Asymmetric Synthesis of 12-*epi*-PGF$_{2\alpha}$ by a Palladium-Mediated, Three-Component Coupling Reaction

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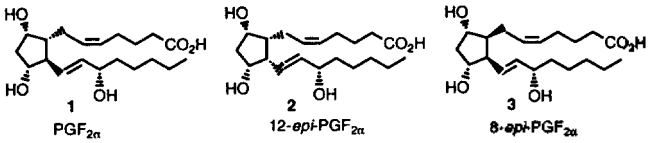
The prostaglandin analogue 12-*epi*-PGF$_{2\alpha}$ (**2**) has been synthesized from optically active *cis*-4-*t*-butyldimethylsilyloxy-2-cyclopenten-1-ol (**4b**) in 4 steps in an overall yield of 21%. An extremely efficient Pd(II)-mediated, three-component coupling reaction is employed to obtain the key intermediate **9**.

Introduction

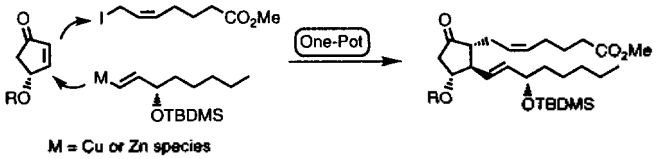
Prostaglandins (PG's) control a wide range of physiological responses in the human body. Several naturally-occurring prostaglandins and their synthetic analogues are presently being used as drugs.[1] Thus, prostaglandins have been the focus of extensive efforts in synthetic chemistry.[2] Recently, isoprostanes, such as 12-*epi*-PGF2 (**2**)[3] and 8-*epi*-PGF$_{2\alpha}$ (**3**),[4] have attracted much attention, because of their nonenzymatic



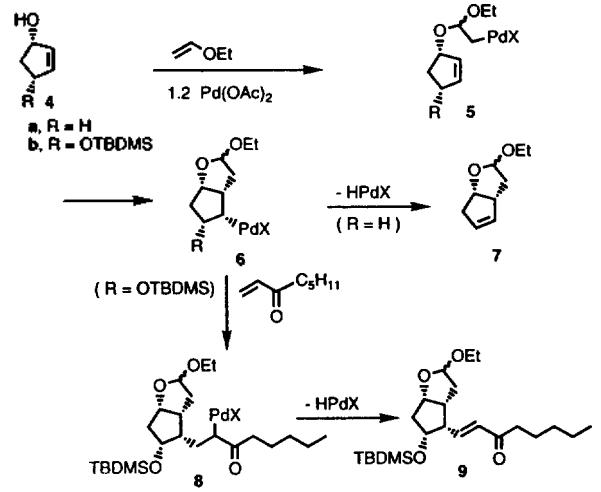
formation pathway and biological toxicity. To further illuminate the role of isoprostanes in the human body, an efficient synthetic approach to these compounds is necessary. We have previously communicated the first asymmetric synthesis of 12-*epi*-PGF$_{2\alpha}$ using a palladium-mediated, tandem alkene insertion strategy.[3] In this paper, we want to disclose the full experimental details of our methodology.

One of the most attractive routes to the natural PG carbon skeleton is a one-pot, three-component coupling process utilizing an organometallic mediated Michael addition, followed by trapping of the resulting enolate by an electrophile, such as an allylic iodide[5] (Scheme 1). This approach, however, has not yet proven amenable to the synthesis of isoprostanes.

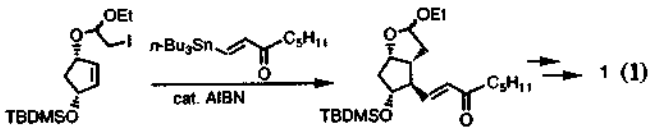
Another attractive approach for the construction of the prostaglandin framework involves radical-promoted cyclization and trapping. This process, initially investigated by Stork and co-workers[6a] and later improved by Keck and Burnett,[6b] employs an organotin compound as a radical trapping agent (eq. 1). Because of the stereochemistry of free radical addition to the C-C double bond, this approach is also not applicable to the synthesis of the isoprostanes.



Scheme 1.

