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Insight into Rh(I)-catalyzed Cyclization of 6-Octen-1-als with a Chiral Protecting Group

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Abstract: Rh(I)(Wilkinson)[ClRh(PPh$_3$)$_3$]-catalyzed cyclization of 6-octen-1-als with a chiral protecting group at the C$_2$-position afforded only cis-cyclohexanol derivatives, and in the case of C$_4$-position yielded a mixture of cis and trans cyclohexanol. These findings were remarkably different from the case of the C$_3$-position, in which the trans cyclohexanol derivative was obtained. Wilkinson's complex acts as [ClRh(PPh$_3$)$_3$] a Lewis acid, and this bulkier Lewis acid affords higher diastereoselectivity. Rh(I)-catalyzed cyclization of 6-octen-1-al derivatives is not affected by chiral ligands.

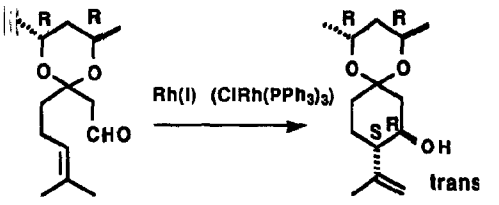
Introduction

Stereoselective cyclization reactions using organometallic catalysts have been studied extensively in connection with natural product synthesis.[1] In further studies on a cyclization reaction by Rh(I) complexes developed by our group, we have succeeded in the highly stereocontrolled cyclization of substituted 4-pentenals into substituted cyclopentanones,[2] which could be widely applied for the synthesis of natural products.[3]

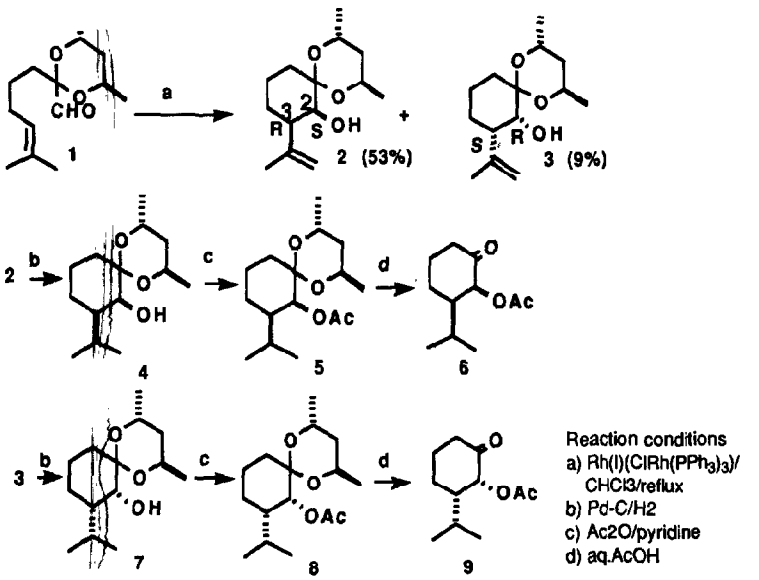
After our first cyclization[7a] of 6-octenal (citronellal) with ClRh(PPh$_3$)$_3$ (Wilkinson complex) to the mixture of *cis*- and *trans*-cyclohexanol derivatives, Larock and co-workers[4] reported that Rh(I)-catalyzed cyclization of 5-hexenal afforded 2-methylcyclopentanone but no cyclized product was obtained from 6-heptenal. According to Gable and Benz,[5] Rh(I)([(Ph$_3$P)$_2$RhCl]$_2$)-catalyzed cyclization of 4-methyl-5-hexenal affords a cyclohexanone derivative rather than methylcyclopentanone, and 5-methyl-5-hexenal gives a cyclohexanol derivative. Recently, we have reported that ClRh(PPh$_3$)$_3$-catalyzed cyclizations of 6-octenals with a chiral protecting group, (4*R*,6*R*)-dimethyl-1,3-dioxane, at the C$_3$-position proceed in a highly diastereoselective fashion (99%de) to the *cis* and *trans*-hexanol (Scheme 1),[6a,7] and that cyclohexanone derivatives were not obtained. On the basis of the above information, we have examined the effect of substituents at the C$_2$ or C$_4$-positions on the cyclization reaction.

Cyclization of 6-octen-1-al with chiral acetal at C$_2$-position

It is presumed that the Rh(I)-catalyzed cyclization of the aldehyde (1) with a chiral cyclic acetal group, (4*R*,6*R*)-dimethyl-1,3-dioxane (with the C$_2$ axis), at the C$_2$-position is sterically hindered by the bulky acetal, compared with the case of C$_3$-substituent. However, when the aldehyde 1 was heated in CHCl$_3$ at reflux in the



Scheme 1



Scheme 2

presence of an equimolar amount of $ClRh(PPh_3)_3$, the reaction proceeded smoothly to afford diastereomeric mixtures of only the *cis* configuration in 62% yield, which could be separated by column chromatography on silica gel into **2** (53%, $[\alpha]_D$-5.63, c 3.8, $CHCl_3$) and **3** (9%, $[\alpha]_D$-25.5, c 1.3, $CHCl_3$). Previously, we reported findings[7] that in cyclohexanol derivatives with the hydroxy function adjacent to the isopropenyl group, the two olefinic protons in the cis isomers were observed as separate peaks, while both olefinic protons in the trans isomers were observed as a broad singlet. On the basis of this finding, the relative configuration of each diastereomer was determined to be cis from the analysis of their ^{1}H-NMR spectroscopy. That is to say, one of the two olefinic protons in each cyclized product was observed upfield (**2**,**3** both; δ 4.83) from the other (**2**; δ 4.90, **3**; δ 4.92), indicating that the relative configuration of each cyclized product is *cis*. In addition, NOE differential experiments of C_2-H and C_3-H in **2** and **3** also supported this conclusion. In this cyclization reaction, the trans isomer was not obtained. The above Rh(I)-catalyzed cyclization was in sharp contrast to the case of the

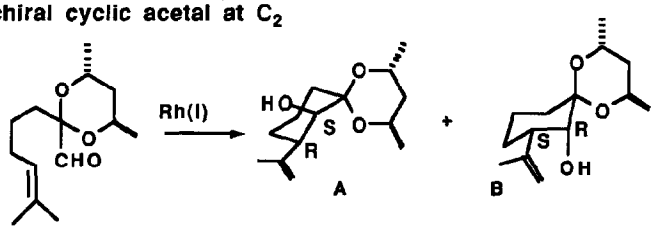
aldehyde with the same cyclic acetal at the C_3-position,[6,7b] in which the trans isomer was obtained as the sole cyclized product.

