The Regioselective Dehydration of Unsymmetrical Secondary Alcohols under Mitsunobu's Reaction Conditions

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Dehydration of the four diastereomers of tetrahydropyran 8—11 involving the 4-hydroxyl and 5-methyl groups with diethylazodicarboxylate–PPh_3–toluene was undertaken to clarify the relation between the configurations of these substituents and the direction of dehydration. Compound 8 with 4β(equatorial)-hydroxyl and 5β(axial)-methyl groups was found to give the trisubstituted olefin 12 exclusively, and the isomers 13 and 14 were shown to be produced from 9 and 11, respectively, with high selectivity. The mechanisms involved are discussed.

Keywords regioselective dehydration; Mitsunobu's reagent; tetrahydropyran; dihydropyran; venturicidin

In the course of our synthetic studies of venturicidins A and B, we designed a strategy for constructing the bottom half (**2**) of the molecules, involving the multi-substituted dihydropyran moiety, based on its presumed biogenetic pathway.[1] The crucial stage in this strategy is apparently a regioselective dehydration of the secondary alcohol at the 4-position in the precursor tetrahydropyran **1**, producing the trisubstituted double bond. In the process of synthetic studies of the taxane ring skeleton, we have found[2] that the 4β-hydroxy-5β-methylcyclohexane derivative **3** having large equatorial substituents at the 2- and 6-positions is selectively dehydrated to give **4** under Mitsunobu's reaction conditions.[3] Based on this unexpected observation, we carried out detailed studies to clarify the relation between the configurations of the 4-hydroxyl and 5-methyl groups and the direction of dehydration using model compounds **8**, **9**, **10** and **11** (all the possible diastereomers with respect to the 4- and 5-positions).

Tetrahydropyrans **8**—**11** were synthesized starting from (±)-*syn*- and (±)-*anti*-α-methyl-β-hydroxy ester **5**[4] and **6** as shown in Chart 2. After protection of the secondary hydroxyl group of *syn*-**5**, the ester group was transformed into an aldehyde in 2 steps: 1) $LiAlH_4$, 2) pyridinium dichromate (PDC)/Zeolite 3A. The resulting aldehyde was condensed with the dianion of methyl acetoacetate to give a mixture of alcohols **7**, which was treated with $CH(OMe)_3$ in the presence of camphorsulfonic acid (CSA), producing the 5β-methyl-4β-hydroxytetrahydropyran **8** and its 4α-hydroxyl isomer **9** in 16% and 20% yields from **5**, respectively. The other diastereomers **10** and **11** having the 5α-methyl group were synthesized from (±)-*anti*-**6** by the same procedure as described for the 5β-methyl derivatives in 13% and 33% yields, respectively. The stereochemistry of these isomers was confirmed as follows. The *syn* relationship of the side chains at the 2- and 6-positions of the tetrahydropyran ring was confirmed by nuclear Overhauser effect (NOE) measurement. Namely, upon irradiation of the 6α-proton in each compound, NOE was observed at the 2-OMe group: **8**, 5.4%; **9**, 6.1%; **10**, 5.4%; **11**, 4.1%. Furthermore, the configurations of the hydroxyl groups (axial for **9** and **10** and equatorial for **8** and **11**) were determined from the coupling constant between the 3-methylene and 4-methine protons (**8**, $J_{3\beta,4\alpha}=11.6$ Hz, $J_{3\alpha,4\alpha}=5.1$ Hz; **9**, $J_{3,4}=2.8$, 3.6 Hz; **10**, $J_{3,4}=3.0$, 3.8 Hz, **11**, $J_{3\beta,4\alpha}=11.0$ Hz, $J_{3\alpha,4\alpha}=4.7$ Hz).

