An Efficient Synthesis of 12-*epi*-Carbacyclins Using a Palladium-Mediated Tandem Alkene Insertion Strategy

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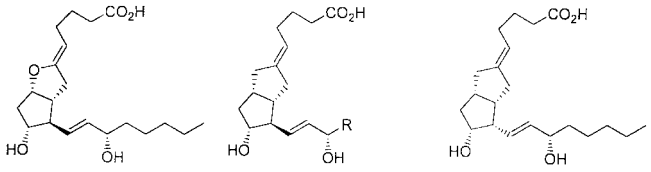
A short synthesis of novel prostanoids, 12-*epi*-carbacyclins **3** and **24**, has been accomplished using palladium chemistry as a key step. The silyl enol ether **10a** prepared through organopalladium chemistry has been allowed to react with 1-octen-3-one in the presence of $Pd(OAc)_2$ to give compound **12** in a single step. The unusual chemo- and stereoselective reduction of the α,β-unsaturated ketone in **12** has been effected with (*S*)-BINAL-H. Subsequent desilylation and Wittig reaction have provided the PGI_2 analogues **3** and **24**.

Keywords : Prostacyclin, Carbacyclin, Palladium, Organic synthesis, Alkene insertion.

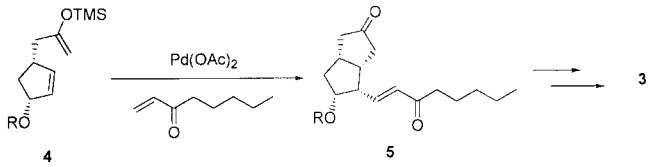
Introduction

Prostacyclin (PGI_2, **1**) was discovered by Vane and co-workers in 1976,[1] and its structure was subsequently determined by Johnson and co-workers at Upjohn in collaboration with the Vane group.[2] Once discovered, it was clearly recognized to have many clinical applications for the treatment of cardiovascular disease, because of its potent anti-platelet and vasodilating effect. However, prostacyclin's chemical instability due to enol ether hydrolysis has limited its pharmaceutical utility. Since its discovery, therefore, many attempts have been made to develop chemically and metabolically stable PGI_2 analogues.[3]



Among the stable PGI_2 mimics, carbacyclin (**2a**) and its analogues have attracted special attention. Carbacyclin, where prostacyclin's enolic oxygen is replaced by a methylene moiety, was first independently synthesized in 1978 by four groups.[4] The compound **2a** was found to have a pharmacological profile similar to that of **1**. It is, for example, a potent inhibitor of platelet aggregation, a vasodialator and an inhibitor of gastric acid secretion.[5] Even though **2a** has failed to achieve clinical usage due to side effects, the ω-chain modified carbacyclin analogue known as iloprost (**2b**) has been utilized as a drug to treat peripheral vascular disease.[6]

In our continuing effort to synthesize prostaglandins,[7] 12-*epi*-carbacyclin (**3**) appeared to be an interesting carbacyclin analogue that we might approach using organopalladium chemistry (Scheme 1).[8] Silyl enol ethers have previously been studied as organopalladium precursors leading to

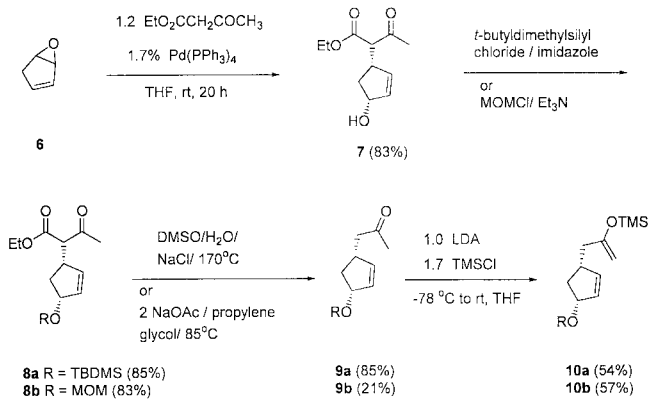


Scheme 1

cyclization products *via* alkene insertion.[9] The coupling of 1-octen-3-one and an organopalladium intermediate generated by the cyclization of compound **4** should give compound **5** in a single step. Subsequent reactions, including selective reduction of the α,β-unsaturated ketone and a Wittig reaction should provide the novel PGI_2 analogue in very few steps. Unlike all of the carbacyclin analogues previously synthesized, **3** has an all-*cis* configuration around the cyclopentane ring.