In order to establish the absolute stereochemistry of the two cyclized products, **2** and **3** were hydrogenated by H_2/Pd-C, acetylated with Ac_2O/pyridine, and then deacetalized with aq. AcOH to **6** and **9**, respectively. The circular dichroism (CD) spectrum of **6** in $CHCl_3$ showed negative Cotton effect at 304 nm ($\Delta\varepsilon$=-3.37 x 10^{-3}), while **9** showed positive effect at 304 nm ($\Delta\varepsilon$=+3.23 x 10^{-3}). From these results, the absolute stereochemistry of **2** and **3** was determined to be (2*S*,3*R*) and (2*R*,3*S*), respectively.

Results and Discussion

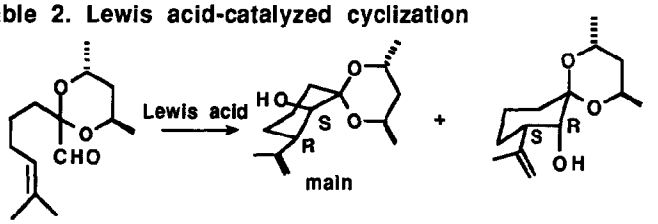
The effect of chiral ligands on the Rh(I)-catalyzed cyclization of 6-octenals to the corresponding cyclohexanols was examined, because Rh(I)(chiral ligand)-catalyzed cyclizations of substituted 4-pentenals to the substituted cyclopentanones proceeded in highly diastereoselective or enantioselective fashion.[2d] Chiral phosphine ligands such as (4*S*,5*S*)-(+)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane (DIOP)[8] and (1*S*,2*S*)-(+)-1,2-bis(diphenylphosphinomethyl)cyclohexane (DIPMC)[9] were employed. However, the cyclization reaction of the aldehyde **1** proceeded in a similar manner to the case of $ClRh(PPh_3)_3$, and it was observed that the chiral ligand had no effect on the diastereoselectivity (Table 1).

Table 1. Rh(I)-catalyzed cyclization of 6-octen-1-al with chiral cyclic acetal at C_2



Ligand	Yield (%) A	B	d.e.
$ClRh(PPh_3)_3$	53	9	71
(-)-DIOP	50	8	72
(+)-DIPMC	46	10	64

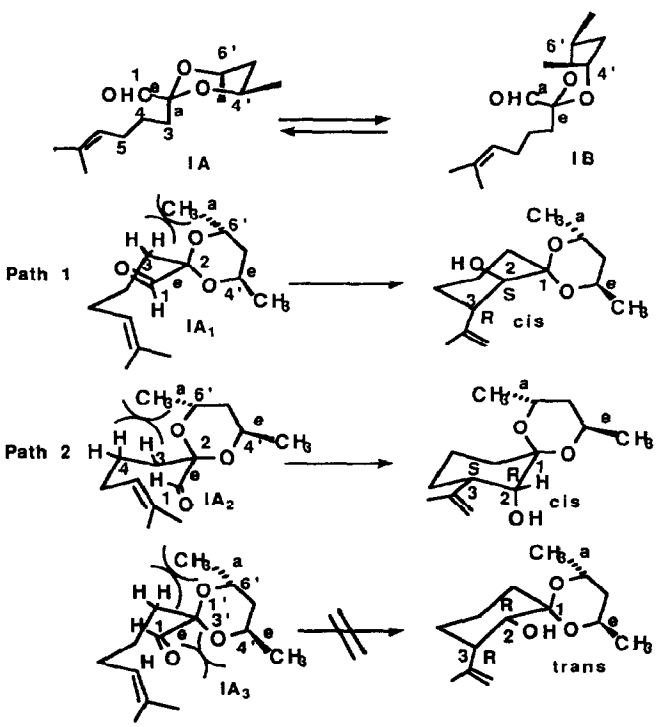
Table 2. Lewis acid-catalyzed cyclization



Lewis acid	Yield(%)	d.e.	Conditions
$ZnBr_2$	27	27	0°C, 5h
$RhCl_3$	58	55	0°C, 3h
$PtCl_4$	54	70	-78°C, 5h
$ClRh(PPh_3)_3$	60	72	refl., 13h

The above result suggested that $ClRh(PPh_3)_3$ acts as Lewis acid. Thereupon, the cyclization reaction of **1** by Lewis acids such as $ZnBr_2$, $RhCl_3$, and $PtCl_4$ was examined. As shown in Table 2, the Lewis acid-catalyzed cyclization afforded only the *cis*-cyclohexanol, similarly to the case of $ClRh(PPh_3)_3$-catalyzed cyclization. The diastereomeric excess (d.e.) of the cyclized products seems to depend on the bulkiness of the Lewis acid. As the Lewis acid becomes bulkier, the diastereoselectivity of cyclization product appears to be higher.

In Rh(I)-catalyzed cyclizations of the aldehyde **1** with a chiral acetal at the C_2-position, two conformations **IA** and **IB** as shown in Scheme 3 are assumed. Conformation **IA** seems to be more favorable than **1B** for the cyclization, because, in **IB**, approach of bulky Rh(I) complex to the axial aldehyde on the 1,3-dioxane ring may be hindered by 4'-axial methyl. There are two possible pathways (path 1 and path 2) for the cyclization from **IA**. Consideration of a Dreiding stereomodel suggests that, in $\mathbf{IA_1}$, there is slight steric repulsion between C3-Hα and $C_{6'}$-axial Me. On the other hand, in $\mathbf{IA_2}$, $C_{6'}$-axial Me occupies a sterically more hindered position between C_3-H(β) and C_4-H(β). Thus, the cyclization reaction proceeds via a favorable $\mathbf{IA_1}$ conformation to afford the