Dehydration of these alcohols was then examined. Initially, dehydration with $(CF_3SO_2)_2O$[5]/2,6-di-*tert*-butylpyridine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was attempted, but the yields of olefins were extremely poor in every case. On the other hand, when alcohols were treated

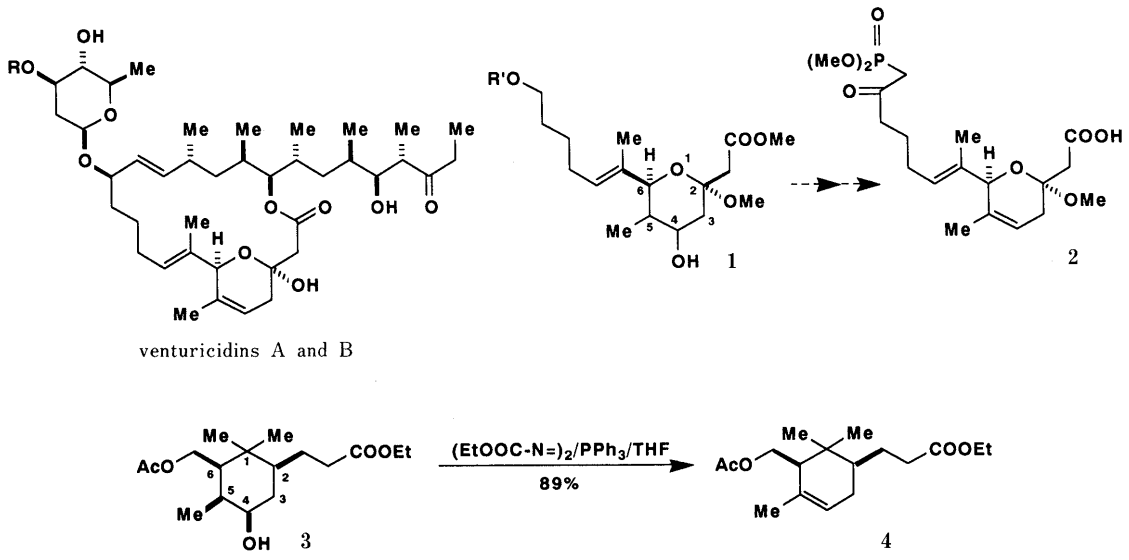


Chart 1

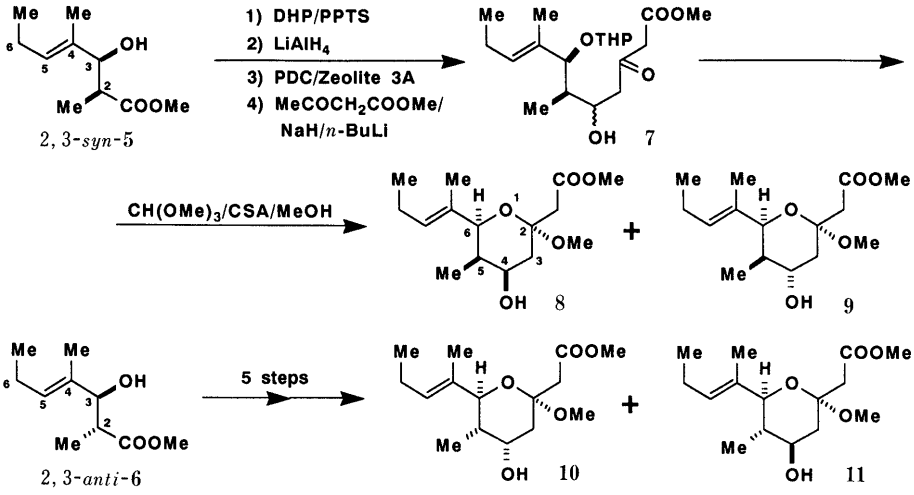


Chart 2

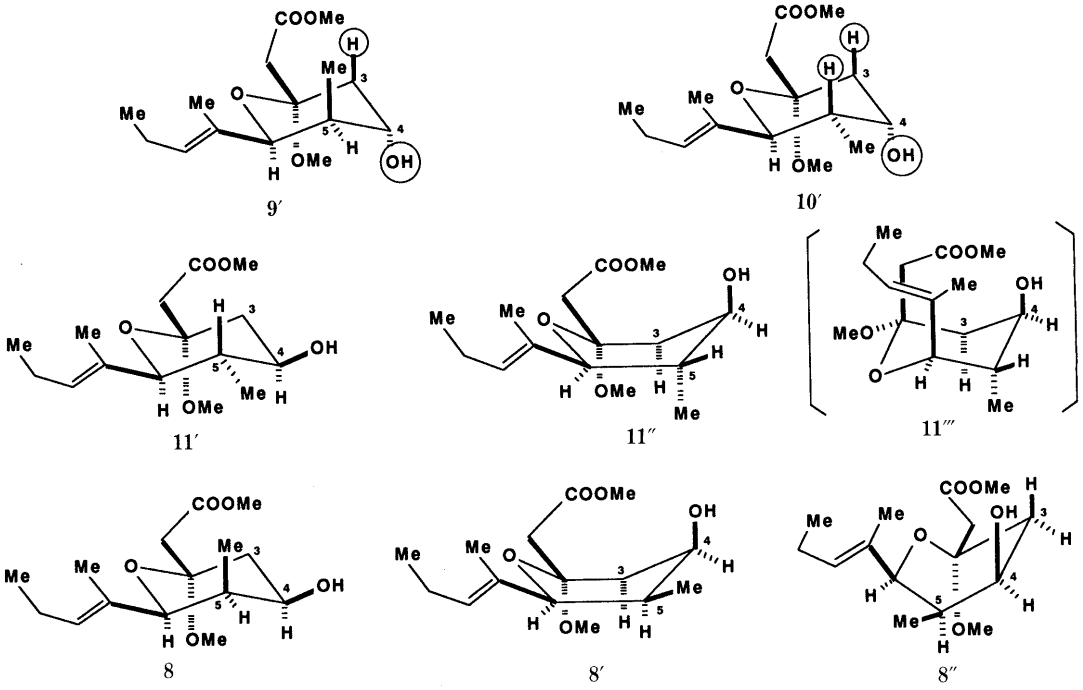


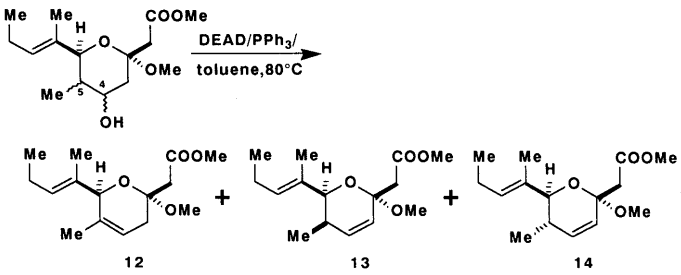
Chart 3

with diethylazodicarboxylate (DEAD) and PPh_3 in toluene at 80 °C, as previously used for the dehydration of **3**,[2] olefins were produced. In every case, after the spot due to the starting materials (**8**—**11**) was no longer detectable on thin layer chromatography (TLC), the reaction mixtures were chromatographed on silica gel to separate the less polar dehydration products (**12**—**14**) and the more polar complex mixtures. The results are shown in Table I. It should be emphasized that here again the trisubstituted olefin **12** was produced preferentially from **8** having the same 4β(equatorial)-hydroxyl and 5β(axial)-methyl structure as **3**.

The elimination reaction under Mitsunobu's reaction conditions seems to proceed through an *E*2 (not *E*1) mechanism, since the substitution reaction with the same reagent system usually takes place with complete inversion of configuration.[3] The 4-hydroxyl group to be eliminated is presumed to be converted to a quaternary phosphonium salt of phosphorane[6] and this activated hydroxyl group and the hydrogen atom at the adjacent 3- or 5-positions should be *anti* periplanar for a facile elimination to take place. Both **9**(**9′**) and **10**(**10′**) satisfy this requirement. In fact, **9** produced **13** exclusively in 82% yield. However, although **10** afforded a mixture of **12** and **14** (ratio, 1 : 3, respectively),[7] the total yield was only 28%. The reason for this is not clear. In the case of **11**(**11′**) where the hydroxyl and methyl groups are both equatorial, the reaction proceeded much more slowly than in the former cases,[8] but **14** was obtained as a sole product in 42% yield. In the transition state, when the tetrahydropyran ring flips to a boat form such as **11″** or another chair form **11‴**, the resultant quasi-axial 4β-hydroxyl group can be *anti* periplanar only with the hydrogen atom at the 3-position, which may account for the preferential formation of $\Delta^{3(4)}$**14**.