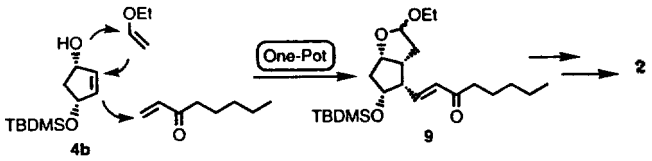


Scheme 2.

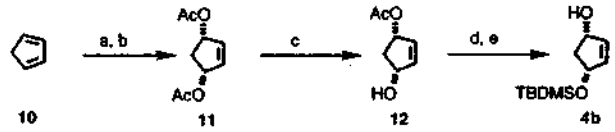


Our synthetic strategy for the synthesis of the all-*cis*-PGF$_{2\alpha}$ was based on the previous reports of Pd(II)-promoted cyclic acetal formation from allylic alcohols and vinylic ethers.[7] Thus, Larock and Stinn[7b] reported the synthesis of bicyclic acetals *via* oxypalladation and subsequent cyclization, followed by palladium hydride beta-elimination, as exemplified by the formation of **7** in Scheme 2.

A close look at the reaction mechanism in Scheme 2 suggests that the isoprostane skeleton might be obtained using this methodology. The utilization of a protected alcohol, such as silyloxy derivative **4b**, should prevent *syn*-elimination of palladium hydride. Subsequent trapping of the resulting organopalladium intermediate **6b** with 1-octen-3-one should afford the desired product **9**, which should be readily transformed to prostaglandin **2** in relatively few steps.[8] Therefore, the crucial intermediate **9** for the synthesis of 12-*epi*-PGF$_{2\alpha}$ should be easily prepared by a very efficient, three-component coupling process from readily available chiral alcohol **4b**[6] (Scheme 3).



Scheme 3.



[a]Reaction conditions: (a) $^1O_2$/hv, rose bengal, thiourea, CH_3OH/0 ℃, 42%; (b) 2.0 equiv of Ac_2O, pyridine, room temp, 12 h, 80%; (c) Ref. 10; (d) 1.5 equiv of *t*-butyldimethylsilylchloride, imidazole, CH_2Cl_2, room temp, 95%; (e) cat. KCN, 95% EtOH, room temp, 60 h, 90%

Scheme 4[a]

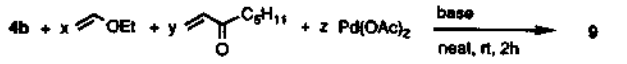
Results and Discussion

The key starting material, optically pure *cis*-4-*t*-butyldimethylsilyloxy-2-cyclopenten-1-ol (**4b**), was prepared following the literature procedure[6] depicted in Scheme 4. The prochiral diester **11** was obtained *via* dye-sensitized photooxygenation of cyclopentadiene **10**,[10] followed by acetylation of the resulting diol. Enzymatic hydrolysis[9] of diester **11** afforded the optically active monohydrolyzed product **12**. Subsequent protection and hydrolysis gave the desired alcohol **4b** whose optical purity is over 98%.

With **4b** as a starting material, the one-pot procedure for the three-component coupling was successfully effected to give the desired product **9**. The results obtained under various reaction conditions are summarized in Table 1. The best results are presented in entries 10 and 11. As seen in Table 1, the product yield is highly dependent on the amount of external olefin, 1-octen-3-one (entries 1-5); the yield improved from 27% to 57% as the amount of 1-octen-3-one was increased from 5 to 20 equivalents. This observation seems to indicate that the critical yield-determining step in this three-component coupling is the insertion of 1-octen-3-one into the organopalladium intermediate **6b** in Scheme 2. Since we suspected that the acetic acid generated during the reaction might destroy the enol ether initially added, the amount of ethyl vinyl ether was doubled (entry 6). No increase in yield was observed. For similar reasons, the effect of a base on the reaction was examined (entries 7 and 8). With triethylamine as a base, less than 10% of the desired product **9** was obtained. This reaction also gave a 41% yield of 1-acetoxy-3-octanone, which was probably generated by 1,4-addition of acetate ion to 1-octen-3-one. The addition of sodium acetate, however, provided slightly better results (entry 8).

