# A HIGHLY STEREOSELECTIVE SYNTHESIS OF METHOXYCARBONYL-SUBSTITUTED EXOCYCLIC ENOL ETHERS: A SYNTHESIS OF 5-METHOXYCARBONYLPROSTACYCLIN†

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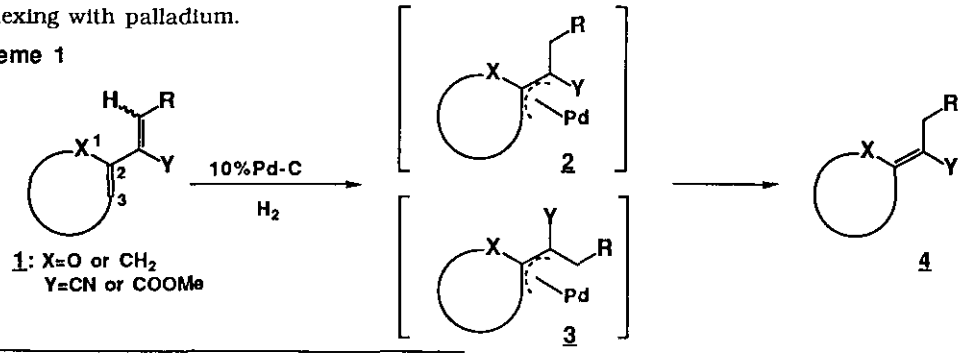
**Abstract**—Treatment of the diene **9** with a catalytic amount of 10% Pd-C in toluene at -50 °C under $H_2$ (1 atm) afforded the *E*-methoxycarbonyl-substituted exocyclic enol ether **10E** in a highly stereoselective manner (*E*:*Z*=41:1, 98%). **10E** was successfully transformed into 5-methoxycarbonylprostacyclin (**5**).

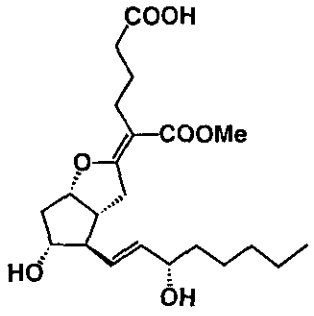
Recently we have established a general method for the stereoselective synthesis of exocyclic tetrasubstituted enol ethers and olefins **4** as shown in Scheme 1.[1] This method involves the stereocontrolled reduction-isomerization of endocyclic olefins having a 1'-cyano-1'-alkenyl or 1'-methoxycarbonyl-1'-alkenyl functionality at C-2 as a key step. Namely, treatment of **1** with a catalytic amount of 10% Pd-C in toluene under hydrogen (1 atm) provided exocyclic tetrasubstituted enol ethers or olefins **4** in a highly stereoselective manner. The stereoselectivity is ascribed to the selective formation of π-allyl intermediates **2**, which are believed to be more stable than **3** for the electronic and/or steric reasons. In **2** a cyano or methoxycarbonyl functionality is capable of complexing with palladium.

**Scheme 1**




†Dedicated to the late Professor Tetsuji Kametani.

Recently Schering chemists reported a stereoselective synthesis of 5-methoxycarbonylprostacyclin (**5**), which consists of chlorosulfonyl isocyanate addition to an enol ether followed by hydrolysis and esterification.[2] We describe herein a completely different synthesis of **5** by the use of the reduction-isomerization reaction of the conjugated diene **9** as a key step.