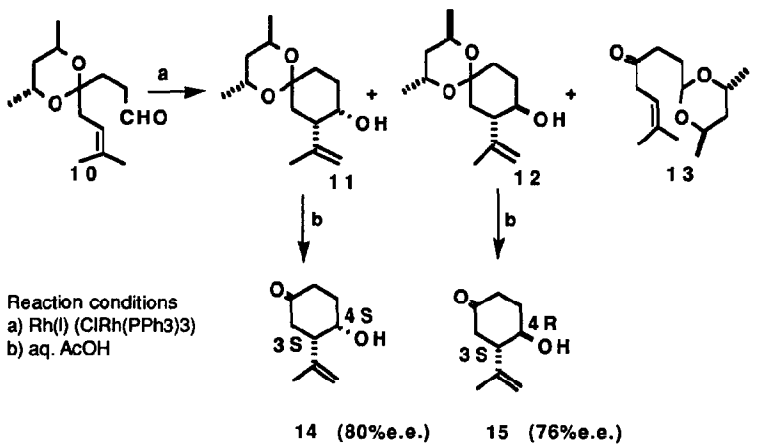
Scheme 3

cis-cyclohexanol (2*S*,3*R*) as the main product. In addition, it is likely that conformation $\mathbf{IA_1}$ rather than $\mathbf{IA_2}$ with the aldehyde hindered by the isopropenyl group allows approach of the bulky Lewis acid to afford the cyclized product in a diastereoselective manner. As mentioned above, the trans isomer was not obtained in this cyclization reaction. This finding may be explained as follows. In the Rh(I)-catalyzed cyclization of 6-octenals with chiral

acetal at C_2, conformation **IA**$_3$ seems to be favorable for the cyclization to trans-cyclohexanol. However, the stereoelectronic repulsion between the carbonyl oxygen and the dioxane ring oxygen (3') may interfere with this conformation.

Cyclization of 6-octen-1-al with chiral acetal at C_4-position

Our attention was focused on the cyclization of 6-octen-1-al with the chiral acetal group at the C_4-position (Scheme 4). When the aldehyde (**10**) was heated at reflux in $CHCl_3$ in the presence of $ClRh(PPh_3)_3$, the *cis*-cyclohexanol (**11**) and *trans*-cyclohexanol (**12**) were obtained in 33% yield, accompanied with by-products (**13**) in 18% yield.[10] The relative configuration of **11** and **12** was determined to be *cis* and *trans*, respectively, from the examination (two olefinic protons in **11**; δ 4.97 (s) and 4.78 (d, *J*=16Hz) : **12**; δ 4.94-4.89 (br. s)) of their ^{1}H-NMR spectra. The CD spectra of each keto-alcohol (**14**) and (**15**) obtained by deacetalization with aq. AcOH both showed negative Cotton effect (**14**; 294 nm, $\Delta\varepsilon$=-1.88 x10^{-2} and **15**; 296 nm, $\Delta\varepsilon$=-6.71 x 10^{-2}), indicating **14** to be (3*S*,4*S*) and **15** to be (3*S*,4*R*).



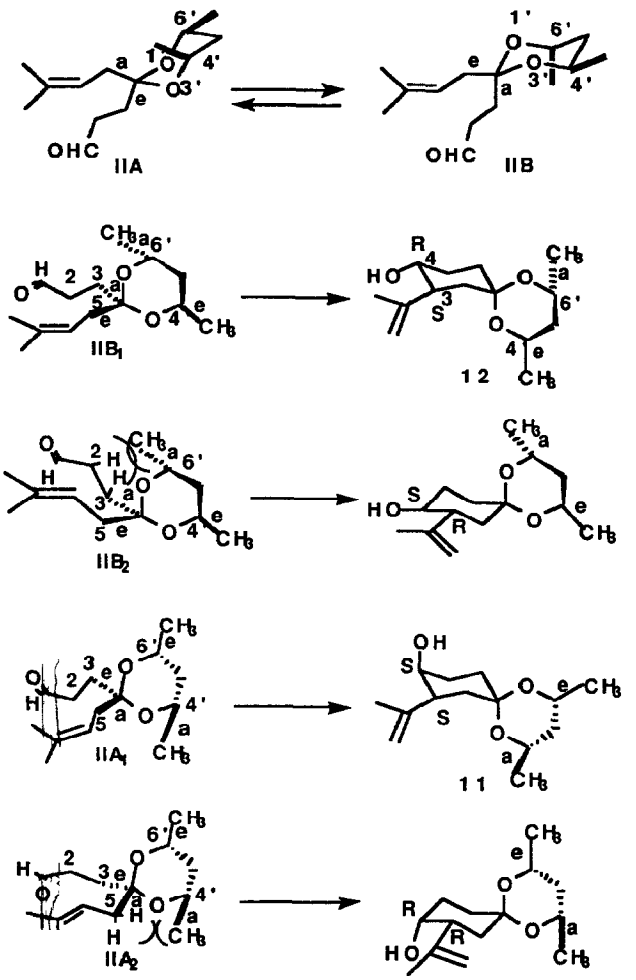
14 (80%e.e.) **15** (76%e.e.)

Scheme 4

Results and Discussion

The optical purities of **14** and **15** were determined to be 80% and 76% e.e, respectively, by examination of their ^{1}H-NMR spectra after conversion to the esters of (+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA). The diastereoselectivity in this cyclization may be explained by two conformations **IIA** and **IIB**, in which there is no real difference in the approach of the Rh(I) complex. Each conformation allows four possible cyclization pathways from **IIA**$_1$ and **IIA**$_2$, and from **IIB**$_1$ and **IIB**$_2$ to be assumed (Scheme 5).

Consideration of a Dreiding stereomodel suggests that **IIA**$_1$ is preferable conformation to **IIA**$_2$, because an undesired steric repulsion between C_4'-Me and C_5-H2 is observed in **IIA**$_2$. Similarly, **IIB**$_1$ is preferable to **IIB**$_2$, because of steric repulsion between C_6'-Me and $C_{2,3}$β-H in **IIB**$_2$. As a result, **IIB**$_1$ conformation was diastereoselectively cyclized to the *trans* (3*S*,4*R*) isomer **12**, and **A1** to the *cis* (3*S*,4*S*) isomer **11**. From the above findings it can be concluded that Rh(I)-catalyzed cyclization of 6-octenals to the cyclohexanol derivatives is significantly affected by the position of the chiral acetal and the bulkiness of the Lewis acid.

