_{13}$). $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$: 13.9 ($C_{20}$), 18.1 ($C_4$), 22.5 ($C_{19}$), 23.8 ($C_3$), 25 ($C_7$), 28.5 ($C_{17}$), 31.6 ($C_{18}$), 32.8 ($C_2$), 37.2 ($C_{16}$), 41.3 ($C_{10}$), 42 ($C_8$), 51.5 ($OCH_3$), 71.8 ($C_{15}$), 72.5 ($C_9$), 78.8 ($C_6$), 82 ($C_5$), 128.7 ($C_{14}$), 129.8 ($C_{12}$), 133.1 ($C_{13}$), 135.5 ($C_{11}$), 173.6 ($C_1$).

**(15*RS*)-9,11-*O*-Di(triethylsilyl)-5,6-dehydro-15-F2t-IsoP Methyl Ester (24).** To a solution of precursor **9** (51 mg, 72 $\mu$mol) in 5 mL of *p*-xylene was added tributyltin hydride (47 $\mu$L, 170 $\mu$mol) under a stream of dry argon. At rt, a 1 N triethylborane solution (145 $\mu$L, 145 $\mu$mol) was added dropwise under a stream of dry air. The mixture was stirred for 20 min. Triphenylphosphine (38 mg, 145 $\mu$mol) was added, and the solution was stirred for 2 h. The mixture was subjected to flash chromatography (0−5% ethyl acetate in cyclohexane) to give 23 mg (55%) of **24**. UV (EtOH): $\lambda_{max} = 204$ nm. TLC (cyclohexane/ethyl acetate, 7:3): $R_f$ (15*R*) = 0.47, $R_f$ (15*S*) = 0.44. $^1$H NMR (360 MHz, $CDCl_3$) $\delta$: 0.56 (m, 12H, $SiCH_2CH_3$), 0.93 (m, 21H, $H_{20}$, $SiCH_2CH_3$), 1.27 (m, 6H, $H_{17}$, $H_{18}$, $H_{19}$), 1.55 (m, 3H, $H_{10}$, $H_{16}$), 1.78 (m, 2H, $H_3$), 2.15 (m, 5H, $H_4$, $H_7$, $H_8$), 2.34 (m, 1H, $H_{10'}$), 2.41 (t, $J_{2-3} = 7.5$ Hz, 2H, $H_2$), 2.69 (m, 1H, $H_{12}$), 3.65 (s, 3H, $OCH_3$), 3.91 (m, 2H, $H_9$, $H_{11}$), 4.06 (m, 1H, $H_{15}$), 5.52 (m, 2H, $H_{13}$, $H_{14}$). $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$: 4.7 ($SiCH_2CH_3$), 6.7 ($SiCH_2CH_3$), 14 ($C_{20}$), 18.3 ($C_4$, $C_7$), 22.6 ($C_{19}$), 24.2 ($C_3$), 25 ($C_{17}$), 31.7 ($C_{18}$), 32.9 ($C_2$), 37.2 ($C_{16}$), 44.5 ($C_{10}$), 49 ($C_8$), 51.3 ($OCH_3$), 52.2 ($C_{12}$), 72.9 ($C_{15}$), 73 ($C_{11}$), 74.6 ($C_9$), 79.4 ($C_6$), 80.1 ($C_5$), 129.5 ($C_{13}$), 135.9 ($C_{14}$), 173.6 ($C_1$).

**(15*RS*)-5,6-Dehydro-15-$F_{2t}$-IsoP Methyl Ester (25).** A mixture of **24** (70 mg, 117 $\mu$mol) and 1 N tetrabutylammonium fluoride solution (176 mmol) was stirred in 2 mL of THF at rt for 1 h. The solution was quenched with 2 mL of brine and extracted with 3 × 3 mL of ethyl acetate. The organic layers were washed with 2 × 2 mL of brine, dried, and evaporated. The residue was subjected to flash chromatography (0−4% methanol in methylene chloride) to give 39 mg (90%) of **25**. UV (EtOH): $\lambda_{max} = 202$ nm. TLC ($CH_2Cl_2$/MeOH, 95:5): $R_f$ (15*R*) **25a** = 0.22, $R_f$ (15*S*) **25b** = 0.20. $^1$H NMR (360 MHz, $CDCl_3$) $\delta$: 0.87 (m, 3H, $H_{20}$), 1.27 (m, 6H, $H_{17}$, $H_{18}$, $H_{19}$), 1.5−1.69 (m, 3H, $H_{10}$, $H_{16}$), 1.78 (m, 2H, $H_3$), 2.05 (m, 2H, $H_7$), 2.19 (t, $J_{4-3} = 6.6$ Hz, 2H, $H_4$), 2.29 (m, 1H, $H_8$), 2.41 (m, 3H, $H_2$, $H_{10'}$), 2.77 (m, 1H, $H_{12}$), 3.66 (s, 3H, $OCH_3$), 4.05 (m, 2H, $H_{11}$, $H_{15}$), 4.12 (m, 1H, $H_9$), 5.42 (m, 1H, $H_{13}$), 5.58 (dd, $J_{14-15} = 5.8$ Hz, $J_{14-13} = 15.3$ Hz, 1H, $H_{14}$). $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$: 13.9 ($C_{20}$), 18.1 ($C_4$), 19.1 ($C_7$), 22.6 ($C_{19}$), 24.1 ($C_3$), 25.1 ($C_{17}$), 31.7 ($C_{18}$), 32.9 ($C_2$), 37.3 ($C_{16}$), 42.4 ($C_{10}$), 49.8 ($C_8$), 51.6 ($OCH_3$), 53.6 ($C_{12}$), 72.8 ($C_{15}$), 76.1 ($C_{11}$), 76.2 ($C_9$), 80.2 ($C_5$, $C_6$), 127.7 ($C_{13}$), 136.7 ($C_{14}$), 174.2 ($C_1$); HPLC conditions: see Scheme 6.