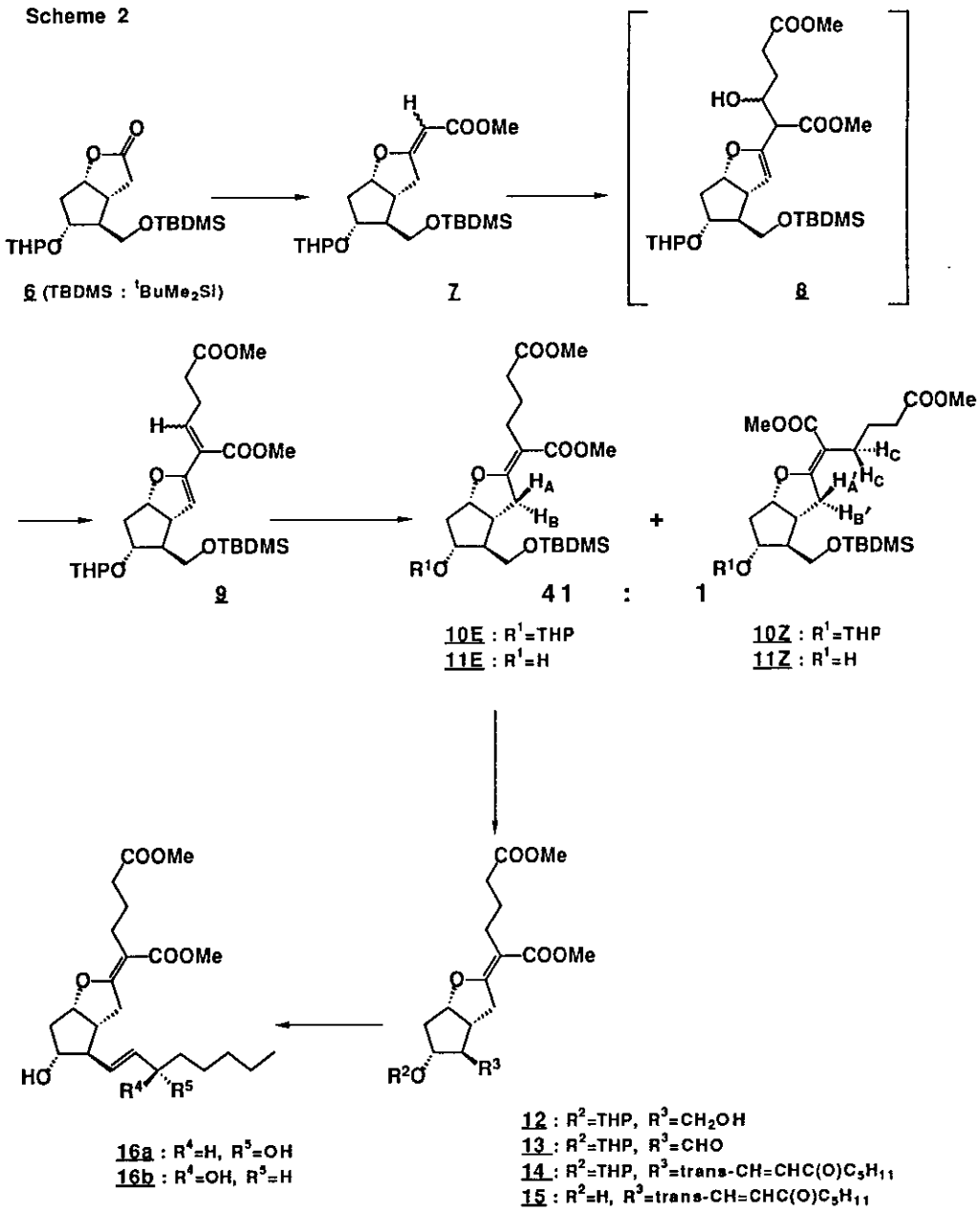



**5**

The requisite diene **9** for the reduction-isomerization reaction was synthesized from the Corey lactone (**6**) as follows. Treatment of **6** with the lithium enolate of methyl (trimethylsilyl)acetate afforded the α,β-unsaturated ester **7** in 49% yield as a mixture of the stereoisomers (*E*:*Z*=1.7:1). The α,β-unsaturated ester **7** was further treated with LDA followed by addition of methyl 3-formylpropionate,[3] giving a mixture of the aldols **8**, which was directly treated with methanesulfonyl chloride and triethylamine in methylene chloride at -30 °C to afford the diene **9** in 60% yield (*E*:*Z*=1.6:1). When the elimination reaction was carried out at higher temperature, formation of the by-products was observed, decreasing the yield of **9**.

With the requisite diene **9** in hand, the reduction-isomerization reaction was carefully investigated. Treatment of the diene **9** with a catalytic amount of 10% Pd-C in toluene under 1 atm of $H_2$ pressure (-50 °C, 5.7 h) provided the desired *E*-exocyclic enol ether **10E** in a highly stereoselective manner (*E*:*Z*=41:1, 98%). Stereoselectivity was determined by hplc analysis (LiChrosorb Si 60 (5μm)), and the stereochemistry was unequivocally assigned from the $^1H$ nmr spectra of **11E** and **11Z** derived from **10E** and **10Z** on exposure to diethylaluminum chloride (*COSY and NOE*).[4] Namely, the allylic protons ($H_A$ and $H_B$) in **11E** possessed a chemical shift value of δ 3.03 (dd) and δ 3.50 (dd) owing to the presence of a *cis*-methoxycarbonyl functionality, while $H_{A'}$ and $H_{B'}$ possessed δ 2.48 (m) and δ 2.72 (dd). Furthermore, irradiation of $H_{A'}$ in **11Z** showed an enhancement of $H_C$ and irradiation of $H_C$ showed an enhancement of $H_{A'}$. As anticipated,[1] the reduction-isomerization reaction of **9** at higher temperature lowered the stereoselectivity (-30 °C→*E*:*Z*=34:1 (98%), -10 °C→*E*:*Z*=24:1 (95%)),