During our work on the synthesis of carbacyclins,[8b] it was observed that the addition of sodium iodide to the reaction system increased the yield of the desired product. This observation led us to investigate the reaction using a catalytic amount of sodium iodide (entry 9). When 0.2 equivalents of sodium iodide was added to the reaction conditions, the desired product was obtained in a 58% yield, along with recovery of 16% of the starting material. The presence of the unreacted starting material suggested that Pd(II) was being destroyed during the reaction for some unknown reason. Hence, the reaction was conducted with 1.5 equivalents of $Pd(OAc)_2$. The product **9** was obtained in 72% yield (entry 10). When the same reaction was carried out with sodium acetate as a base (entry 11), the same result was obtained. The reason for the improvement in product yield, when using sodum iodide in this reaction, is not clear. One might postulate that the reactive species is an organopalladium iodide, rather than an organopalladium acetate. Because iodide is a monodendate ligand, it may provide more room around the palladium for 1-octen-3-one coordination and thus lead to a more favorable alkene insertion process.

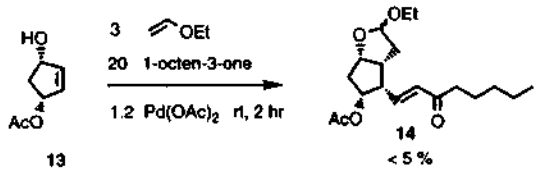
Table 1. Reaction Conditions for the Synthesis of Compound **9**



Entry	x	y	z	Base	9 (% isolated yield)
1	3	5	1.2	none	27
2		10			40
3		13			44
4		16			55
5		20			57
6	6				57
7	3	10		2.4 Et_3N	<10
8				5 NaOAc	44
9[a]		20		none	58[b]
10[a]			1.5		72
11[a]				5 NaOAc	72

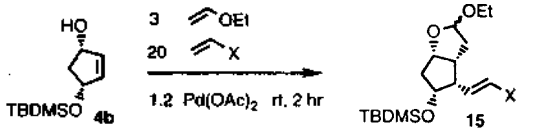
[a]0.2 NaI was added as an additive. [b]16% compound **4b** was recovered.

Since *cis*-4-acetoxy-2-cyclopenten-1-ol (**13**) is more readily available in optically active form, we examined this alcohol as a possible starting material. Unfortunately, the reaction gave only a trace amount of the desired product **14**, indicating that the choice of the alcohol protecting group is very important in this process (eq. 2).



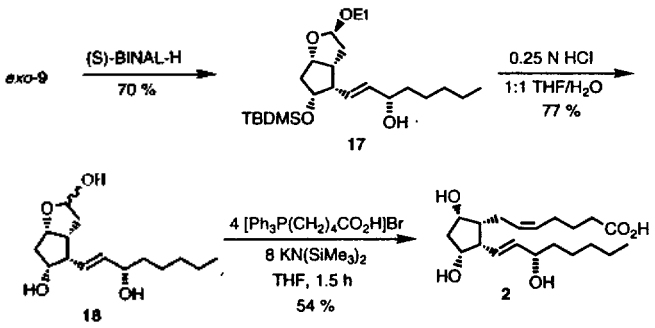
(2)

This unique multiinsertion process affords easy entry into the highly congested bicyclic system. We, therefore, examined various olefins as external palladium trapping agents under our reaction conditions (eq. 3). It was observed that



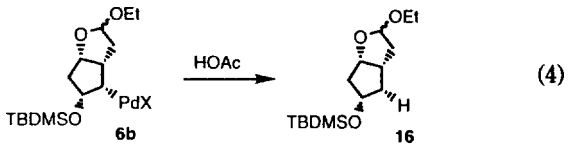
(3)

15a (X = *n*-C_5H_{11}), 54 % (0.2 NaI added); **15b** (X = COEt), 65 %; **15c** (X = Ac), 35 %; **15d** (X = CO_2Me), 26 %; **15e** (X = Ph), 13 %



Scheme 5.

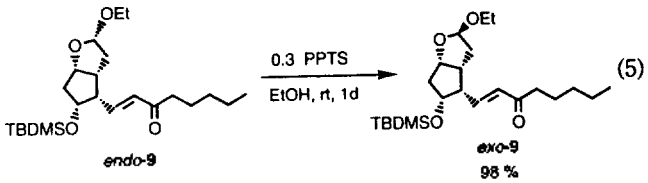
the reaction is highly influenced by the electronic and steric nature of the substituents located on the C-C double bond of the olefin. However, no obvious pattern is evidented. The use of 1-octene provided the cyclic acetal **15a**, which has been identified as a mixture of double bond isomers; C_{13}-C_{14} and C_{14}-C_{15} double bond isomers are present in a 6 : 1 ratio. The major side product observed is the bicyclic acetal **16**, which is apparently produced *via* protonolysis of the intermediate **6b** (eq. 4). This observation once again indicates