**(15*RS*)-5,6-Dehydro-15-$F_{2t}$-IsoP Methyl Ester (25).** The diol **11** (30 mg, 63 $\mu$mol) was converted into 23 mg (33%) of the isoprostane **25** by a method similar to that described in the preparation of **24**.

**(+)-(15*R*)-15-$F_{2t}$-IsoP Methyl Ester (26a).** To nickel acetate (2.7 mg, 11 $\mu$mol) in 1 mL of 95% ethanol was added 0.5 N sodium borohydride solution in ethanol (14 $\mu$L, 7 $\mu$mol). The flask was flushed with hydrogen. Ethylenediamine (1 $\mu$L) was added. Hydrogenation was then initiated by introducing **25a** (22 mg, 37 $\mu$mol) in 2 mL of ethanol. The mixture was stirred for 1 d with hydrogen at rt. The solution was filtered through Celite. A 5 mL portion of water was added, and the aqueous layer was extracted with 3 × 5 mL of ether. The organic extracts were washed with 3 × 2 mL of brine, dried, and evaporated to give 20 mg (90%) of **26a**. (15*R*)-$F_{2t}$-IsoP. [$\alpha$] = +5 ($c = 10^{-3}$, MeOH). UV (EtOH): $\lambda_{max} = 202$ nm. TLC ($CH_2Cl_2$/MeOH, 95:5): $R_f$ (15*R*) = 0.22, $R_f$ (15*S*) = 0.20. $^1$H NMR (360 MHz, $CDCl_3$) $\delta$: 0.86 (t, $J_{20-19} = 6.8$ Hz, 3H, $H_{20}$), 1.28 (m, 6H, $H_{17}$, $H_{18}$, $H_{19}$), 1.49 (m, 2H, $H_{16}$), 1.66 (m, 3H, $H_3$, $H_{10}$),

2.02 (m, 4H, $H_4$, $H_7$), 2.13 (m, 1H, $H_8$), 2.29 (t, $J_{2-3} = 7.3$ Hz, 2H, $H_2$), 2.42 (dt, $J_{10'-9,10'-11} = 7.3$ Hz, $J_{10'-10} = 13.1$ Hz, 1H, $H_{10'}$), 2.75 (m, 1H, $H_{12}$), 3.65 (s, 3H, $OCH_3$), 3.93 (m, 1H, $H_9$), 4.03 (m, 2H, $H_{11}$, $H_{15}$), 5.39 (m, 2H, $H_5$, $H_6$), 5.44 (dd, $J_{13-12} = 9.4$ Hz, $J_{13-14} = 15.3$ Hz, 1H, $H_{13}$), 5.56 (dd, 1H, $J_{14-15} = 6.7$ Hz, $J_{14-13} = 15.3$ Hz, $H_{14}$). $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$: 14 ($C_{20}$), 22.6 ($C_{19}$), 24.7 ($C_7$), 25.1 ($C_3$), 26.6 ($C_{17}$), 26.7 ($C_4$), 31.7 ($C_{18}$), 33.3 ($C_2$), 37.2 ($C_{16}$), 42.2 ($C_{10}$), 50.8 ($C_8$), 51.6 ($OCH_3$), 53.5 ($C_{12}$), 72.8 ($C_{15}$), 76.3 ($C_9$), 76.4 ($C_{11}$), 129.1 ($C_5$, $C_6$), 129.6 ($C_{13}$), 136.2 ($C_{14}$), 174.2 ($C_1$).

**(+)-(15*S*)-15-$F_{2t}$-IsoP Methyl Ester (26b).** The compound **25b** (30 mg, 50.4 $\mu$mol) in 2 mL of ethanol was converted into 21 mg (95%) of compoud **26b** by the similar method described in the preparation of **26a**. (15*S*)-$F_{2t}$-IsoP. $[\alpha] = +7$ ($c = 10^{-3}$, MeOH).[47]

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**Supporting Information Available:** Copies of $^1$H and $^{13}$C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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