Scheme 2


THPO
OTBDMS
COOMe
HO
H
6 (TBDMS : $^tBuMe_2Si$)
7
8
9
41 : 1
10E : R1=THP
11E : R1=H
10Z : R1=THP
11Z : R1=H
12 : R2=THP, R3=CH2OH
13 : R2=THP, R3=CHO
14 : R2=THP, R3=trans-CH=CHC(O)C5H11
15 : R2=H, R3=trans-CH=CHC(O)C5H11
16a : R4=H, R5=OH
16b : R4=OH, R5=H

and the reaction in methanol at -10 °C resulted in the formation of *E*:*Z*=5.5:1 (98%). Furthermore, we confirmed that **10E** and **10Z** did not undergo isomerization under the reduction-isomerization conditions, indicating that the above stereoselectivity is ascribed to the stability difference between the two π-allyl intermediates.[5]

Exposure of **10E** to tetrabutylammonium fluoride gave the alcohol **12** (100%), which was further oxidized with $SO_3$•Py complex in DMSO containing triethylamine to furnish the aldehyde **13**. Treatment of **13** with the β-keto phosphonate anion provided the α,β-unsaturated ketone **14** in 85% yield from **12.** After deprotection of the THP group (81%), the hydroxy-enone **15** underwent reduction with the reagent derived from diisobutylaluminum hydride and 2,6-di-*tert*-butyl-4-methylphenol,[6] giving the more polar α-isomer **16a** (81%) together with the less polar β-isomer **16b** (12%). The α-isomer **16a** was finally hydrolyzed by treatment with NaOH in aqueous methanol to afford 5-methoxycarbonylprostacyclin (**5**) as a colorless viscous oil (74%), whose spectral data were identical with those of an authentic material.[2]

In conclusion, we have achieved a highly stereoselective synthesis of 5-methoxycarbonylprostacyclin (**5**) by the use of the stereoselective reduction-isomerization reaction of conjugated dienes as a key step. Ar•$Cr(CO)_3$ catalyzed 1,4-hydrogenation reaction of **9** should give **10Z** in a stereocontrolled manner. Therefore, now, from the diene **9** both the *E*- and *Z*-exocyclic enol ethers can be synthesized stereoselectively depending on the conditions.

ACKNOWLEDGMENTS

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**EXPERIMENTAL**

Ir spectra were measured on a JASCO A-300 infrared spectrophotometer. $^1H$ Nmr spectra were recorded with a JEOL JNM-FX100 or JEOL JNM-GX 270 NMR spectrometer with tetramethylsilane as an internal standard. Low-resolution ms spectra and high resolution ms spectra were obtained from a JEOL JMS-DX 303 mass spectrometer. Optical rotation was measured on a JASCO DIP-370 digital polarimeter. Melting points were determined using an Ishii melting point apparatus and are uncorrected.

In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned.