On the other hand, the 4β(equatorial)-alcohol **8** with the

TABLE I. Dehydration under Mitsunobu's Reaction Conditions



Entry	4-OH	5-Me	12	13	14
1	**8**: β (equatorial)	β (axial)	42%		
2	**9**: α (axial)	β (axial)		82%	
3	**10**: α (axial)	α (equatorial)	7%		21%
4	**11**: β (equatorial)	α (equatorial)			42%

axial methyl group at the 5-position afforded exclusively **12**, a regioisomer of **13** and **14**. In this case, the intermediacy of **8'** (corresponding to **11''**) seems to be ruled out, because the same product distribution as observed in entry 3 (*cf.* **10'**) should result from this conformer. A plausible explanation for this regioselective reaction is that elimination takes place from conformer **8''** in which only the 5α-hydrogen atom can be *anti* periplanar with respect to the 4-hydroxyl group. However, a more quantitative explanation why **8''** is preferred over other conformers is desirable.

Dehydration under Mitsunobu's reaction conditions is reported to take place with hydroxyl compounds having an acidic hydrogen atom adjacent to the hydroxyl group.[3] However, dehydration proceeded in the present compounds and **3**, where the hydrogen atom to be eliminated is not particularly activated. The mechanism of DEAD–PPh_3-induced dehydration is presumed to be more complex than had been supposed. The scope of the dehydration under these conditions should be investigated further.

From the model experiments thus far discussed, it became apparent that the minimum requirement for the desired regioselective dehydration giving more substituted olefins was the 4β(equatorial)-hydroxyl group and the 5β(axial)-methyl group in the tetrahydropyran skeleton **1**. This remarkable finding was successfully applied to the synthesis of the bottom half (**2**) of venturicidins from the precursor **1**, which will be reported elsewhere.

Experimental

Physical data were measured as follows. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-GSX 400 (400 MHz) instrument. Mass spectra (MS) were taken on a Hitachi M-80. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer.

Methyl (2*R,3*R**)-3-Hydroxy-2,4-dimethyl-4-heptenoate (5) and Methyl (2*R**,3*S**)-3-Hydroxy-2,4-dimethyl-4-heptenoate (6)** Activated Zn powder (9.52 g) was added to a solution of 2-methyl-2-pentenal (9.51 g) and methyl 2-bromopropionate (19.45 g) in benzene (100 ml) and the mixture was stirred for 1.5 h at reflux. The reaction mixture was poured into 10% aqueous HCl and extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The residue was chromatographed on a silica gel column with hexane–AcOEt (49 : 1 to 80 : 20) to provide the less polar fraction **5** (7.06 g, 39%) and the more polar fraction **6** (9.94 g, 55%). (±)-**5**: *Anal.* high-resolution MS Calcd for $C_{10}H_{18}O_3$ (M^+, *m/z*): 186.125. Found: 186.125. IR (CCl_4): 3620, 3520, 1735, 1720 cm^{-1}. NMR ($CDCl_3$) δ: 0.96 (3H, t, *J*=7.6 Hz, 6-Me), 1.15 (3H, d, *J*=7.1 Hz, 2-Me), 1.59 (3H, br s, 4-Me), 2.04 (2H, quintette, *J*=7.3 Hz, 6-H_2), 2.69 (1H, dq, *J*=7.1, 7.1 Hz, 2-H), 3.67 (3H, s, COOMe), 4.24 (1H, m, 3-H), 5.46 (1H, br t, *J*=7.1 Hz, 5-H). (±)-**6**: *Anal.* high-resolution MS Calcd for $C_{10}H_{18}O_3$ (M^+, *m/z*): 186.125. Found: 186.126. IR (neat): 3450, 1725, 1710 (sh) cm^{-1}. NMR ($CDCl_3$) δ: 0.97 (3H, t, *J*=7.6 Hz, 6-Me), 1.03 (3H, d, *J*=7.3 Hz, 2-Me), 1.60 (3H, br s, 4-Me), 2.05 (2H, quintette, *J*=7.3 Hz, 6-H_2), 2.66 (1H, dq, *J*=9.2, 7.3 Hz, 2-H), 3.72 (3H, s, COOMe), 4.08 (1H, d, *J*=9.2 Hz, 3-H), 5.44 (1H, br t, *J*=7.0 Hz, 5-H).