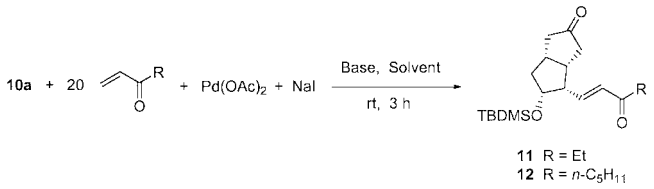
Results and Discussion

Organopalladium precursors **10a** and **10b** have been prepared by the sequence shown in Scheme 2. Compound **7** was prepared stereoselectively from cyclopentadiene monoepoxide (**6**) and ethyl acetoacetate using π-allylpalladium



Scheme 2

Table 1. Reaction conditions for synthesis of the carbacyclin framework using a palladium-mediated tandem alkene insertion strategy

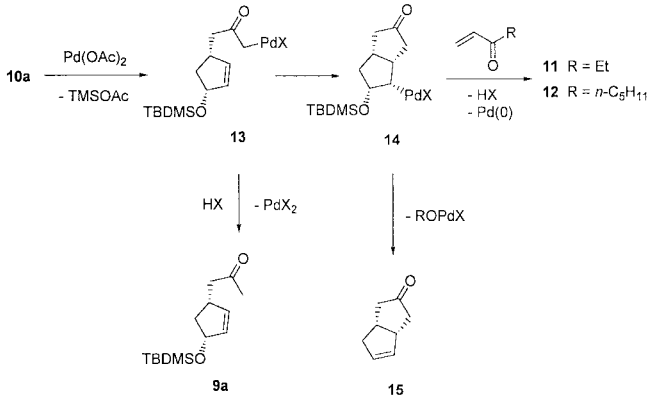


Entry	R	Equivalents		Base	Solvent	Product
		$Pd(OAc)_2$	NaI			% yield[a]
1	Et	1.2	0	NaOAc	–	23
2				Et_3N	–	0
3				NaOAc	THF	22
4					Acetone	28
5					CH_2Cl_2	7
6					THF[b]	4
7					THF[c]	0
8			1.2		THF	45
9			0.2			42
10		1.5				55
11	*n*-C_5H_{11}					42
12					Acetone	38
13					$CHCl_3$	49
14					CH_2Cl_2	62

[a]Isolated yields. [b]Li_2PdCl_4 was used instead of $Pd(OAc)_2$. [c]1.0 equiv. of PPh_3 was added.

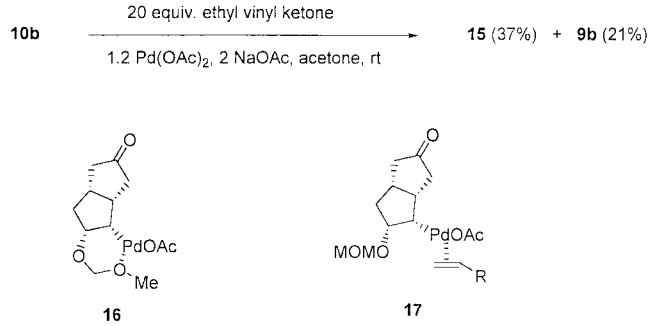
chemistry.[10] The decarboalkoxylation of alcohol **7** using Krapcho's method[11] provided only unidentified product possibly due to rearrangement of hydroxyl group. However, protection of the hydroxy group in compound **7**, followed by thermal decarboalkoxylation, provided ketone **9a** in 85% yield. Subsquent treatment of ketone **9a** with LDA and trimethylsilyl chloride[12] afforded silyl enol ether **10a**.

The key step for the synthesis of **3** was examined using enol silane **10a** as the organopalladium precursor. Various reaction conditions were studied to effect the Pd(II)-mediated cyclization and subsequent enone coupling as a single-step procedure. The results are summarized in Table 1. As a model study, ethyl vinyl ketone (20 equiv.) which was easily removed after the reaction due to its volatility was first tried as an organopalladium trapping agent. Previously we have developed a Pd(II)-mediated tandem alkene insertion procedure[7a] for the synthesis of 12-*epi*-$PGF_{2\alpha}$. Accordingly we have first tried the previous reaction conditions, *i.e.*, 1.2 equiv. of $Pd(OAc)_2$ and NaOAc as a base, with no solvent (entry 1). Using these conditions, the product **11** was obtained in only a 23% yield. An examination of a number of other bases, including Na_2CO_3, K_2CO_3, and $LiOAc{\cdot}2H_2O$ provided similar results, whereas an organic base, such as triethylamine, gave none of the desired product. In this reaction, usually the reduced product **9a** and elimination product **15** were obtained as side-products (Scheme 3). For example, **9a** and **15** were obtained in 20% and 5% yields respectively in the reaction shown in entry 1. An examination of several solvents failed to improve product yields (entries 3-5). Switching the Pd(II) species from $Pd(OAc)_2$ to Li_2PdCl_4 gave worse results (entry 6). Employing PPh_3 as an additive gave none of the desired product, and **9a** was obtained as the only product. This implies that PPh_3 coordination to Pd(II) inhibits cyclopentane coordination, which makes intramolecular organopalladium insertion difficult. Even though, employing different solvents did not make much difference in the product yield (entry 3), the side-product distribution was somewhat different from that obtained under neat reaction conditions. For example, compared to the result in entry 1, **15** was obtained in higher yield (44%) than **9** (5%) when THF was employed as the solvent (entry 3). This implies that, under dilute conditions, the lowered HOAc concentration produces less of ketone **9**. Also, lowered the enone concentration provides a higher chance of forming the elimination product **15**. For all of the above reactions (entries 1-7), some starting material **10a** was observed to be converted to unidentified products, which resulted in a poor material balance (~60%).