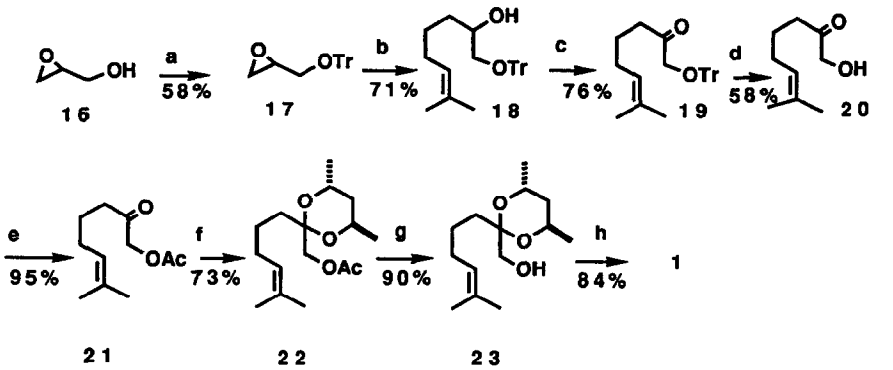


Scheme 5

Synthesis of the aldehyde (1) and (10).

Glycidol (**16**) was converted to the triphenylmethyl (trityl) ether (**17**, 59%) by treatment with trityl chloride in pyridine. Reaction of **17** with 4-methyl-3-pentenylmagnesium bromide in the presence of CuI in THF afforded 7-methyl-1-trityloxy-6-octen-2-ol (**18**, 71%). Oxidation of **18** with pyridinium chlorochromate (PCC) in CH_2Cl_2 at room temperature gave the keto ether (**19**, 76%), which was converted to the alcohol (**20**, 58%) by treatment with aqueous 80% AcOH . Acetylation (**21**, 95%) of **20** and subsequent acetalization with (2*R*,4*R*)-2,4-pentanediol by standard procedures afforded the acetal (**22**, 73%), which was converted to the aldehyde (**1**) by hydrolysis (**23**, 90%) and subsequent Swern oxidation (84%) (Scheme 6).

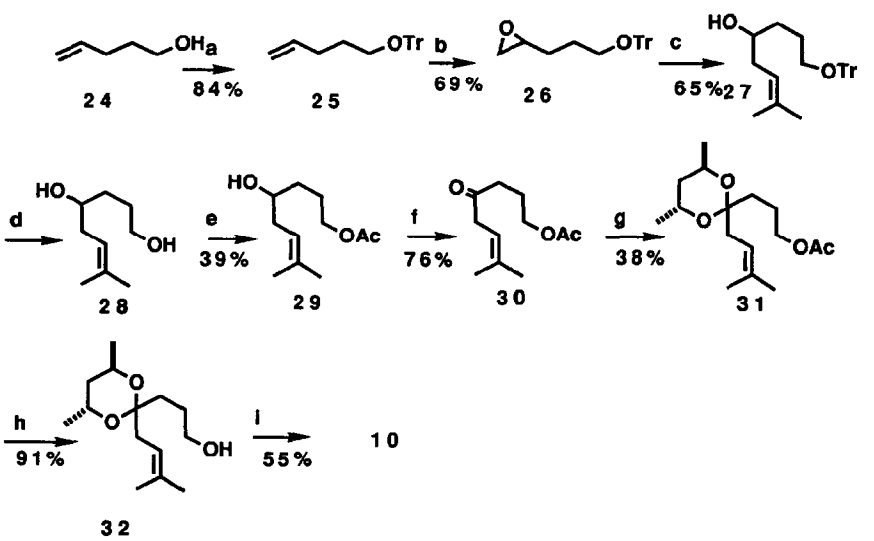
Synthesis of the aldehyde (1)



Reaction conditions;
a) TrCl/pyridine; b) 4-methyl-3-pentenyl bromide/Mg,CuI; c) PCC; d) 80%AcOH;
e) Ac_2O/DMAP; f) (2*R*,4*R*)-2,4-pentanediol/TsOH; g) K_2CO_3/MeOH; h) $(COCl)_2$/DMSO/Et_3N

Scheme 6

Synthesis of the aldehyde (10)



Reaction conditions;
a) TrCl/pyridine; b) MCPBA; c) 1-Bromo-2-methylpropene/Mg;d) 80%AcOH;
e) Ac_2O/pyridine; f) PCC; g) (2*R*,4*R*)-2,4-Pentanediol/TsOH; h) K_2CO_3/MeOH;
i) PDC

Scheme 7

Synthesis of the aldehyde (**10**) is as follows. 4-Penten-1-ol (**24**) was converted to the trityl ether (**25**, 84%) by treatment with trityl chloride in pyridine, and subsequent oxidation with m-chloroperbenzoic acid (MCPBA) afforded the epoxide (**26**, 69%). Synthesis of **10** from **26** was achieved in a manner similar to that described for the preparation of **1** from **17** (Scheme 7).

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. 1H-NMR spectra were measured on a JEOL JNM-SP-100 or a GX-270 spectrometer. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. Specific rotation was measured on a JASCO DIP-360 polarimeter at 25 °C. Each reaction was carried out under N_2 and was monitored by TLC (silica gel 60F-254 plates). For gravity column chromatography, silica gel (Merck, Kiesel-gel 60, 70-230 mesh) was used and for flash column chromatography, 230-400 mesh silica gel was used. All organic extracts were washed with brine, and dried over $MgSO_4$. Commercially available (Aldrich) $RhCl_3$(hydrate), $ZnBr_2$, and $PtCl_4$ were used.

General Procedure of $ClRh(PPh_3)_3$-catalyzed Cyclization.

A mixture of $ClRh(PPh_3)_3$ (4.56 mmol) and the aldehyde (4.56 mmol) in $CHCl_3$ (300 ml) was heated at reflux for 4 h under Ar atmosphere. After removal of the solvent *in vacuo*, the residue was diluted with ether, and the precipitate was filtered off. The ether layer was concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel.