**(1*S*, 5*R*, 6*S*, 7*R*)-6-(*tert*-Butyldimethylsilyloxymethyl)-3-methoxycarbonylmethylidene-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octane 7.** To a stirred solution of LDA prepared from diisopropylamine (4.15 ml, 30 mmol) and BuLi (1.72 M hexane sol., 17.4 ml, 30 mmol) in THF (60 ml) was added methyl (trimethylsilyl)acetate (4.92 ml, 30 mmol) in THF (20 ml) at -78 °C, and the reaction mixture was stirred at the same temperature for 2 h. To a stirred solution of the Corey lactone (**6**)(3.52 g, 9.5 mmol) in THF (20 ml) was added the lithium enolate in THF (-78 °C), and the reaction mixture was gradually warmed to -25 °C over a period of 6.25 h, quenched with saturated aqueous $NH_4Cl$, and extracted with ether. The extract was successively washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated. The oily residue was purified by silica gel column chromatography to afford the less polar *E*-isomer of **7** (1.26 g, 31%) as a colorless oil and the more polar *Z*-isomer (723 mg, 18%, colorless oil): For the *E*-isomer $^1H$ nmr ($C_6D_6$) δ 0.02, 0.06 (6H, s and s), 0.98 (9H, s), 3.56 (3H, s), 4.41 (1H, m), 4.59, 4.68 (1H, m and m), 5.80 (1H, m); ir (neat) 1740, 1705, 1635, 1435, 1360, 1250 $cm^{-1}$; ms (*m/z*), 411 ($M^+$-$CH_3$), 395 ($M^+$-$OCH_3$), 369 ($M^+$-$^t$Bu), 159, 85 (base peak); hrms ($M^+$) calcd for $C_{22}H_{38}O_6Si$ 426.2438, found 426.2414; For the **Z**-isomer $^1H$ nmr ($C_6D_6$) δ 0.02, 0.04 (6H, s and s), 0.95, 0.97 (9H, s and s), 3.64 (3H, s), 4.56 (1H, m), 4.66 (1H, m), 5.05 (1H, m); ir (neat) 1715, 1695, 1645, 1235, 1200 $cm^{-1}$; ms (*m/z*), 426 ($M^+$), 395 ($M^+$-$OCH_3$), 369 ($M^+$-$^t$Bu), 159, 85 (base peak); hrms ($M^+$) calcd for $C_{22}H_{38}O_6Si$ 426.2437, found 426.2456.

**(1*S*, 5*R*, 6*S*, 7*R*)-6-(*tert*-Butyldimethylsilyloxymethyl)-3-(1,4-dimethoxycarbonyl-1-butenyl)-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]oct-3-ene 9.** To a stirred solution of LDA (1.88 mmol) in THF (8 ml) was added **7** (417 mg, 0.98 mmol) in THF (8 ml) at -78 °C, and the reaction mixture was stirred at the same temperature for 70 min. To this enolate solution was added methyl 3-formylpropionate (272 mg, 2.3 mmol) in THF (8 ml) at -98 °C, and the reaction mixture was stirred at the same temperature for 4 h, quenched with saturated aqueous $NH_4Cl$ (-98 °C), and extracted with ether. The extract was successively washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated. To a stirred solution of the oily residue (657 mg) in $CH_2Cl_2$ (6.5 ml) was successively added triethylamine (5.45 ml, 39.1 mmol) and methanesulfonyl chloride (0.69 ml, 8.92 mmol) at -78 °C, and the reaction mixture was stirred at -30 °C for 25.5 h, quenched with $H_2O$ (-78 °C), extracted with ether. The extract was successively washed with 1% aqueous HCl, $H_2O$, saturated aqueous $NaHCO_3$,

$H_2O$ and brine, dried($Na_2SO_4$), and concentrated. The oily residue was purified by silica gel column chromatography (ether-hexane-$NEt_3$, 25:100:1) to give the less polar *Z*-isomer (117 mg, 23%) as a colorless oil and the more polar *E*-isomer (188 mg, 37%, colorless oil): For the *Z*-isomer $^1H$ nmr ($C_6D_6$) δ *0.04, 0.05, 0.06 0.08 (6H, 4s)*, 0.98, 1.00 (9H, *s and s*), 1.30-2.73 (14H, m), 3.29 (3H, s), 3.45 (3H, s), 3.10-3.65 (4H, m), 3.84 (1H, m), 3.91, 4.09 (1H, ddd and ddd, *J*=6.96, 6.96, 6.96 Hz), 4.66, 4.77 (1H, m and m), 4.82 (1H, m), 5.53, 5.57 (1H, d and d, *J*=2.93 Hz), 6.58, 6.60 (1H, t and t, *J*=7.70 Hz); ir (neat) 1740, 1630, 1440, 1260, 840, 780 $cm^{-1}$; ms (*m/z*), 524 ($M^+$), 493 ($M^+$-$OCH_3$), 435 ($M^+$-THP), 247, 85 (base peak); hrms ($M^+$) calcd for $C_{27}H_{44}O_8Si$ 524.2805, found 524.2820; For the *E*-isomer $^1H$ nmr ($C_6D_6$) δ 0.04, 0.05, 0.06, 0.07 (6H, 4s), 0.97, 0.98 (9H, s and s), 1.00-3.00 (14H, m), 3.31 (3H, s), 3.42 (3H, s), 3.10-3.62 (4H, m), 3.83 (1H, m), 3.94, 4.09 (1H, ddd and ddd, *J*=6.60, 6.60, 6.60 Hz), 4.65, 4.74 (1H, m and m), 4.84 (1H, m), 5.52, 5.54 (1H, d and d, *J*=2.75 Hz), 6.95, 6.96 (1H, t and t, *J*=7.70 Hz); ir (neat) 1730, 1630, 1440, 1250, 840, 780 $cm^{-1}$; ms (*m/z*), 524 ($M^+$), 493 ($M^+$-$OCH_3$), 467 ($M^+$-$^t$Bu), 435 ($M^+$-THP), 85 (base peak); hrms ($M^+$) calcd for $C_{27}H_{44}O_8Si$, 524.2805, found 524.2808.