(4)

that insertion of the external olefin is the crucial step in this overall reaction. Even though we didn't fully examine each reaction, this chemistry looks promising for the synthesis of natural all-*cis* cyclopentanoids, such as 12-oxophytodienoic acid,[11] (−)-preclavulone A,[12] and (+)-methylepijasmonate.[13]

The product **9** was obtained as a mixture of *exo* and *endo* diastereomers, whose ratio ranges from 1 : 1 to 5 : 1, depending on the experimental conditions. The diastereomers *exo*-**9** and *endo*-**9** are separable by flash chromatography. Moreover, the *endo* isomer can be cleanly isomerized to the *exo* isomer by a catalytic amount of pyridinium *p*-toluenesulfonate in ethanol (eq. 5). Thus, all subsquent work has been carried out on pure *exo*-**9** to facilitate spectroscopic identification of the products.



(5)

Asymmetric synthesis of the desired product **2** was accomplished efficiently from the key compound **9** through the sequence described in Scheme 5. The diastereoselective reduction of the C-15 carbonyl group in **9** was achieved using Noyori's (S)-BINAL-H.[14] The reaction was very clean. No spots other than alcohol **17** were observed by TLC analysis. Since the reagent, (S)-BINAL-H, has been known to reduce a variety of unsaturated carbonyl compounds in a predictable manner, it is quite reasonable to assign the stereochemistry at C-15 in compound **17** the (S)-configuration.

Deprotection of the silyl group and hydrolysis of the cyclic acetal in compound **17** were effected in one step by aqueous HCl to give compound **18** in 77% yield. A subsequent Wittig reaction on compound **18** was expected to produce 12-*epi*-$PGF_{2\alpha}$ (**2**). A literature survey revealed that $PGF_{2\alpha}$ was obtained from the corresponding lactol by treatment of the appropriate phosphonium salt with methylsulfinyl carbanion in DMSO[15] or potassium *t*-butoxide in THF.[16] Subjection of lactol **18** to these literature procedures, however, provided no reaction, and returned the starting material in 70% yield. It was assumed that the sterically congested configuration around the cyclopentane ring in compound **18** must be causing difficulties in the Wittig reaction. Hence, we decided to try potassium hexamethyldisilazide as a base for generation of the ylide, since it has been used in the synthesis of a cyclopentane analogue which has side chains with the all-*cis* configuration.[12] We were quite pleased to see that the target molecule **2** was obtained under these reaction conditions as a single product in 54% yield. Compound **2** was characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy, plus high resolution mass spectrometry. Also, satisfactory results were obtained upon elemental analysis.

The biological activity of optically pure 12-*epi*-$PGF_{2\alpha}$ (**2**) was tested by the Bristol-Meyers Squibb. Unfortunately, compound **2** has relatively little activity against blood platelet aggregation; IC_{50}>1000 μM against ADP-induced aggregation, and IC_{50}=178.858 μM against arachidonic acid-induced aggregation. The observed biological activity of compound **2** indicates that the natural configuration of the lower side chain is of great importance, at least for anti-coagulation activity in $PGF_{2\alpha}$.

Experimental

General. All chemicals were used directly as obtained commercially unless otherwise noted. Tetrahydrofuran was distilled over sodium benzophenone ketyl and used immediately. NMR spectra were recorded on a Nicolet NT-300 spectrometer (^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz), and chemical shifts are reported in ppm relative to TMS (δ 0.00) as an internal standard. IR spectra were obtained on an IBM IR 98. High-resolution mass spectra were recorded on a Kratos MS-50 spectrometer.