Compound 2: 53% yield. $[\alpha]_D$ -5.63 (c 3.8, $CHCl_3$). IR(neat): 3500, 2920, 1640, 1440, 1150, 1020 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.20 (3H, d, *J*=6.3 Hz, -CH_3), 1.21 (3H, d, *J*=6.3 Hz, -CH_3), 1.34-1.70 (4H, m), 1.82 (3H, d, *J*=0.7 Hz, =-CH_3), 1.75-2.40 (5H,m), 2.28 (1H, d, *J*=12.5 Hz, =-CH), 3.86 (1H, s, -CH-O), 3.95-4.11 (2H, m, >CH-OR), 4.83 (1H, s, olefinic-H), 4.90 (1H, s, olefinic-H). ^{13}C-NMR δ; 147.19(s), 110.77(t), 100.85(s), 69.23(d), 62.66(d), 62.29(d), 44.46(d), 41.41(t), 27.41(t), 22.94(t), 22.20(q), 21.87(q), 21.72(q), 21.61(t). MS m/z: 240 (M^+), 209, 141, 128, 69.

Compound 3: 9% yield. $[\alpha]_D$ -25.5 (c 1.3, $CHCl_3$). IR(neat): 3480, 2920, 1640, 1440, 1380, 1160 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.21 (3H, d, *J*=6.3 Hz, -CH_3), 1.23 (3H, d, *J*=6.3 Hz,-CH_3), 1.35-1.71 (4H,m), 1.82 (3H, d, *J*=0.7 Hz, =-CH_3), 1.74-2.41 (5H, m), 2.31(1H, d, *J*=11.2 Hz, =-CH), 3.89 (1H, s, -CH-O), 3.99-4.14 (2H, m, >CH-OR), 4.82 (1H, m, olefinic-H), 4.91 (1H, m, olefinic-H). ^{13}C-NMR($CDCl_3$) δ: 146.91(s), 110.97(t), 99.91(s), 70.11(d), 63.59(d), 62.82(d), 45.07(d), 40.44(t), 29.63(t), 22.87(t), 22.18(q), 22.12(q), 21.87(q), 21.47(t). MS m/z: 240 (M^+) , 209, 141, 128, 69.

Compound 4: A suspended solution of **3**(100 mg, 0.42 mmol) and 10% Pd-C(50 mg) in MeOH(4ml) was stirred at room temperature under H_2 atmosphere. The Pd-C was filtered off and the solvent was removed to dryness. The residue was purified by column chromatography on silica gel to give **4** (97 mg, 96%) as a colorless oil. $[\alpha]_D$ -28.1 (c 1.6, $CHCl_3$). IR(neat): 3500, 2930, 1440, 1380, 1150 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.93 (3H, d, *J*=6.6 Hz, -CH_3), 0.99 (3H, d, *J*=6.6 Hz, -CH_3), 1.19 (3H, d, *J*=6.3 Hz, -CH_3), 1.20 (3H, d, *J*=6.3 Hz, -CH_3), 1.40-2.03 (11H, m), 3.83 (1H,s, -CH-O), 3.85-4.12 (2H, m, -CH-OR). MS m/z: 242 (M^+), 225, 141, 69.

Compound 5: To a solution of **4** (82 mg) and catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2 (3 ml) was added Ac_2O (150 mg). After being stirred for 5 h, the mixture was diluted with CH_2Cl_2, washed with $NaHCO_3$ aq. and brine, dried over Na_2SO_4. The solvent was removed and the residue was purified by column chromatography on silica gel. Compound **5** was given in 98% yield (97 mg) as a colorless oil. $[\alpha]_D$ -22.3 (c 1.3, $CHCl_3$). IR(neat) : 2930, 1740, 1440, 1370, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H,d, *J*=6.3 Hz, -CH_3), 0.91 (3H, d, *J*=6.3 Hz, -CH_3), 1.06 (3H, d, *J*=6.3 Hz, -CH_3), 1.19 (3H, d, *J*=6.3 Hz, -CH_3), 2.06 (3H, s, -$COCH_3$), 3.91 (1H, m, >CH-OR), 4.07 (1H, m, >CH-OR), 5.30 (1H, s, -CH-OAc). 1.35-1.83 (10H, other-H). Ms m/z: 284 (M^+), 225, 141, 69, 43.

Compound 6: A solution of **5** (30 mg) in 80% AcOH aq. (5 ml) was heated at reflux for 1 h. The reaction mixture was made alkaline with $NaHCO_3$ aq, extracted with ether, washed with brine, then dried over Na_2SO_4.

The solvent was removed and the residue was purified by column chromatography on silica gel. The fraction eluted with hexane-AcOEt(10:1) gave **6** as a colorless oil (20 mg, 96%). $[\alpha]_D$ -30.1 (c 1.9, $CHCl_3$). IR(neat): 2950, 1740, 1720, 1375, 1210 cm^{-1}. ^1H-NMR($CDCl_3$) δ: 0.95(6H, d, *J*=6.3 Hz, $-CH_3$), 2.14 (3H, s, $-COCH_3$), 2.27 (1H, m, >CH-CO), 2.59 (1H, m, >CH-CO), 5.18 (1H, m, -CH-OAc), 1.54-2.06 (6H, m, other-H). Ms m/z: 198 (M^+), 155, 138, 109, 43.

Compound 7: In a manner similar to the preparation of **4**, compound **7** (62 mg, quant.) was obtained from **3** (61mg) as a colorless oil. $[\alpha]_D$ -15.7 (c 1.5, $CHCl_3$). IR(neat): 3500, 2950, 1450, 1380, 1160 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.93 (3H, d, *J*=6.6 Hz, $-CH_3$), 0.96 (3H, d, *J*=6.6 Hz, $-CH_3$), 1.20 (3H, d, *J*=6.3 Hz, $-CH_3$), 1.21 (3H, d, *J*=6.3 Hz, $-CH_3$), 3.86 (1H, s, >CH-OH), 3.95-4.11 (2H, m, >CH-OR), 1.5-2.00 (11H, other-H). Ms m/z: 242 (M^+), 225, 141, 69.