**(1*S*, 5*R*, 6*S*, 7*R*)-6-(*tert*-Butyldimethylsilyloxymethyl)-3-(1,4-dimethoxycarbonyl-1-butylidene)-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octane 10E and 10Z.** A suspension of 10% Pd-C (10.7 mg, 0.010 mmol) in toluene (2 ml) was stirred at 25 °C for 80 min under hydrogen atmosphere (1 atm). To a cooled (-50 °C) suspension was added **9** (*E*:*Z*=1.6:1, 50.6 mg, 0.097 mmol) in toluene (2 ml), and the reaction mixture was stirred under 1 atm of $H_2$ pressure for 5.7 h (-50 °C). The reaction mixture was filtered through silica gel and washed with ether. The combined filtrates were concentrated to give the oily residue, which was purified by silica gel column chromatography (ether-hexane-$NEt_3$, 200:100:1) to give **10E** (49 mg, 96%) as a colorless oil and more polar **10Z** (1 mg, 2%, colorless oil): For **10E** $^1H$ nmr ($C_6D_6$) δ 0.03, 0.05, 0.06 (6H, 3s), 0.98, 0.99 (9H, s and s), 1.20-2.35 (14H, m), 2.75 (2H, m), 3.10, 3.16 (1H, m and m), 3.34 (1H, m), 3.39-3.65 (3H, m), 3.41 (3H, s), 3.55 (3H, s), 3.82 (1H, m), 4.01, 4.15 (1H, ddd and ddd, *J*=6.23, 6.23, 6.23Hz), 4.43 (1H, m), 4.61, 4.68 (1H, m and m); ir (neat) 1735, 1690, 1620, 1460, 1430 $cm^{-1}$; ms (*m/z*), 526 ($M^+$), 495 ($M^+$-$OCH_3$), 437 ($M^+$-THP), 353, 85 (base peak);hrms ($M^+$) calcd for $C_{27}H_{46}O_8Si$ 526.2962, found 526.2951; For **10Z** $^1H$ nmr ($C_6D_6$) δ 0.06, 0.07 (6H, s and s), 0.98, 0.99 (9H, s and s), 1.20-2.50 (16H, m), 2.59, 2.63 (1H, dd and dd, *J*=9.53, 17.21 Hz), 2.78, 2.86 (1H, dd and dd, *J*=2.20, 17.21 Hz), 3.44-3.50 (3H, m), 3.40 (3H, s), 3.64 (3H, s) , 3.84 (1H, m), 3.90, 4.15 (1H, m and m), 4.61 (1H, m), 4.60, 4.74 (1H, m and m); ir (neat) 1730, 1710, 1680, 1630, 1460,

1430 $cm^{-1}$; ms (*m/z*), 526 ($M^+$), 495 ($M^+$-$OCH_3$), 437 ($M^+$-THP), 353, 159, 85 (base peak), 73; hrms ($M^+$) calcd for $C_{27}H_{46}O_8Si$ 526.2962, found 526.2981.