Scheme 3

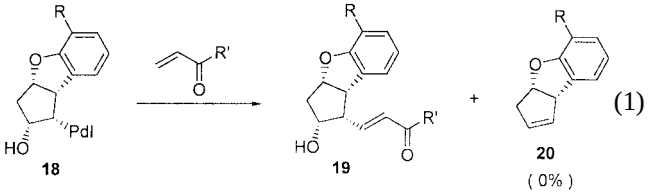
While silyloxy palladium elimination in intermediate **14** appeared to be a major problem in this reaction, we decided to employ other protecting group in compound **10** to prevent the elimination. The MOM protecting group was considered to be a better choice, because the organopalladium intermediate **14** might be stabilized by the coordination of a nearby oxygen as in intermediate **16**. Then, the stabilized intermediate **16** might have sufficient time to undergo intermolecular enone insertion. However, that was not the case. The



Scheme 4

oxygen coordination appararently makes olefin coordination to form intermediate **17** more difficult. As a result, none of the desired product was obtained (Scheme 4).

Working on the other project on prostaglandins, we found it very interesting that none of eliminated product such as **20** was observed in our synthesis of the 12-*epi*-benzoprostacyclins (Eq. 1).[7b] The difference in the chemistry of organopalladium intermediates **14** and **18** may depend on the ligand present on palladium. Thus, we decided to change the ligand from acetate to iodide. The reaction was conducted simply by adding sodium iodide to the reaction mixture. By doing this, we observed considerable improvement in product yield (entry 8). Thus, product **11** was obtained in 45% yield compared to the 22%, yield obtained without NaI (compare entries 3 and 8). A catalytic amount of sodium iodide provided a very similar result (entry 9). When we increased the amount of $Pd(OAc)_2$ to 1.5 equiv., some improvement in the yield of **11** was also observed (entry 10).



(1)

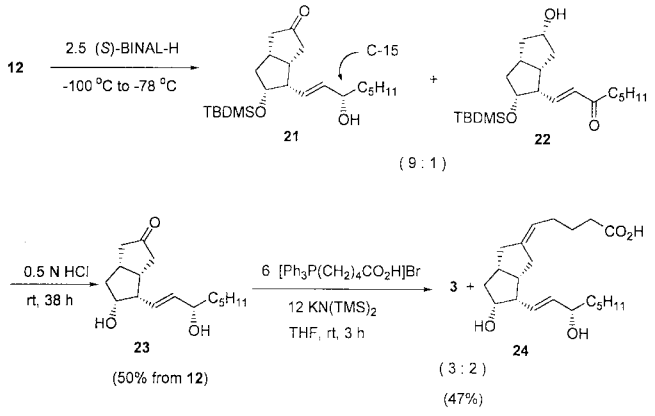
Now, the reaction was conducted with 1-octen-3-one, instead of ethyl vinyl ketone, using the reaction conditions shown in entry 10. The desired product **12** was obtained in 42% yield. The reaction was then examined using different bases and solvents. It was finally found that the reaction was best conducted in CH_2Cl_2 which afforded **12** in 62% yield (entry 14).

A reaction mechanism for this interesting tandem alkene insertion process is proposed in Scheme 3. In the presence of NaI, the reaction is considered to proceed first by a ligand exchange reaction (Eq. 2). Since the color change of $Pd(OAc)_2$ from brown to a dark purple was immediately observed as soon as NaI was added to the THF solution without any other substrates, one might suppose that the metathesis reaction in eq. 2 is occurring very fast.

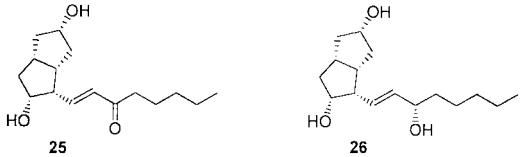
$$Pd(OAc)2 + NaI \rightleftharpoons IPdOAc + NaOAc \qquad (2)$$

The treatment of precursor **10a** with a Pd(II) species should generate acyl palladium intermediate **13**, which can either cyclize to **14** or be protonated to **9a** depending on the reaction conditions. When Et_3N or PPh_3 are present in the reaction mixture, they presumably coordinate to the Pd(II) in **13**, preventing olefin coordination and thus favoring formation of compound **9a**. The cyclized intermediate **14** can either couple with the enone to afford **12** (or **11**) or undergo alkoxy-palladium elimination to produce enone **15**. The ratio of **11** to **15** increased when adding NaI, which implies that the presence of the moiety PdI rather than PdOAc in **14** favors the alkene insertion. Presumably the more electrophilic palladium in the organopalladium acetate can more readily coordinate with the neighboring oxygen moiety eventually producing the elimination product **15**.