Compound 8: In a similar manner to the preparation of **5**, compound **8** (66 mg, 92%) was obtained from **7** (60 mg) as a colorless oil. $[\alpha]_D$ -31.9 (c 1.6, $CHCl_3$): IR (neat): 2930, 1740, 1440, 1370, 1150 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.89 (3H, d, *J*=6.3 Hz, $-CH_3$), 0.93 (3H, d, *J*=6.3 Hz, $-CH_3$), 1.10 (3H, d, *J*=6.3 Hz, $-CH_3$), 1.20 (3H, d, *J*=6.3 Hz), 2.05 (3H, s, $-COCH_3$), 3.98 (1H, s, >CH-OR), 4.06 (1H, m, >CH-OR), 5.40 (1H, s, >CH-OAc), 1.30-1.85 (other-H). Ms m/z: 284 (M^+), 225, 141, 69, 43.

Compound 9: In a manner similar to the preparation of **6**, compound **9** (31 mg, 74%) was obtained from **8** (60 mg) as a colorless oil. $[\alpha]_D$ +31.7 (c 3.1, $CHCl_3$). IR(neat): 2950, 1740, 1720, 1375, 1210 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.95 (6H, d, *J*=6.3 Hz, $-CH_3$), 2.13 (3H, s, $-COCH_3$), 2.26 (1H, m, >CH-CO), 2.59 (1H, m, >CH-CO), 5.18 (1H, m, >CH-OAc), 1.54-2.06 (6H, m, other-H). Ms m/z: 198 (M^+), 155, 137, 109, 43.

Cyclization of 10: In a similar manner to that described for general procedure, a solution of **10** (345 mg, 14.4 mmol) and $ClRh(PPh_3)_3$ (1.33 g, 1.44 mmol) in $CHCl_3$ (50 ml) was heated at reflux for 2 h, *cis*-product (**11**) (73 mg, 21%), trans-product (**12**) (44 mg, 12%), and by-product (**13**) (62 mg, 18%) were obtained.

Compound 11: $[\alpha]_D$ -14.5 (c 0.3, $CHCl_3$). IR(neat): 3500, 2950, 1650, 1440, 1380, 1160 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.19 (3H, s, $-CH_3$), 1.22 (3H, s, $-CH_3$), 1.81 (3H, s, $-CH_3$), 2.38 (1H, br.s, -OH), 3.92 (1H, m, >CH-OH), 4.00-4.13 (2H, m, >CH-OR), 4.78 (1H, d, *J*=16.5 Hz, olefinic-H), 4.97 (1H, s, olefinic-H), 1.43-1.95 (9H, m, other-H). ^{13}C-NMR($CDCl_3$) δ: 146.45(d), 111.61(d), 100.35(d), 64.78(d), 62.52(d), 45.45(d), 41.56(d), 33.25(s), 31.30(d), 26.38(s), 22.74(d), 21.82(d). Ms m/z: 240 (M^+), 209, 141, 128, 71.

Compound 12: $[\alpha]_D$ -22.4 (c 0.3, $CHCl_3$). IR(neat): 3450, 2940, 1640, 1440, 1380, 1150 cm^{-1}. ^1H-NMR($CDCl_3$) δ: 1.189 (3H, s, $-CH_3$), 1.192 (3H, s $-CH_3$), 1.35-1.70 (5H, m), 1.71 (3H, s, $-CH_3$), 1.74-2.17 (4H, m), 2.33 (1H, m, -OH), 3.49 (1H, m, >CH-OH), 3.87-4.09 (2H, m, >CH-OR), 4.89-4.94 (2H, m, olefinic-H). ^{13}C-NMR($CDCl_3$) δ: 145.60(d), 113.59(d), 99.38(d), 70.20(d), 62.71(q), 50.10(d), 41.37(d), 38.19(s), 31.50(d), 29.75(q), 21,80(q), 18.80(d). Ms m/z: 240 (M^+), 141.

Compound 13: $[\alpha]_D$ +14.7 (c 0.5, $CHCl_3$). IR(neat): 3000, 1720, 1380, 1150 cm^{-1}. ^1H-NMR($CDCl_3$) δ: 1.18 (3H, d, *J*=6.3 Hz, $-CH_3$), 1.33 (3H, d, *J*=6.3 Hz, $-CH_3$), 1.62 (3H, s, $-CH_3$), 1.74 (3H,s, $-CH_3$), 1.79-1.92 (4H, m), 2.54 (2H, t, *J*=7.3 Hz, $-COCH_2$), 3.12 (2H,d, *J*=7.3 Hz,=C-CH_2), 3.92 (1H, m, >CH-OR), 4.23 (1H, m, >CH-OR), 4,89 (1H, t, *J*=5.0 Hz, -CH), 5.30 (1H, t, *J*=8.6 Hz, olefinic-H). Ms m/z: 240 (M^+),171, 141, 125, 115, 97, 69.

Compound 14 and 15: In a similar manner to the preparation of **6**, **14** (37 mg, 82%) and **15** (23 mg,29%) were obtained from **11**(70 mg) and **12**(120 mg).

Compound 14: $[\alpha]_D$ +4.23 (c 1.8, $CHCl_3$). IR(neat): 3500, 2950, 1650, 1440, 1160 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.84 (3H, s, $-CH_3$), 1.97 (2H, s, $-CH_2$), 2.15-2.37 (3H, m), 2.49 (1H, br.s, -OH), 2.68-2.85 (2H, m, $-CH_2$), 4.13 (1H, s, >CH-OH), 4.80 (1H, s, olefinic-H), 5.06 (1H, s, olefinic-H).
Ms m/z: 154 (M^+), 136, 85, 69.

Compound 15: $[\alpha]_D$ -5.1 (c 0.8, $CHCl_3$). IR(neat): 3400, 2930, 1690, 1430 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.76 (3H, s, $-CH_3$), 1.75 (1H, m, >CH), 2.06 (1H, br.s,-OH), 2.26-2.33 (2H, $-CH_2$), 2.34-2.53 (4H, m, $-CH_2$), 3.96 (1H, m, >CH-OH), 5.00 (1H, s, olefinic-H), 5.01 (1H, s, olefinic-H). Ms m/z: 154 (M^+), 136, 85, 69.