**(1*S*, 5*R*, 6*S*, 7*R*)-6-(*tert*-Butyldimethylsilyloxymethyl)-(*E*)-3-(1,4-dimethoxycarbonyl-1-butylidene)-7-hydroxy-2-oxabicyclo[3.3.0]octane 11E.** To a stirred solution of **10E** (112 mg, 0.213 mmol) in $CH_2Cl_2$ (4 ml) was added diethylaluminum chloride (1 M hexane sol., 1.7 ml, 1.7 mmol) at -50 °C, and the reaction mixture was stirred at 0 °C for 1.8 h, quenched with saturated aqueous $KHCO_3$ (-70 °C), and extracted with ethyl acetate. The extract was washed with brine, dried ($Na_2SO_4$), and concentrated. The oily residue was purified by silica gel column chromatography (ether-hexane, 2:1) to give **11E** (89.1mg, 95%) as a colorless oil: $^1H$ nmr ($C_6D_6$) δ 0.01 (6H, s), 0.95 (9H, s), 1.69 (1H, m), 1.91 (1H, ddd, *J*=2.57, 6.23, 14.70 Hz), 2.07 (5H, m), 2.35 (2H, m), 2.72 (2H, m), 3.03 (1H, dd, *J*=9.16, 18.6 Hz), 3.31 (1H, dd, *J*=5.86, 9.89 Hz), 3.39 (3H, s), 3.48 (1H, dd, *J*=5.13, 9.89 Hz), 3.50 (1H, dd, *J*=1.10, 18.69 Hz), 3.55 (3H, s), 3.86 (1H, m), 4.30 (1H, ddd, *J*=2.57, 6.23, 6.60 Hz); ir (neat) 3450, 1735, 1690, 1620, 1460, 1430 $cm^{-1}$; ms (*m/z*), 442 ($M^+$), 411 ($M^+$-$OCH_3$), 385 ($M^+$-$^t$Bu), 353 (base peak), 169, 75; hrms ($M^+$) calcd for $C_{22}H_{38}O_7Si$ 442.2387, found 442.2381.

**(1*S*, 5*R*, 6*S*, 7*R*)-6-(*tert*-Butyldimethylsilyloxymethyl)-(*Z*)-3-(1,4-dimethoxycarbonyl-1-butylidene)-7-hydroxy-2-oxabicyclo[3.3.0]octane 11Z.** **11Z** was prepared from **10Z** in 73% yield as a colorless oil by the same procedure as described in the synthesis of **11E**: $^1H$ nmr ($C_6D_6$) δ 0.04 (6H, s), 0.96 (9H, s), 1.74 (1H, m), 2.00 (6H, m), 2.24 (2H, t, *J*=7.14 Hz), 2.47 (2H, m), 2.48 (1H, m), 2.72 (1H, dd, *J*=1.47, 17.22 Hz), 3.38 (1H, dd, *J*=5.49, 9.89 Hz), 3.39 (3H, s), 3.48 (1H, dd, *J*=5.49, 9.89 Hz), 3.62 (3H, s), 3.83 (1H, m), 4.46 (1H, m); ir (neat) 3450, 1740, 1680, 1625, 1460, 1430 $cm^{-1}$; ms (*m/z*), 442 ($M^+$), 411 ($M^+$-$OCH_3$), 385 ($M^+$-$^t$Bu), 353 (base peak), 169, 75; hrms ($M^+$) calcd for $C_{22}H_{38}O_7Si$ 442.2387, found 442.2388.

**(1*S*, 5*R*, 6*S*, 7*R*)-(*E*)-(1,4-Dimethoxycarbonyl-1-butylidene)-6-hydroxymethyl-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octane 12.** To a stirred solution of **10E** (413 mg, 0.79 mmol) in THF (5 ml) was added $Bu_4N^+F^-$ (1.1 M THF sol., 0.97 ml, 1.07 mmol) at 25 °C, and the reaction mixture was stirred at the same temperature for 1 h, quenched with brine, extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The oily residue was purified by silica gel column chromatography (ethyl acetate-hexane, 5:1) to give **12** (323 mg, 100%) as a colorless oil: $^1H$ nmr ($CDCl_3$) δ 1.44-2.26 (10H, m), 2.28-2.76 (6H, m), 2.84-3.28 (2H, m), 3.62 (3H, s), 3.64 (3H, s), 3.40-4.32 (5H, m), 4.66 (2H, m); ir (neat) 3450, 1740, 1700, 1620, 1440, 1280,

1020 $cm^{-1}$; ms (*m/z*), 412 ($M^+$), 381 ($M^+$-$OCH_3$), 296, 85 (base peak); hrms ($M^+$) calcd for $C_{21}H_{32}O_8$ 412.2097, found 412.2068.