To complete the synthesis of prostaglandin **3**, we needed to convert compound **12** to compound **21**. For this conversion, we needed a method for the selective reduction of an α,β-unsaturated ketone in the presence of a saturated ketone. Moreover, carbonyl reduction at C-15 required a diastereoselectivity producing the (S)-alcohol. No general method was found to meet these requirements in the literature.[13] So, we decided to examine Noyori's (*S*)-BINAL-H as a stereo- and regioselective reducing agent.[14] Even though BINAL-H has been well documented to reduce α,β-unsaturated ketones stereoselectively in a predictable manner, no example has been reported where this reagent chemoselectively reduces enones in the presence of saturated ketones. However, we were pleased to observe that the stereo- and chemoselective reduction of compound **12** could be efficiently carried out using (*S*)-BINAL-H (Scheme 5). When compound **12** was subjected to reduction with (*S*)-BINAL-H, the desired product **21** was obtained selectively over compound **22** in a ratio of 9 : 1. The incidental overlap of compounds **21**, **22** and (*S*)-binaphthol on TLC made isolation of the product difficult. However, assignment of the olefinic hydrogens of compounds **21** and **22** in the crude product by ^1H NMR spectral analysis was possible. The olefinic hydrogens in compounds **21** and **22** have been compared to those in compounds **23** and **25,** which could be isolated cleanly after desilylation. None of the over-reduced product **26** was observed upon ^1H NMR spectral analysis. Even though an excess of the reducing agent was employed, some of the starting material **12** was left upon ^1H NMR spectral analysis. Since the R_f value of compound **12** was also close to (*S*)-binaphthol, no attempt was made to recover the starting material **12**.



Scheme 5



Deprotection of the silyl group in compound **21** was effected using aqueous hydrochloric acid to yield compound **23**, which was then separable from (*S*)-binaphthol and compound **25**. None of the C15-(*R*) isomer was observed. Since only one stereoisomer at C-15 was obtained, we assigned it as the desired C15-(*S*) isomer based on a previous report where (*S*)-BINAL-H was used to effect a similar reduction.[14] Therefore, compound **12** was reduced chemo- and stereoselectively to give crude product **23,** which was, without further purification, subjected to hydrolysis to provide compound **23** in an overall 50% yield from compound **12**.

A subsequent Wittig reaction on compound **23** provided the desired 12-*epi*-carbacyclin (**3**), along with its C5-Z isomer **24**. The assignment of stereochemistry for these two compounds was based on the product ratio and the polarity of compounds **3** and **24**. A literature survey revealed that the C5-E isomer is always obtained as the major product upon Wittig reaction in analogous carbacyclin syntheses.[14] For example, in the synthesis of carbacyclin **2a**, the C5-E isomer was obtained in about a 3 : 1 ratio over its Z isomer upon Wittig reaction.[4] In the case of **23**, compound **3** was also obtained in larger amounts than compound **24**. We can explain this by proposing that the steric congestion in compound **3** is more favorable than that present in compound **24**. A literature survey[15] also revealed that the more polar isomers are generally those with an E-configuration at C-5 in similar prostaglandins. Compound **3** was obtained as the more polar isomer, which also supports our configurational assignment. Compounds **3** and **24** were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy, plus high resolution mass spectrometry.

In conclusion, a very efficient synthesis of the novel carbacyclins **3** and **24** has been accomplished using a palladium-promoted cyclization-tandem alkene insertion of an enol silane as the key step. The subsequent chemo- and stereoselective reduction of the resulting enone, and eventual Wittig reaction complete the process.

Experimental Section

General. All chemicals were used directly as obtained commercially unless otherwise noted. Tetrahydrofuran was distilled over sodium benzophenone ketal and used immediately. Methylene chloride was distilled over phosphorous pentoxide and stored over 4 Å molecular sieves. DMF was distilled over calcium hydride and stored over 4 Å molecular sieves. Acetone was distilled over calcium hydride and stored over 4 Å molecular sieves.