Glycidyl trityl ether (17): To a solution of trityl chloride (25.0 g, 90 mmol) in pyridine (30 ml) and CH_2Cl_2 (30 ml) was added dropwise glycidol (20.0 g, 270 mmol) at 0°C, and then stirred at room temperature for 12 h. The mixture was poured onto ice-conc.HCl (140 ml), extracted with CH_2Cl_2, washed with $NaHCO_3$ aq, brine, then dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica-gel column chromatography to afford **17** (16.5 g, 59%). IR(neat): 1620, 1050, 880, 820 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.58 (1H, m, -CH-O), 2.74 (1H, m, -CH-O), 3.10-3.42 (3H, m), 7.10-7.59 (15H, m, aromatic). Ms m/z: 316 (M^+), 298, 243, 165, 105.

7-Methyl-1-trityloxy-6-octen-2-ol (18): To a stirred solution of 4-methyl-3-pentenylmagnesium bromide [prepared from Mg (565 mg, 24 mmol) and 4-methyl-3-pentenyl bromide (3.41 g, 21 mmol)] in THF (30 ml) was added a suspended solution of CuI (300 mg, 1.57 mmol) at 0°C. After 25 min a solution of **17** (5.52 g,17 mmol) in THF (20 ml) was added, and stirred at 0 °C for 2 h. A saturated NH_4Cl aq. was added and the precipitate was filtered off,washed with brine, dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with hexane-AcOEt (50:1) afforded **18** as a colorless oil (5.32 g, 76%). IR (neat): 3400, 1660, 1450 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.59 (3H, s, $-CH_3$), 1.66 (3H, d, *J*=0.8 Hz, $-CH_3$), 2.92-3.25 (2H, m, $-CH_2$-O), 3.77 (1H, m, -CH-OH), 5.07 (1H, m, olefinic-H), 7.15-7.50 (15H, m, aromatic). Ms m/z: 400 (M^+), 243, 165, 82.

7-Methyl-1-trityloxy-6-octen-2-one (19): To a suspended solution of pyridinium chlorochromate (2.63 g, 12 mmol) and AcONa (0.49 g, 5.1 mmol) in CH_2Cl_2 (15 ml) was added a solution of **18** (3.60 g, 9 mmol) in CH_2Cl_2 (15 ml) and stirred at room temperature for 5 h. Ether (100 ml) was added to the reaction mixture and passed through a florisil column. After removal of the ether, the residue was purified by column chromatography on silica gel to afford a colorless oil **19** (2.72 g, 76%). IR(neat): 2930, 1740, 1600, 1450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.58(3H, s, $-CH_3$), 1.68 (3H, s, $-CH_3$), 2.53 (2H, t, *J*=7.2 Hz, $-CH_2CO$), 3.73 (2H, s, CH_2-OTr), 5.07 (1H, m, olefinic-H), 7.16-7.52 (15H, m, aromatic). Ms m/z: 397 (M^+-1), 243, 165, 82.

1-Hydroxy-7-methyl-6-octen-2-one (20): A solution of **19** (3.00 g, 7.5 mmol) in 80% AcOH aq (20 ml) was stirred at 55°C for 1.5 h. After neutralization of the mixture with Na_2CO_3, the whole was extracted with AcOEt, washed with brine, dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with hexane-AcOEt (3:1) afforded **20** as a colorless oil (0.74 g, 63%). IR(neat): 3430, 2920, 1720, 1670, 1440 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.59(3H, d, *J*=0.7 Hz,-CH_3), 1.68 (3H, d, *J*=1.5 Hz, $-CH_3$), 2.41 (2H, t, *J*=7.3 Hz, $-CH_2$-CO), 3.12 (1H, t, *J*=4.6 Hz, -OH), 4.23 (2H, d, *J*=4.6 Hz, $-CH_2$-O), 5.07 (1H, m, olefinic-H). Ms m/z: 156 (M^+), 138, 125, 82, 55.

1-Acetoxy-7-methyl-6-octen-2-one (21): To a solution of **20** (520 mg, 3.3 mmol) in pyridine (3 ml) was added acetic anhydride (700 mg, 6.8 mmol) at 0°C. After being stirred at room temperature for 1 h, the whole was diluted with AcOEt, washed with brine, dried over Na_2SO_4. Removal of the solvent afforded the oily residue, which was purified by silica gel column chromatography to afford **21** (629 mg, 95%). IR(neat): 2930, 1750, 1730, 1390, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (3H, s,-CH_3), 1.68 (3H, m, $-CH_3$), 2.17 (2H, s, $COCH_3$), 2.39 (2H, t, *J*=7.4Hz, CO-CH_2-), 4.64 (2H, s, CO-CH_2-O), 5.07 (1H, m, olefinic-H). Ms m/z: 198 (M^+), 180, 138, 82.

1-Acetoxy-7-methyl-2,2-[(2*R*,4*R*)-2,4-pentanedioxy]-6-octene (22): A mixture of **21** (480 mg, 2.4 mmol) and (2*R*,4*R*)-2,4-pentanediol (327 mg, 3.1 mmol) in benzene (40 ml) was refluxed in the presence of p-toluenesulfonic acid (208 mg, 1.1mmol) with azeotropic removal of H_2O. The reaction mixture was washed with brine, and dried, then removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with hexane-AcOEt (50:1) afforded **22** (338 mg, 49%) as a colorless oil. $[\alpha]_D^{24}$ -35.6 (c 1.6, $CHCl_3$). IR(neat): 2960, 2020, 1750, 1440, 1370, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (6H, d, *J*=4.0 Hz,-CH_3), 1.60 (3H, s, $-CH_3$), 1.67 (3H, d, *J*=0.6 Hz, $-CH_3$), 2.06(3H, s,

-$COCH_3$), 3.67-4.16 (2H, m, -CH-O), 4.28 (2H, s, -CH_2-OAc), 5.06(1H, m, olefinic-H). Ms m/z: 284 (M^+), 224, 211, 82, 69.