**(1S, 5R, 6R, 7R)-(E)-3-(1,4-Dimethoxycarbonyl-1-butylidene)-6-(3-oxo-E-1-octenyl)-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octane 14.** To a stirred solution of **12** (169 mg, 0.41 mmol) in DMSO (1.5 ml) containing $NEt_3$ (0.57 ml, 4.1 mmol) was added $SO_3$•Py complex (654 mg, 4.1 mmol) in DMSO (1.5 ml) at 25 °C, and the reaction mixture was stirred at the same temperature for 0.5 h, quenched with ice-water, extracted with ethyl acetate. The extract was successively washed with $H_2O$ and brine, dried ($MgSO_4$), and concentrated to give **13** (183 mg) as a brown oil. The aldehyde **13** in THF (2.5 ml) was added to the sodium anion of dimethyl (2-oxoheptyl)phosphonate at 0 °C which was prepared from dimethyl (2-oxoheptyl)phosphonate (228 mg, 1.03 mmol) and NaH (60% dispersion in mineral oil, 27.9 mg, 0.70 mmol) in THF (5.5 ml), and the reaction mixture was stirred for 1 h at 25 °C, quenched with saturated aqueous $NH_4Cl$, and extracted with ethyl acetate. The extract was successively washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated. The oily residue was purified by silica gel column chromatography (ethyl acetate-hexane, 1:1) to give **14** (176.5 mg, 85%) as a colorless oil: $^1H$ nmr ($CDCl_3$) $\delta$ 0.96 (3H, t, *J*=6.8 Hz), 1.20-2.20 (14H, m), 2.20-2.82 (8H, m), 3.20 (2H, m), 3.32-4.30 (5H, m), 3.64 (6H, s), 4.59 (1H, m), 4.80 (1H, m), 6.14, 6.22 (1H, d and d, *J*=16.0 Hz), 6.62, 6.72 (1H, dd and dd, *J*=8.0, 16.0 Hz); ir (neat) 1740, 1700, 1680, 1630, 1440, 1280 $cm^{-1}$; ms (*m/z*), 506 ($M^+$), 475 ($M^+$-$OCH_3$), 169, 85 (base peak); hrms ($M^+$) calcd for $C_{28}H_{42}O_8$ 506.2880, found 506.2879.

**(1S, 5R, 6R, 7R)-(E)-(1,4-Dimethoxycarbonyl-1-butylidene)-7-hydroxy-6-(3-oxo-E-1-octenyl)-2-oxabicyclo[3.3.0]octane 15.** The enone **14** (176.5 mg, 0.35 mmol) was dissolved in THF (5 ml) and 65% aqueous $CH_3COOH$ (8 ml), and the reaction mixture was stirred at 60 °C for 5.25 h, neutralized with saturated aqueous $NaHCO_3$, extracted with ethyl acetae. The extract was washed with $H_2O$ and brine, dried ($MgSO_4$), and concentrated. The oily residue was purified by silica gel column chromatography (ether) to give **15** (119 mg, 81%) as a colorless oil: $^1H$ nmr ($CDCl_3$) $\delta$ 0.90 (3H, t, *J*=6.8 Hz), 1.12-2.20 (12H, m), 2.20-2.82 (7H, m), 3.16(2H, m), 3.64 (3H, s), 3.66 (3H, s), 4.05 (1H, ddd, *J*=7.6, 7.6, 7.6 Hz), 4.77 (1H, ddd, *J*=3.1, 6.3, 6.3 Hz), 6.18 (1H, d, *J*=16.0 Hz), 6.68 (1H, dd, *J*=8.0, 16.0 Hz); ir ($CHCl_3$) 3400, 1720, 1690, 1620, 1430, 1320, 1270, 1150 $cm^{-1}$; ms (*m/z*), 422 ($M^+$), 404 ($M^+$-$CH_3$), 391 ($M^+$-$OCH_3$), 291, 222, 169, 99 (base peak); hrms ($M^+$) calcd for $C_{23}H_{34}O_7$ 422.2304, found 422.2315; $[\alpha]^{21}_D$ +4.71 ° (c 1.53, $CHCl_3$).