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. The 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*-carbacyclin (3). To a solution of (4-carboxybutyl)triphenylphosphonium bromide (Aldrich, dried for 12 h at 100 °C under reduced pressure, 1.15 g, 2.66 mmol) in 9 ml of freshly distilled THF was added KHMDS (Aldrich, 0.5 M in THF, 10.7 mL, 5.32 mmol) at room temperature under a N_2 atmosphere. At this point, the reaction mixture turned a deep red color. The reaction mixture was stirred for 15 min at room temperature. To this was slowly added ketone **23** (118 mg, 0.44 mmol) in 2 ml of THF. The reaction mixture turned a brown color. After stirring for 3 h at room temperature, the reaction was quenched by adding H_2O (25 mL). The reaction mixture was washed with ethyl acetate (25 mL) to remove any organic soluble side-product. The aqueous layer was acidified by adding 2 N aqueous HCl (2.4 mL). The solution was extracted with CH_2Cl_2 (20 mL × 3). The organic phase was washed with water (15 mL), then dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography with 500 : 1 EtOAc/acetic acid to give compounds **3** (44 mg) and **24** (29 mg) as oils in an overall 47% yield. Compound **3**: R_f = 0.31 (500 : 1 EtOAc/AcOH); ^{1}H NMR ($CDCl_3$) δ 5.66 (dd, J = 15.3 and 9.0 Hz, 1H, HC=C), 5.52 (dd, J = 15.3 and 6.6 Hz, 1H, HC=C), 5.16 (t, J = 6.9 Hz, 1H, HC=C), 4.63 (br s, 2H, OH's), 4.09 (m, 2H), 2.71-2.45 (m, 3H), 2.45-2.23 (m, 5H), 2.23-2.08 (m, 2H), 2.08-1.95 (m, 2H), 1.78-1.63 (m, 2H), 1.63-1.42 (m, 3H), 1.42-1.18 (m, 7H), 0.89 (t, J = 6.9 Hz, 3H, CH_3): ^{13}C NMR ($CDCl_3$) δ 177.87, 144.71, 136.69, 129.18, 119.96, 76.92, 73.18, 51.33, 44.50, 41.49, 40.54, 37.07, 36.04, 35.80, 33.50, 31.80, 28.79, 25.26, 24.74, 22.71, 14.12; IR (neat) 3414 (OH), 2930, 2858, 1709 (C=0), 1437 cm^{-1}; HRMS m/z 332.23463 [calculated for $C_{21}H_{32}O_3$ $(M-H_2O)^+$, m/z 332.23515]; Ammonia CI Mass, m/z 368.2 for $M^+ + NH_4$. Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 70.19; H, 8.77. Compound **24**: R_f = 0.38 (500 : 1 EtOAc/AcOH); ^{1}H NMR ($CDCl_3$) δ 6.00 (br s, 2H, OH's), 5.69 (dd, J = 15.3 and 7.8 Hz, 1H, HC=C), 5.57 (dd, J = 15.3 and 6.3 Hz, 1H, HC=C), 5.19 (t, J = 7.2 Hz, 1H, HC=C), 4.12 (m, 2H), 2.64-1.95 (m, 12H), 1.78-1.25 (m, 11H), 0.88 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 178.90, 144.57, 136.22, 129.69, 119.96, 76.47, 73.26, 51.28, 45.83, 41.45, 40.32, 37.05, 33.27, 31.81, 30.29, 28.55, 26.42, 25.25, 24.54, 22.69, 14.15; IR (neat) 3425 (OH), 1710 (C=0) cm^{-1}; HRMS m/z 332.23470 [calculated for $C_{21}H_{32}O_3$ $(M-H_2O)^+$, 332.23515]; Ammonia CI Mass, m/z 368.4 for $M^+ + NH_4$. Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 67.63; H, 9.93.

Preparation of compound 7. Cyclopentadiene monoepoxide (**6**, 4.9 g, 60 mmol) dissolved in 10 mL of THF was added to a solution of $Pd(PPh_3)_4$ (1.18 g, 1.0 mmol) and ethyl acetoacetate (9.4 g, 72 mmol) in 50 mL of THF dropwise over 20 min at 0 °C. After stirring for 40 min at 0 °C, the mixture was allowed to warm to room temperature, then stirring was continued for 24 h at room temperature. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash chromatography using 1 : 1 hexane/EtOAc to give compound **7** as an inseparable mixture of diastereomers: 10.6 g, 83% yield; R_f = 0.25 (1 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 2H, HC=CH), 4.72 (m, 1H), 4.19 (dq, J = 1.8 and 7.2 Hz, 2H), 3.53 (dd, J =

8.1 and 6.0 Hz, 1H), 3.26 (m, 1H), 2.52 (dt, *J* = 17.1 and 7.8 Hz, 1H), 2.23 (ddt, *J* = 42.3 and 14.1 and 3.9 Hz, 1H), 2.24 (s, 3H), 1.44 (dd, *J* = 4.8 and 7.8 Hz, 1H), 1.26 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 202.36, 169.08, 168.72, 135.62, 135.29, 134.80, 134.31, 76.49, 64.59, 64.43, 61.52, 43.43, 43.22, 38.02, 37.28, 30.08, 29.72, 14.13; IR (neat) 3423 (OH), 1715 (C=0) cm^{-1}.

Preparation of compound 8a. To a solution of alcohol **7** (2.90 g, 13.7 mmol) and imidazole (2.33 g, 34.3 mmol) in 20 mL of DMF was added with stirring at room temperature *t*-butyldimethylsilyl chloride (2.27 g, 15.1 mmol) dissolved in 16 mL of DMF. After stirring for 14 h at room temperature, the reaction was quenched by adding 20 mL of H_2O. The mixture was extracted with hexane (50 mL × 3), and the organic phase was washed with brine (50 mL), then dried and concentrated. The residue was purified by flash chromatography using 4 : 1 hexane/EtOAc to give compound **8a**: 4.27 g, 96% yield; R_f = 0.53 (4 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.79 (m, 2H, HC=CH), 4.79 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.48 (dd, *J* = 10.5 and 3.6 Hz, 1H), 3.24 (m, 1H), 2.40 (m, 1H), 2.24 (s, 3H), 1.27 (m, 4H), 0.88 (s, 9H, *t*-BuSi), 0.06 (s, 6H, $SiMe_2$).