Preparation of 12-epi-$PGF_{2\alpha}$ (2). To a solution of (4-carboxybutyl)triphenylphosphonium bromide (Aldrich, dried for 12 h at 100 ℃ under reduced pressure, 707 mg, 1.6 mmol) in 6.5 mL of freshly distilled THF was added KHMDS (Aldrich, 0.5 M in THF, 6.6 mL, 3.3 mmol) at room temperature under N_2 gas. At this point the reaction mixture turned a deep red color. The mixture was stirred for 15 min at room temperature. To this was slowly added the lactol **18** (110 mg, 0.41 mmol) in 1.5 mL of THF. The reaction mixture turned a deep brown color. After being stirred for 1.5 h at rt, the mixture was quenched by the addition of water (25 mL). The reaction mixture was washed with ethyl acetate (25 mL) to remove any organic soluble material. The aqueous layer was acidified by adding 2 N aq. HCl. The solution was extracted with CH_2Cl_2 (20 mL×2). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash

chromatography with EtOAc/MeOH/HOAc (90 mL/15 mL/0.1 mL) to give the product **2** (77 mg, 54% yield) as a white solid: R_f=0.29 (EtOAc/MeOH/HOAc, 90 mL/15 mL/0.1 mL); ^{1}H NMR ($CDCl_3$) δ 5.90-5.70 (br s, 3H, OH's), 5.80 (dd, *J*= 15.0, 10.5 Hz, 1H, HC=C), 5.49 (dd, *J*=15.0, 6.9 Hz, 1H, C=CH), 5.38 (m, 2H, HC=CH), 4.19 (m, 2H), 4.10 (m, 1H), 2.72 (m, 1H), 2.32 (t, *J*=6.6 Hz, 2H), 2.27 (m, 1H), 2.13 (m, 1H), 1.86 (m, 2H), 1.66 (m, 3H), 1.50 (m, 2H), 1.28 (m, 6H, CH_2's), 0.87 (t, *J*=6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 178.1, 167.1, 129.8, 129.3, 129.0, 75.4, 73.5, 72.9, 50.0, 47.2, 42.6, 36.8, 33.2, 31.9, 26.5, 25.3, 24.6, 24.3, 22.7, 14.1; IR (neat) 3387 (OH), 2926, 2856, 1707 (C=O), 1439, 1410 cm^{-1}; HRMS m/z 336.2295 [calcd for $C_{20}H_{32}O_4$ $(M-H_2O)^+$, m/z 336.2301]; Ammonia CI Mass m/z 372.4 ($M^+ + NH_4$). Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.77; H, 9.67. Found C, 67.57; H, 9.52.

Preparation of compound 9. In a vial were placed chiral alcohol **4b** (195 mg, 0.91 mmol; $[\alpha]_D^{22}$=+18.4°, c 1.28, $CHCl_3$), ethyl vinyl ether (262 mg, 3.6 mmol), 1-octen-3-one (2.3 g, 18.2 mmol), sodium acetate (149 mg, 1.8 mmol) and sodium iodide (27 mg, 0.18 mmol). The reaction mixture was stirred for 3 min at room temperature. To this was added palladium acetate (306 mg, 1.4 mmol). After stirring for 3 h at room temperature, the reaction mixture was filtered through a silica gel pad using 1 : 1 hexane/EtOAc. The solution was concentrated under reduced pressure, and the residue was purified by flash chromatography with 6 : 1 to 2 : 1 hexane/EtOAc to give compound **9** (269 mg, 72% yield) as a diastereomeric mixture. *Exo*-**9**: $[\alpha]_D^{22}$=−51.1° (c 0.83, $CHCl_3$); R_f=0.41 (4 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.93 (dd, *J*=16.2, 8.7 Hz, 1H, HC=CHCO), 6.08 (dd, *J*=16.2, 0.9 Hz, 1H, HC=CHCO), 5.10 (d, *J*=4.5 Hz, 1H, ROCHOR'), 4.61 (dd, *J*=7.2, 6.9 Hz, 1H, CHOR), 4.19 (dd, *J*=3.9, 4.2 Hz, 1H, CHOSi), 3.64 (ddq, *J*=6.9, 7.2, 9.6 Hz, 1H, OCH_2CH_3), 3.37 (ddq, *J*=6.9, 7.2, 9.6 Hz, 1H, OCH_2CH_3), 2.99 (dt, *J*=16.5, 8.4 Hz, 1H), 2.58 (dd, *J*=4.2, 8.7 Hz, 1H), 2.51 (dt, *J*=7.5, 2.4 Hz, 2H), 2.33 (ddd, *J*=12.8, 8.5 , 4.2 Hz, 1H), 1.98 (d, *J*=15.0 Hz, 1H), 1.90 (dd, *J*=6.9, 4.5 Hz, 1H), 1.83 (dd, *J*= 12.3, 9.3 Hz, 1H), 1.58 (m, 2H), 1.28 (m, 4H), 1.14 (t, *J*=6.9 Hz, 3H, OCH_2CH_3), 0.86 (t, *J*=6.1 Hz, 3H, CH_3), 0.83 (s, 9H, *t*-BuSi), 0.01 (s, 3H, $SiCH_3$), -0.02 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 200.6, 145.3, 132.0, 105.1, 83.3, 77.7, 62.1, 50.2, 45.8, 42.2, 39.5, 33.8, 31.5, 25.7, 24.2, 22.2, 18.0, 15.3, 14.4, −4.5, −5.4; IR (neat) 2959, 2930, 1676 (C=O), 1474, 1371, 1254, 1107 cm^{-1}; HRMS calcd for $C_{23}H_{41}O_4Si$ 409.2774, found 409.2780. *Endo*-**9**: R_f=0.32 (4 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.07 (dd, *J*=16.2 , 9.6 Hz, 1H, HC=CHOH), 5.96 (d, *J*=16.2 Hz, 1H, HC=CHCO), 5.07 (t, *J*=8.1 Hz, 1H, OCHRO), 4.53 (m, 1H, CHOR), 4.19 (m, 1H, CHOSi), 3.79 (m, 1H, OCH_2), 3.45 (m, 1H, OCH_2), 2.72-2.29 (m, 8H), 1.59 (m, 4H), 1.29 (m, 4H), 1.20 (t, *J*=7.2 Hz, 3H), 0.87 (t, *J*=6.6 Hz, 3H, CH_3), 0.85 (s, 9H, *t*-BuSi), 0.02 (s, 3H, $SiCH_3$), −0.02 (s, 3H, $SiCH_3$).