Methyl [(2*R,4*R**,5*R**,6*S**)-Tetrahydro-4-hydroxy-2-methoxy-5-methyl-6-(1-methyl-(*E*)-1-butenyl)-2*H*-pyran-2-yl]acetate (8) and Methyl [(2*R**,4*S**,5*R**,6*S**)-Tetrahydro-4-hydroxy-2-methoxy-5-methyl-6-(1-methyl-(*E*)-1-butenyl)-2*H*-pyran-2-yl]acetate (9)** 1) A solution of *syn*-**5** (5.08 g), dihydropyran (3.45 g) and pyridinium *p*-toluene sulfonate (PPTS) (0.64 g) in CH_2Cl_2 (40 ml) was stirred for 2.5 h at room temperature, then poured into water. The organic layer was separated and the aqueous layer was extracted with ether. Each organic layer was washed with brine. The combined extract was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude tetrahydropyran (THP) ether (7.34 g).

2) The crude THP ether (7.34 g) in ether (20 ml) was added to a suspension of $LiAlH_4$ (0.93 g) in ether (100 ml) under ice-cooling and the mixture was stirred for 2 h at room temperature. After successive addition of water (0.9 ml), 15% aqueous NaOH (0.9 ml) and water (2.8 ml) under ice-cooling, the mixture was stirred for 10 min at room temperature and then $MgSO_4$ was added. The resulting suspension was filtered and the filtrate was concentrated *in vacuo* to give the crude alcohol (6.61 g).

3) A solution of the crude alcohol (2.04 g) and PDC (6.05 g), in CH_2Cl_2 (40 ml) with powdered Zeolite 3A (6 g) was stirred at room temperature under an argon atmosphere. After 1.5 h, ether (150 ml) was added to the reaction mixture. The resulting suspension was filtered with the aid of Florisil (50 g) and Celite, and the filter pads were washed with ether. The filtrate and washing were combined and evaporated *in vacuo* to give the crude aldehyde (1.69 g).

4) Methyl acetoacetate (1.13 ml) was added to a suspension of 60% NaH (435 mg) in tetrahydrofuran (THF) (25 ml) at 5 °C under an argon atmosphere, and the mixture was stirred for 15 min. Then a 1.5 M solution of *n*-BuLi in hexane (7.3 ml) was added to the above solution and the mixture was stirred for a further 20 min. A solution of the crude aldehyde (1.69 g) in THF (5 ml) was added to the above reaction mixture under dry ice/acetone cooling and the whole was stirred for 20 min at the same temperature, then poured into saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude aldol product (2.75 g).

5) CSA (172 mg) was added to a solution of the crude aldol product (2.75 g) and trimethyl orthoformate (6 ml) in MeOH (25 ml), and the mixture was stirred at room temperature. After 1 h, the mixture was poured into dilute aqueous $NaHCO_3$ under ice-cooling and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The residue was chromatographed on a silica gel column with hexane–AcOEt (90 : 10 to 75 : 25) to provide the less polar fraction **9** (495 mg, 21% from **5**) as a colorless oil and the more polar fraction **8** (388 mg, 16% from **5**) as a colorless oil. (±)-**9**: *Anal.* high-resolution MS Calcd for $C_{15}H_{24}O_4$ ($M^+ - H_2O$): 268.167. Found: 268.168. IR (neat): 3500, 1730 cm^{-1}. NMR (C_6D_6) δ: 0.68 (3H, d, *J*=7.3 Hz, 5-Me), 0.96 (3H, t, *J*=7.5 Hz, prim.-Me), 1.47 (3H, br s, olefinic-Me), 2.00 (1H, dd, *J*=2.8, 14.6 Hz, 3-H), 2.20 (1H, dd, *J*=3.6, 14.6 Hz, 3-H), 2.42 (1H, d, *J*=13.7 Hz, methylene-H), 2.48 (1H, d, *J*=13.7 Hz, methylene-H), 2.90 (3H, s, 2-OMe), 3.32 (3H, s, COOMe), 3.86 (1H, m, 4-H), 4.43 (1H, br s, 6-H), 5.70 (1H, br t, *J*=7.5 Hz, olefinic-H). (±)-**8**: *Anal.* high-resolution MS Calcd for $C_{15}H_{24}O_4$ ($M^+ - H_2O$): 268.167. Found: 268.166. IR (neat): 3400, 1740 cm^{-1}. NMR (C_6D_6) δ: 0.84 (3H, d, *J*=6.9 Hz, 5-Me), 0.97 (3H, t, *J*=7.5 Hz, prim.-Me), 1.43 (3H, br s, olefinic-Me), 2.02 (1H, dd, *J*=11.6, 13.0 Hz, 3-H), 2.12 (1H, ddd, *J*=0.5, 5.1, 13.0 Hz, 3-H), 2.60 (2H, s, methylene-H_2), 3.05 (3H, s, 2-OMe), 3.35 (3H, s, COOMe), 3.94 (1H, br s, 6-H), 4.16 (1H, m, 4-H), 5.72 (1H, br t, *J*=7.3 Hz, olefinic-H).