Preparation of compound 8b. To a solution of alcohol **7** (1.0 g, 4.7 mmol) and triethyl amine (2.0 mL, 14.1 mmol) in 10 mL of THF was added MOMCl (Aldrich, 0.72 mL, 9.4 mmol) dropwise over 5 min. After stirring for 9 h at room temperature, the mixture was filtered, and then concentrated. The residue was purified by flash chromatography to give compound **9a**: 1.04 g, 83% yield; R_f = 0.52 (1 : 1 hexane/ EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.90 (m, 2H), 4.85 (m, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.45 (dd, *J* = 10.5 and 5.4 Hz, 1H), 3.35 (d, *J* = 2.1 Hz, 3H), 3.30 (m, 1H), 2.47 (m, 1H), 2.24 (s, 3H), 1.41 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H).

Preparation of compound 9a. To a round bottomed flask attached with a reflux condenser were placed compound **8a** (6.7 g, 20.6 mmol), DMSO (20.6 ml), H_2O (1.1 mL) and NaCl (1.8 g, 31.0 mmol). The reaction was placed in a hot oil bath (165-170 °C), and stirring was continued for 9 h. The mixture was cooled to room temperature, then poured into 150 mL of diethyl ether. The phases were separated, and the organic phase was washed with water (3 × 30 mL) and brine (30 mL). After being dried and concentrated *in vacuo*, the reaction mixture was purified by flash chromatography to give compound **9a** as a colorless oil: 4.44 g, 85% yield; R_f = 0.50 (4 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.74 (m, 2H, HC=CH), 4.81 (m, 1H, CHOSi), 2.95 (m, 1H), 2.55 (m,3H), 2.18 (s, 3H, O=CCH_3), 1.23 (ddd, *J* = 13.2 and 6.0 and 5.4 Hz, 1H), 0.89 (s, 9H, *t*-BuSi), 0.06 (s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 207.79, 135.83, 134.41, 76.43, 50.15, 40.71, 39.04, 30.22, 25.78, 18.02, -4.75; IR (neat) 1718 (C=O) cm^{-1}; HRMS m/z calculated for $C_{14}H_{25}O_2Si$ 253.16238, found 253.16260.

Preparation of compound 9b. A mixture of anhydrous propane-1,2-diol (16 mL) and sodium methoxide (343 mg, 6.4 mmol) was heated at 85 °C for 15 min. To this was added compound **8a** (812 mg, 3.2 mmol) and heating was continued for 40 min. The reaction mixture was cooled to room temperature and H_2O (5 mL) was added, and then the reaction mixture was extracted with ether (30 mL × 3). The organic phase was washed with saturated NH_4Cl (20 mL) and brine (20 mL). Concentration, followed by flash chromatography, gave product **9b**: 122 mg, 21% yied; ^{1}H NMR (CDCl3) δ 5.86 (m, 2H), 4.67 (m, 3H), 3.36 (s, 3H), 2.99 (s, 1H), 2.55 (s, 3H), 2.13 (s, 3H), 1.35 (dt, *J* = 13.8 and 7.5 Hz, 1H).

Preparation of compound 10a. To a solution of diisopropylamine (2.93 mL, 21.0 mmol) in 44 mL of THF was added *n*-BuLi (Aldrich, 2.5 M in hexane, 6.99 mL, 17.5 mmol) at -78 °C. The resulting mixture was stirred for 2 min at that temperature. To this was added ketone **9a** (4.42 g, 17.5 mmol) over 10 min under N_2 at -78 °C. The solution was stirred for 1 h, then freshly distilled trimethylsilyl chloride (3.78 mL, 29.7 mmol) was added over 10 min. The solution was allowed to warm to room temperature and stirring was continued for an additional 1 h. The reaction mixture was concentrated under vacuum pressure, then hexane was added and the LiCl solid precipitated was filtered off. After concentration, the residue was purified by vacuum distillation (110 °C/ 0.6 mm Hg) to give compound **10a** as a light yellow oil: 3.1 g, 54% yield; R_f = 0.48 (15 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.83 (m, 1H, HC=C), 5.69 (m, 1H, HC=C), 4.82 (m, 1H, CHOSi), 4.06 (m,2H, C=CH_2), 2.74 (m, 1H), 2.37 (dt, *J* = 13.2 and 7.5 Hz, 1H), 2.18 (dd, *J* = 13.8 and 6.97 Hz, 1H), 2.03 (dd, *J* = 13.8 and 8.1 Hz, 1H), 1.32 (dt, *J* = 13.2 and 6.3 Hz, 1H), 0.90 (s, 9H, *t*-BuSi), 0.21 (s, 9H, $SiMe_3$), 0.08 (s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 158.11, 136.80, 133.99, 90.86, 77.55, 43.47, 41.68, 40.67, 26.05, 18.33, 0.23, -4.47; IR (neat) 2957, 2930, 1252 cm^{-1}: HRMS calculated for $C_{17}H_{13}O_2Si_2$ 326.20974, found 326.20917.