Preparation of compound 17. To a solution of $LiAlH_4$ (Aldrich, 0.54 M in THF, 4.0 mL, 2.2 mmol) was added ethanol (2 M in THF, 1.1 mL, 2.2 mmol) dropwise over 10 min at room temperature. Subsequently, a THF solution of (S)-binaphthol (Aldrich, [α]=−34°, 607 mg in 4.3 mL THF, 2.2 mmol) was added dropwise, and the resulting mixture was stirred for 30 min at room temperature. To this was added the enone *exo*-**9** (330 mg in 2.6 mL of THF, 0.80 mL) dropwise over 3 min at −100 ℃ (liq. N_2 and methanol bath). The reaction mixture was stirred for 2 h at −100 ℃, and then for another 2 h at −78 ℃. Methanol (1 mL) was added at −78 ℃ to destroy the excess reducing agent and the mixture was allowed to warm to room temperature. After the addition of water (25 mL) and diethyl ether (30 mL), stirring was continued for 10 min. The reaction solution was neutralized with 2 N aqueous HCl, and extracted with ether (3×30 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography with 3 : 1 hexane/EtOAc to give the product **17** (232 mg, 70% yield) as an oil; $[\alpha]_D^{22}$ =−45.1°, (c 1.00, $CHCl_3$); R_f=0.40 (3 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.80 (dd, *J*=15.9, 8.4 Hz, 1H, HC=C), 5.53 (dd, *J*=15.9, 7.2 Hz, 1H, C=CH), 5.11 (d, *J*=4.8 Hz, 1H, OCHR), 4.65 (t, *J*=7.2 Hz, 1H, CHOR), 4.12 (m, 1H), 4.06 (m, 1H), 3.68 (dq, *J*=7.2, 9.6 Hz, 1H, OCH_2CH_3), 3.38 (dq, *J*=7.2, 9.6 Hz, 1H, OCH_2CH_3), 2.94 (m, 1H), 2.45 (dt, *J*=4.2, 8.1 Hz, 1H), 2.35 (ddd, *J*=12.6, 8.1, 4.8 Hz, 1H), 1.95 (d, *J*=15.0 Hz, 1H), 1.84 (m, 1H), 1.80 (dd, *J*=12.3, 9.3 Hz, 1H), 1.50 (m, 1H), 1.38 (d, *J*=1.2 Hz, 1H), 1.29 (m, 6H, CH_2's), 1.17 (t, *J*=7.2 Hz, 3H, CH_3), 0.89 (m, 3H), 0.87 (s, 9H, *t*-BuSi), 0.03 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 135.1, 129.7, 105.3, 83.2, 77.6, 73.4, 62.1, 50.0, 45.8, 42.2, 37.3, 35.9, 31.8, 25.8, 22.7, 18.1, 15.4, 14.0, −4.9; IR (neat) 3472 (OH), 2957, 2928, 1472, 1464, 1371, 1254 cm^{-1}; HRMS m/z 411.2932 [calcd for $C_{23}H_{43}O_4Si$ $(M-H)^+$, m/z 411.2931]