**(1*S*, 5*R*, 6*R*, 7*R*)-(*E*)-3-(1,4-Dimethoxycarbonyl-1-butylidene)-7-hydroxy-6-(3(*S*)-hydroxy-*E*-1-octenyl)-2-oxabicyclo[3.3.0]octane 16a.** To a stirred solution of 2,6-di-*tert*-butyl-4-methylphenol (831 mg, 3.77mmol) in toluene (4 ml) was added diisobutylaluminum hydride (1 M toluene sol., 2.8 ml, 2.8 mmol) at -20 °C, and the reaction mixture was stirred at the same temperature for 1 h. To the cooled solution was added **15** (119 mg, 0.28 mmol) in toluene (6 ml) at -78 °C, and the reaction mixture was stirred for 1 h at the same temperature and gradually warmed to -10 °C over a period of 3.5 h, quenched with brine, extracted with ethyl acetate. The extract was successively washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated. The oily residue was purified by silica gel column chromatography (ethyl acetate-hexane, 5:1) to give more polar **16a** (97 mg, 81%) as a colorless oil together with less polar **16b** (14 mg, 12%, colorless oil): For **16a** $^1$H nmr ($CDCl_3$) δ 0.88 (3H, t, *J*=6.8 Hz), 1.10-2.72 (20H, m), 3.04 (2H, m), 3.64 (3H, s), 3.65 (3H, s), 3.82 (1H, m), 4.02 (1H, m), 4.70 (1H, ddd, *J*=3.0, 7.0, 7.0 Hz), 5.49 (2H, m); ir (neat) 3400, 1740, 1700, 1620, 1430, 1320, 1280, 1150, 1100, 1090, 1030, 965 cm$^{-1}$; ms (*m/z*), 424 ($M^+$), 406 ($M^+$-$H_2O$), 393 ($M^+$-$OCH_3$), 374, 222, 99, 43 (base peak); hrms ($M^+$) calcd for $C_{23}H_{36}O_7$ 424.2461, found 424.2452; $[\alpha]^{21}_D$ -17.24 ° (*c* 0.852, $CHCl_3$); For **16b** $^1$H nmr ($CDCl_3$) δ 0.90 (3H, t, *J*=6.8 Hz), 1.10-2.64 (21H, m), 3.04 (1H, m), 3.62 (3H, s), 3.65 (3H, s), 3.86 (1H, ddd, *J*=8.3, 8.3, 8.3 Hz), 4.02 (1H, m), 4.72 (1H, ddd, *J*=3.0, 7.0, 7.0 Hz), 5.52 (2H, m); ir (neat) 3400, 1730, 1710, 1620, 1440, 1260, 1090 cm$^{-1}$; ms (*m/z*), 424 ($M^+$), 406 ($M^+$-$H_2O$), 393 ($M^+$-$OCH_3$), 222, 99, 43 (base peak); hrms ($M^+$) calcd for $C_{23}H_{36}O_7$ 424.2461, found 424.2458; $[\alpha]^{21}_D$ -16.94 ° (*c* 1.28, $CHCl_3$).

**5-Methoxycarbonylprostacyclin (5).** To a stirred solution of **16a** (32 mg, 0.075 mmol) in MeOH (2 ml) was added 10% aqueous NaOH (2 ml) at 0 °C, and the reaction mixture was stirred at the same temperature for 15 h, neutralized with 5% aqueous HCl, evaporated to remove methanol, acidified to pH 4 with 5% aqueous HCl, extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The oily residue was purified by silica gel column chromatography (methanol-ethyl acetae, 1:10) to give **5** (23 mg, 74%) as a colorless viscous oil: $^1$H nmr ($CDCl_3$) δ 0.88 (3H, t, *J*=6.80 Hz), 1.85 (4H, m), 2.12 (2H, m), 2.25-2.73 (5H, m), 2.97 (1H, dd, *J*=8.79, 19.05 Hz), 3.21 (1H, dd, *J*=1.10, 19.05 Hz), 3.68 (3H, s), 3.87 (1H, ddd, *J*=8.06, 8.06, 8.06 Hz), 4.07 (1H, dt, *J*=6.60, 6.60 Hz), 4.72 (1H, m), 5.46 (1H, dd, *J*=8.06, 15.02 Hz), 5.60 (1H, dd, *J*=6.96, 15.02 Hz); ir (neat) 3400, 1740, 1700, 1610, 1440, 1240, 1150, 1090, 970 cm$^{-1}$; ms (*m/z*), 410 ($M^+$), 392 ($M^+$-$H_2O$), 379 ($M^+$-$OCH_3$); hrms ($M^+$) calcd for $C_{22}H_{34}O_7$ 410.2304, found 410.2305; $[\alpha]^{21}_D$ -35.96 ° (*c* 1.18, $CHCl_3$); When kept in a refrigerator, **5** solidified as a colorless powder of mp 108-111.5 °C.

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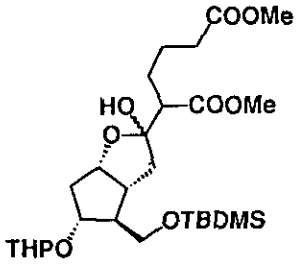


**i**

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