Preparation of compound 10b. To a solution of LDA (0.65 mmol) was added compound **9b** (120 mg, 0.65 mmol) at -78 °C. After stirring for 1 h at that temperature, TMSCl was added at -78 °C. The reaction mixture was warmed to room temperature, and stirring was continued for an additional 2 h. The reaction mixture was concentrated, and then hexane was added and the LiCl solid which precipitated was filtered off. After concentration and flash chromatography using 4 : 1 hexane/EtOAc, compound **10b** was obtained: 96 mg, 57% yield; R_f = 0.52 (4 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.93 (m, 1H, C=CH), 5.80 (m, 1H, HC=C), 4.69 (m, 3H), 4.06 (s, 2H), 3.37 (s, 3H), 2.78 (m, 1H), 2.42 (dt, *J* = 13.8 and 7.5 Hz, 1H), 2.18 (dd, *J* = 13.2 and 6.9 Hz, 1H), 2.04 (m, 1H), 1.44 (dt, *J* = 13.5 and 5.1 Hz, 1H), 0.22 (s, 9H, $SiMe_3$).

Compound 11. R_f = 0.27 (3 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) 6.95 (dd, *J* = 16.2 and 8.7 Hz, 1H, HC=CHCO), 6.12 (d, *J* = 16.2 Hz, 1H, HC=CHCO), 4.29 (m, 1H, CHOSi), 2.94 (m, 2H), 2.69 (m, 1H), 2.59 (m, 4H), 2.25 (m, 3H), 1.65 (m, 1H), 1.10 (t, *J* = 7.2 Hz, 3H, CH_3), 0.85 (s, 9H, *t*-BuSi), 0.02 (s, 6H, $SiMe_2$): ^{13}C NMR ($CDCl_3$) δ 219.57, 200.79, 145.02, 132.05, 78.43, 51.94, 46.32, 44.15, 43.74, 40.16, 38.18, 32.58, 25.74, 18.04,8.22, -4.63; IR (neat) 2955, 1748 (C=O), 1674 (C=O), 1256 cm^{-1}; HRMS m/z 321.18885

[calculated for $C_{18}H_{29}O_3Si$ $(M\text{-}CH_3)^+$, 321.18860].

Preparation of compound 12. In a vial were placed compound **10a** (256 mg, 0.78 mmol), 1-octen-3-one (2.3 mL, 16 mmol), K_2CO_3 (216 mg, 1.6 mmol), NaI (23 mg, 0.16 mmol) and CH_2Cl_2 (2.3 mL). The resulting mixture was stirred for 2 min at room temperature. To this was added $Pd(OAc)_2$ (263 mg, 1.2 mmol), then stirring was continued for 2 h at room temperature. After the reaction mixture was filtered through a silica gel pad using 1 : 1 hexane/EtOAc, it was concentrated under reduced pressure. The residue was purified by flash chromatography with 3 : 1 hexane/EtOAc to give compound **12** as a yellow oil: 179 mg, 62% yield; R_f = 0.21 (3 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.96 (dd, *J* = 16.2 and 8.7 Hz, 1H, HC=CHCO), 6.11 (d, *J* = 16.2 Hz, 1H, HC=CHCO), 4.29 (t, *J* = 3.9 Hz, 1H, CHOSi), 2.94 (m, 2H), 2.70 (m, 1H), 2.61 (m, 1H), 2.53 (dt, J = 2.4 and 7.2 Hz, 2H), 2.30-2.20 (m, 3H), 1.67-1.55 (m, 3H), 1.34-1.22 (m, 5H), 0.88 (t, *J* = 6.3 Hz, 3H, CH_3), 0.85 (s, 9H, *t*-BuSi), 0.01 (s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 219.42, 200.47, 145.08, 132.23, 78.36, 60.30, 51.84, 46.23, 43.67, 40.05, 39.38, 36.10, 31.45, 25.66, 23.93, 22.41, 17.96, 13.90, -4.74; IR (neat) 2957, 2930, 1740 (C=O), 1672 (C=O), 1464, 1364 cm^{-1}; HRMS m/z 377.25070 [calculated for $C_{22}H_{37}O_3Si$ $(M\text{-}H)^+$, m/z 377.25119]; Ammonia CI Mass, m/z 396.3 for $M^+ + NH_4$.