Preparation of compound 18. To a solution of compound **17** (220 mg, 0.53 mmol) in 5.3 mL of THF was added 5.3 mL of 0.5 N aqueous HCl at room temperature. After the reaction was stirred for 4 h at room temperature, it was neutralized with 0.9 mL of 3 N NaOH. The organic phase was extracted with CH_2Cl_2 (25 mL×2 and 10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography using 10 : 1 EtOAc/MeOH gave compound **18** (111 mg, 77% yield) as an inseparable 5 : 4 mixture of *exo* and *endo* diastereomers: R_f=0.17 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.91 (dd, *J*=15.0, 8.1 Hz, 1H, HC=C), 5.82 (dd, *J*=15.0, 8.1 Hz, 0.8H, HC=C), 5.65-5.55 (m, 2.8H), 4.50 (m, 1H), 4.84 (t, *J*=6.3 Hz, 0.8 Hz), 4.74 (t, *J*=6.9 Hz, 1H), 4.21-4.07 (m, 4H), 2.88 (m, 3H), 1.69 (m, 1.2H), 2.56 (m, 1H), 2.29-1.89 (m, 9H), 1.54 (m, 4H), 1.30 (m, 10H), 0.89 (t, *J*=6.6 Hz, 6H, CH_3); IR (neat) 3356 (OH), 2930, 2858, 1456, 1340 cm^{-1}; HRMS m/z 252.1722 [calcd for $C_{15}H_{24}O_3$ $(M-H)^+$, m/z 252.1725]

Typical procedure for the reactions in Equation 3. Preparation of compound 15a. In a vial were placed alcohol **4b** (86 mg, 0.4 mmol), ethyl vinyl ether (116 mg, 1.6 mmol), 1-octene (896 mg, 8.0 mmol), sodium acetate (66 mg, 0.8 mmol) and sodium iodide (14 mg, 0.093 mmol). The reaction mixture was stirred for 2 min at room temperature, then palladium acetate (135 mg, 0.6 mmol) was added. Stirring was continued for 6 h at room temperature. The reaction mixture was passed through a silica gel pad using 3 : 1 hexane/EtOAc as an eluent. Concentration and flash chromatography yielded the compound **15a** (85 mg). Later, through the ozonolysis reaction, the compound **15a** was identified to be present as a mixture of C_{13}-C_{14} and C_{14}-C_{15} double bonds in a 6 : 1 ratio. *Exo*-isomer: R_f=0.38 (10 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.43 (m, 2H, HC=CH), 5.09 (d, *J*=4.8 Hz, 1H, ROCHR'OR"), 4.63 (t, *J*=7.2 Hz, 1H, HCOR), 4.06 (t, *J*=3.9 Hz, 1H, HCOSi), 3.67 (dq, *J*=9.6, 7.2 Hz, 1H,

OCH_2), 3.39 (dq, J=9.6, 7.2 Hz, 1H, OCH_2), 2.90 (m, 1H), 2.31 (ddd, J=12.6, 9.3, 4.8 Hz, 1H), 2.16 (m, 1H), 1.93 (m, 4H), 1.77 (m, 3H), 1.27 (m, 6H), 1.17 (t, J=7.2 Hz, 3H, CH_3), 0.86 (s, 9H, *t*-BuSi), 0.80 (m, 3H, CH_3), 0.03 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$); ^{13}C NMR (CDCl3) δ 131.4, 128.8, 105.3, 83.3, 75.9, 62.0, 47.9, 43.9, 42.2, 33.1, 32.7, 31.5, 29.8, 29.3, 25.8, 22.6, 18.0, 13.4, 14.1, −4.5, −5.1; IR (neat) 2950, 1455, 1380, 1250, 1110 cm^{-1}; HRMS m/z calcd for $C_{23}H_{44}O_3Si$ 396. 3060, found 396.3050.