Methyl [(2*R,4*S**,5*S**,6*S**)-Tetrahydro-4-hydroxy-2-methoxy-5-methyl-6-(1-methyl-(*E*)-1-butenyl)-2*H*-pyran-2-yl]acetate (10) and Methyl [(2*R**,4*R**,5*S**,6*S**)-Tetrahydro-4-hydroxy-2-methoxy-5-methyl-6-(1-methyl-(*E*)-1-butenyl)-2*H*-pyran-2-yl]acetate (11)** In the same manner as described for the synthesis of **8** and **9**, **10** (160 mg, 13% from *anti*-**6** (803 mg), colorless oil) and **11** (409 mg, 33% from *anti*-**6** (803 mg), colorless oil) were obtained. Less polar fraction (±)-**10**: *Anal.* high-resolution MS. Calcd for $C_{14}H_{22}O_4$ (M^+ −MeOH): 254.151. Found: 254.151. IR(neat): 3520, 1730 cm^{-1}. NMR (C_6D_6) δ: 0.90 (3H, t, *J*=7.5 Hz, prim.-Me), 0.95 (3H, d, *J*=6.9 Hz, 5-Me), 1.59 (3H, br s, olefinic-Me), 1.98 (1H, dd, *J*=3.8,

14.4 Hz, 3-H), 2.32 (1H, dd, $J=3.0$, 14.4 Hz, 3-H), 2.43 (1H, d, $J=13.8$ Hz, methylene-H), 2.49 (1H, d, $J=13.8$ Hz, methylene-H), 2.96 (3H, s, 2-OMe), 3.30 (3H, s, COOMe), 3.78 (1H, m, 4-H), 3.88 (1H, d, $J=10.8$ Hz, 6-H), 5.36 (1H, br t, $J=7$ Hz, olefinic-H). More polar fraction (±)-**11**: *Anal.* high-resolution MS Calcd for $C_{14}H_{22}O_4$ ($M^+ -MeOH$): 254.151. Found: 254.150. IR (neat): 3400, 1740 cm^{-1}. NMR (C_6D_6) δ: 0.87 (3H, d, $J=6.5$ Hz, 5-Me), 0.88 (3H, t, $J=7.5$ Hz, prim.-Me), 1.61 (3H, br s, olefinic-Me), 1.80 (1H, dd, $J=11.0$, 12.8 Hz, 3-H), 2.46 (1H, dd, $J=4.7$, 12.8 Hz, 3-H), 2.55 (1H, d, $J=13.7$ Hz, methylene-H), 2.67 (1H, d, $J=13.7$ Hz, methylene-H), 3.14 (3H, s, 2-OMe), 3.33 (3H, s, COOMe), 3.58 (1H, d, $J=10.3$ Hz, 6-H), 3.70 (1H, m, 4-H), 5.33 (1H, br t, $J=7$ Hz, olefinic-H).