Compound 15. R_f = 0.46 (3 : 1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 1H, HC=C), 5.72 (m, 1H, C=CH), 3.40 (m, 1H), 2.95 (m, 1H), 2.69 (ddt, *J* = 16.5 and 5.1 and 2.4 Hz, 1H), 2.47 (m, 2H), 2.21 (m, 2H), 1.98 (dd, *J* = 18.9 and 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 220.49, 134.07, 130.43, 46.31, 44.93, 42.67, 40.15, 37.12; IR (neat) 2928, 2903, 1742 (C=O), 1402, 1159 cm^{-1}.

Preparation of compound 23. To a solution of $LiAlH_4$ (Aldrich, 1.0 M in THF, 0.6 mL, 0.6 mmol) was added ethanol (2.0 M in THF, 0.3 ml, 0.6 mmol) dropwise over 10 min at room temperature. Subsequently a THF solution of (*S*)-binaphthol (Aldrich, 170 mg in 1 mL of THF, 0.60 mmol) was added dropwise, and the resulting mixture was stirred for 30 min at room temperature, Enone **12** (91 mg, 0.24 mmol) in 1 mL of THF was added dropwise over 3 min at -100 °C (liquid N_2 and methanol bath). The reaction mixture was stirred for 2 h at -100 °C, and then another 2 h at -78 °C. Methanol (1 mL) was added at -78 °C to destroy the excess reducing agent and the reaction 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 HCl, and then extracted with ether (30 mL × 3). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Crude product (247 mg) was obtained. The relative product ratio was calculated using ^{1}H NMR spectroscopy by integration of the following characteristic peaks: compound **12**, 6.09 ppm (d, *J* = 15.9 Hz, C=CH-C=O); compound **21**, 5.77 ppm (dd, *J* = 15.6 and 8.1 Hz, HC=C); compound **22**, 6.06 ppm (d, *J* = 15.6 Hz, C=CH-C=O). The product ratio of compounds **21** and **22** was calculated to be 9 : 1. The crude product was dissolved in 3 mL of THF. To this was added 3 mL of 0.5 N aqueous HCl at room temperature. After stirring for 38 h at room temperature, the mixture was neutralized with 3 N aqueous NaOH. Water (7 mL) was added to the mixture. After extraction with CH_2Cl_2, the organic phase was dried and concentrated. The residue was purified by flash chromatography to give compound **23**: 32 mg, 50% overall yield: R_f = 0.19 (1 : 2 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.72 (dd, *J* = 15.3 and 7.5 Hz, 1H, HC=C), 5.61 (dd, *J* = 15.3 and 6.3 Hz, 1H, C=CH), 4.29 (m, 1H, CHOH), 4.09 (q, *J* = 6.3 Hz, 1H, CHOH), 2.88 (m, 2H), 2.68 (dt, *J* = 4.5 and 7.5 Hz, 1H), 2.61-2.51 (m, 2H), 2.32-2.20 (m, 3H), 2.03 (br s, 2H, OH's), 1.61 (dt, *J* = 14.4 and 3.0 Hz, 1H), 1.50 (m, 2H), 1.29 (m, 6H), 0.88 (t, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 221.40, 136.80, 128.41, 76.83, 72.91, 51.17, 46.38, 42.20, 40.49, 37.33, 36.97, 31.73, 25.15, 22.60, 14.05 (one aliphatic carbon is missing due to overlap); IR (neat) 3404 (OH), 2930, 1734 (C=O), 1458 cm^{-1}; HRMS m/z calculated for $C_{16}H_{26}O_3$ 266.18819, found 266.18851.

Compound 25. R_f = 0.31 (1 : 2 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.14 (dd, *J* = 16.2 and 7.8 Hz, 1H, HC=CHCO), 6.69 (d, *J* = 16.2 Hz, 1H, C=CH-C=O), 4.32 (m, 1H, CHOH), 4.25 (m, 1H, CHOH), 3.20 (br s, 1H, OH), 2.72 (m, 4H), 2.59 (t, *J* = 7.8 Hz, 2H, O=CCH_2), 2.25 (ddd, *J* = 15.0 and 7.5 and 5.7 Hz, 1H), 2.14 (ddd, *J* = 13.8 and 8.4 and 5.7 Hz, 1H), 1.98 (m, 1H), 1.88-1.79 (m, 2H), 1.62 (m, 2H), 1.31 (m, 5H), 0.89 (t, J = 6.6 Hz, 3H, CH_3).

Typical procedure for the reactions in Table 1. In a vial were placed compound **10a** (98 mg, 0.30 mmol), ethyl vinyl ketone (504 mg, 6.0 mmol), NaOAc (82 mg, 0.6 mmol), NaI (9 mg, 0.06 mmol) and THF (1.8 mL). The resulting mixture was stirred for 5 min at room temperature, then $Pd(OAc)_2$ (81 mg, 0.36 mmol) was added. After stirring for 2 h at room temperature, the reaction mixture was filtered through a silica gel pad. Concentration, followed by flash chromatography, gave compounds **9a**, **11**, and **15**.

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