Compound 15b. *Exo* diastereomer: (R_f=0.38, 4 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.95 (dd, J=16.2, 8.4 Hz, 1H, HC=C), 6.11 (d, J=16.2 Hz, 1H, C=CHC=O), 5.12 (d, J=4.8 Hz, 1H, ROCHR'O), 4.68 (t, J=6.9 Hz, 1H, CHOR), 4.20 (m, 1H, CHOSi), 3.66 (dq, J=9.9, 7.2 Hz, 1H, OCH_2), 3.40 (dq, J=9.9, 7.2 Hz, 1H, OCH_2), 3.00 (m, 1H), 2.56 (m, 3H), 2.34 (ddd, J=12.3, 9.0, 5.1 Hz, 1H), 1.99 (d, J=14.7 Hz, 1H), 1.91 (dd, J=6.9, 4.5 Hz, 1H), 1.85 (dd, J=12.6, 9.6 Hz, 1H), 1.15 (t, J=6.9 Hz, 3H, CH_3), 1.09 (t, J=7.5 Hz, 3H, CH_3), 0.86 (s, 9H, *t*-BuSi), 0.03 (s, 3H, $SiCH_3$), −0.01 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 200.8, 145.2, 131.7, 105.2, 83.2, 77.7, 62.1, 50.2, 45.7, 42.2, 35.8, 32.7, 25.7, 17.2, 15.3, 8.4, −4.8, −5.2; IR (neat) 2955, 1674 (C=O), 1256 cm^{-1}.

Compound 15c. *Exo* diastereomer: ^{1}H NMR ($CDCl_3$) δ 6.95 (dd, J=16.2 and 8.4 Hz, 1H), 6.10 (d, J=16.2 Hz, 1H), 5.14 (d, J=4.8 Hz, 1H), 4.69 (t, J=4.5 Hz, 1H), 4.23 (m, 1H), 3.68 (dq, J=9.6, 7.2 Hz, 1H), 3.41 (dq, J=9.6, 7.2 Hz, 1H), 3.03 (dt, J=16.3, 8.4 Hz, 1H), 2.61 (dt, J=4.2, 8.4 Hz, 1H), 2.36 (ddd, J=12.3, 8.4, 4.8 Hz, 1H), 2.26 (s, 3H), 1.51 (d, J=15.0 Hz, 1H), 1.94 (dd, J=6.6, 4.5 Hz, 1H), 1.88 (dd, J=12.0, 9.0 Hz, 1H), 1.72 (t, J=7.2 Hz, 1H), 0.88 (s, 9H, *t*-BuSi), 0.05 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$).

Compound 15d. *Exo* diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.10 (dd, J=15.9, 8.7 Hz, 1H), 5.86 (d, J=15.9 Hz, 1H), 5.12 (d, J=4.8 Hz, 1H), 4.67 (t, J=6.9 Hz, 1H), 4.19 (m, 1H), 3.72 (s, 3H), 3.65 (dq, J=9.6, 7.2 Hz, 1H), 3.39 (dq, J=9.6, 7.2 Hz, 1H), 2.99 (m, 1H), 2.58 (dt, J=3.9 and 8.4 Hz, 1H), 2.35 (ddd, J=12.3, 8.7, 4.8 Hz, 1H), 2.00 (d, J=15.0 Hz, 1H), 1.91-1.74 (m, 2H), 1.15 (t, J=7.2 Hz, 3H), 0.86 (s, 9H, *t*-BuSi), 0.02 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$).

Compound 15e. *Exo* diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H, Ar), 6.43 (m, 2H), 5.16 (d, J=4.8 Hz, 1H), 4.72 (t, J=6.9 Hz, 1H), 4.23 (m, 1H), 3.64 (dq, J=9.6, 7.2 Hz, 1H), 3.41 (dq, J=9.6, 7.2 Hz, 1H), 3.02 (m, 1H), 2.62 (dt, J=4.2, 7.2 Hz, 1H), 2.47 (ddd, J=12.6, 8.7, 4.8 Hz, 1H), 2.00 (d, J=15.0 Hz, 1H), 1.95-1.83 (m, 2H), 1.17 (t, J=7.2 Hz, 3H), 0.87 (s, 9H, *t*-BuSi), 0.03 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$).

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