Dehydration of 8 under Mitsunobu's Reaction Conditions; Synthesis of Methyl [(2*R,6*S**)-2,3-Dihydro-2-methoxy-5-methyl-6-(1-methyl-(*E*)-1-butenyl)-6*H*-pyran-2-yl]acetate (12)** Diethylazodicarboxylate (0.19 ml) was added to a solution of **8** (81 mg) and PPh_3 (314 mg) in toluene (5 ml, degassed and under argon) at room temperature, then the mixture was heated for 1 h at 80 °C. After cooling to room temperature, the reaction mixture was directly loaded on a silica gel column and chromatographed with hexane–ether (100 : 0 to 80 : 20) to give **12** (32 mg, 42%) as a colorless oil. (±)-**12**: *Anal.* high-resolution MS Calcd for $C_{14}H_{20}O_3$ ($M^+ -MeOH$): 236.141. Found: 236.140. IR (CCl_4): 1735, 1700 (sh), 1630 cm^{-1}. NMR (C_6D_6) δ: 0.88 (3H, t, $J=7.6$ Hz, prim.-Me), 1.46 (3H, br s, 5-Me), 1.59 (3H, br s, olefinic-Me), 2.63 (1H, d, $J=13.7$ Hz, methylene-H), 2.74 (1H, d, $J=13.7$ Hz, methylene-H), 3.27 (3H, s, 2-OMe), 3.32 (3H, s, COOMe), 4.39 (1H, br s, 6-H), 5.41 (1H, br t, $J=7$ Hz, olefinic-H), 5.44 (1H, m, 4-H).

Dehydration of 9 under Mitsunobu's Reaction Conditions; Synthesis of Methyl [(2*R,5*R**,6*S**)-5,6-Dihydro-2-methoxy-5-methyl-6-(1-methyl-(*E*)-1-butenyl)-2*H*-pyran-2-yl]acetate (13)** **9** (84 mg) was subjected to dehydration under the same conditions as described for **8** to afford **13** (65 mg, 82%) as a colorless oil. (±)-**13**: *Anal.* high-resolution MS Calcd for $C_{14}H_{20}O_3$ ($M^+ -MeOH$): 236.141. Found: 236.140. IR(CCl_4): 1740, 1700, 1640 cm^{-1}. NMR (C_6D_6) δ: 0.77 (3H, d, $J=7.0$ Hz, 5-Me), 0.97 (3H, t, $J=7.5$ Hz, prim.-Me), 1.40 (3H, br s, olefinic-Me), 2.73 (1H, d, $J=13.4$ Hz, methylene-H), 2.84 (1H, d, $J=13.4$ Hz, methylene-H), 3.22 (3H, s, 2-OMe), 3.34 (3H, s, COOMe), 4.38 (1H, br s, 6-H), 5.80 (1H, dd, $J=5.9$, 9.9 Hz, 3-H or 4-H), 6.21 (1H, dd, $J=1.2$, 9.9 Hz, 3-H of 4-H).

Dehydration of 11 under Mitsunobu's Reaction Conditions; Synthesis of Methyl [(2*R,5*S**,6*S**)-5,6-Dihydro-2-methoxy-5-methyl-6-(1-methyl-(*E*)-1-butenyl)-2*H*-pyran-2-yl]acetate (14)** **11** (83 mg) was subjected to dehydration under the same condition as described for **8** to afford **14** (33 mg, 42%) as a colorless oil. (±)-**14**: *Anal.* high-resolution MS Calcd for $C_{14}H_{20}O_3$ ($M^+ -MeOH$): 236.141. Found: 236.140. IR(CCl_4): 1735, 1640 cm^{-1}. NMR (C_6D_6) δ: 0.70 (3H, d, $J=7.3$ Hz, 5-Me), 0.87 (3H, t, $J=7.5$ Hz, prim.-Me), 1.66 (3H, br s, olefinic-Me), 2.74 (1H, d, $J=13.7$ Hz, methylene-H), 2.85 (1H, d, $J=13.7$ Hz, methylene-H), 3.27 (3H, s, 2-OMe), 3.34 (3H, s, COOMe), 3.90 (1H, d, $J=10.1$ Hz, 6-H), 5.36 (1H, br t, $J=7$Hz, olefinic-H), 5.64 (1H, dd, $J=1.9$, 10.1 Hz, 3-H or 4-H), 6.23 (1H, dd, $J=2.7$, 10.1 Hz, 3-H or 4-H).

Dehydration of 10 under Mitsunobu's Reaction Conditions **10** (83 mg) was subjected to the dehydration under the same conditions as described for **8** to afford a mixture of **13** and **12** in a ratio of 3 : 1 as a colorless oil (22 mg, 28%).

References and Notes

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8) Elimination was initiated even at room temperature for **9** and **10**, but heating at 80 °C was required in this case.