7-Methyl-2,2-[(2*R*,4*R*)-2,4-pentanedioxy]-6-octen-1-ol (23): A suspended solution of **22** (644 mg, 2.3 mmol) and K_2CO_3 (100 mg) in MeOH was stirred at room temperature for 10 h. The reaction mixture was diluted with CH_2Cl_2, washed with brine and then dried. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel . The fraction eluted with hexane-AcOEt (5:1) afforded **23** (521 mg, 95%) as a colorless oil. $[\alpha]_D^{24}$ -25.5 (c 2.0, $CHCl_3$). IR(neat): 3450, 2920, 1450, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (6H, d, *J*=6.1 Hz,-CH_3), 1.61 (3H, s, -CH_3), 1.69 (3H, s, -CH_3), 3.54 (2H, br, -CH_2-OH), 3.96-4.23 (2H, m, >CH-O), 5.11(1H, m, olefinic-H). Ms m/z: 242 (M^+), 211, 82, 69.

7-Methyl-2,2-[(2*R*,4*R*)-2,4-pentanedioxy]-6-octen-1-al (1): A solution of oxalyl chloride (0.5 ml) in CH_2Cl_2 (15 ml) at -78 °C under N_2 was added dropwise to a solution of DMSO (0.5ml). The resulting mixture was stirred at -78°C for 5 min, then 23 (500 mg, 2.1 mmol) in CH_2Cl_2 (15 ml) was added at the room temperature. After being stirred for 30 min, Et_3N (5 ml) was added. The whole was allowed to warm to room temperature and stirred for 30 min. The mixture was poured into 1N HCl (30 ml) and extracted with CH_2Cl_2. The combined organic layer was dried, concentrated and the residue was purified by column chromatography on silica gel. The fraction eluted with hexane-AcOEt (50:1) gave **1** (450 mg, 73%) as a colorless oil. $[\alpha]_D^{24}$ +34.5 (c 2.3, $CHCl_3$). IR(neat): 2930, 1740, 1450, 1380, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, *J*=6.1 Hz, -CH_3), 1.25 (3H, d, *J*=6.6 Hz,-CH_3),1.59 (3H, s, -CH_3), 1.67 (3H, d, *J*=1.0 Hz, -CH_3), 1.3-2.0 (6H, m, -CH_2-), 3.90-4.30 (2H, m, >CH-O), 5.06(1H, m, olefinic-H), 9.56 (1H, s, -CHO). Ms m/z: 240 (M^+), 211, 141, 125, 69, 55.

1-Trityloxy-4-pentene (25): In a manner similar to that described for tritylation of **16**, compound **25** was obtained as a colorless oil in 84% yield. IR(neat): 2900, 1640, 1595, 1490, 1440, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55-1.83 (2H, m, -CH_2-), 2.05-2.27 (2H, m, -CH_2-), 3.08 (2H, t, *J*=6.4 Hz, -CH_2-O-), 4.86 (1H, m), 5.00(1H, m), 5.79(1H, m), 7.12-7.50 (15H, m, aromatic). Ms m/z: 328 (M^+), 259, 69.

1-Trityloxy-4,5-epoxypentane (26): To a solution of **25** (24.5 g, 75 mmol) in CH_2Cl_2 (450 ml) was added dropwise a solution of MCPBA (20 g, 91 mmol) in CH_2Cl_2 (300 ml) at 0°C. After being stirred at room temperature for 24 h, the precipitate was filtered off. The organic layer was washed with $NaHCO_3$ aq. and brine, then dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with hexane-AcOEt (9:1) afforded **26** (17.5 g, 69%) as a colorless oil. IR(neat): 3030, 1590, 1480, 1440, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55-1.94(4H, m, -CH_2-), 2.42 (1H, dd, *J*=5.1and 2.7 Hz), 2.69(1H, dd, *J*=5.1and4.0 Hz), 2.86 (1H, m), 3.12(2H, t, *J*=6.1 Hz, -CH_2-OTr), 7.13-7.51 (15H, m, aromatic). Ms m/z: 344(M^+), 259, 85.

4-Hydroxy -7-methyl-1-trityloxy-6-octene (27): Compound **27** was obtained from **26** in 65% yield, in a manner similar to that described for the preparation of **18**. IR(neat): 3400, 3050, 1595, 1495, 1445, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.63(3H, s, -CH_3), 1.73 (3H, d, *J*=1.0 Hz, -CH_3), 1.38-1.93 (4H, m, -CH_2-), 2.15 (2H, m, -CH_2-), 3.10 (2H, t, *J*=6.1 Hz, -CH_2-OTr), 3.58 (1H, m, >CH-OH), 5.15 (1H, m, olefinic-H), 7.08-7.58 (15H, m, aromatic). Ms m/z: 400(M^+), 243, 140.

7-Methyl-6-octen-1,4-diol (28): Compound **28** was obtained from **27** in 93% yield as a colorless oil, in a manner similar to that described for the preparation of **20**. IR(neat): 3330, 2910, 1640, 1440, 1370, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.63(3H, s, -CH_3), 1.69-1.70 (4H, m, -CH_2-), 1.74 (3H, s, -CH_3), 2.19 (2H,t, *J*=2.8 Hz, -CH_2-), 2.70 (2H, br.s, -OH), 3.60-3.74 (3H, m, -CH_2-OH; >CH-OH), 5.16 (1H, t, *J*=2.7 Hz, olefinic-H). Ms m/z: 159(M^++1), 140, 89.

1-Acetoxy-7-methyl-6-octen-4-ol (29): Compound **29** was obtained from **28** in 39% yield as a colorless oil, in a manner similar to that described for the preparation of **21**.
IR(neat): 3450, 2930, 1740, 1645, 1450, 1370, 1250, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48-1.57 (2H, m,

-CH_2-), 1.65(3H, s, -CH_3), 1.67-1.73 (2H, m, -CH_2-),1.75 (3H, s, -CH_3), 1.82 (1H, br.s, -OH), 2.05 (3H, s, -$COCH_3$), 2.17 (2H, t, *J*=2.4 Hz, -CH_2-), 3.62 (1H, m, -CH_2-OH), 4.09 (2H, t, *J*=2.4 Hz, -CH_2-OAc), 5.15 (1H, t, *J*=2.8 Hz, olefinic-H). Ms m/z: 201(M^++1), 182, 131.

1-Acetoxy-7-methyl-6-octen-4-one (30): Compound **30** was obtained from **29** in 76% yield as a colorless oil, in a manner similar to that described for the preparation of **19**. IR(neat): 1740, 1710, 1675, 1240, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.64(3H, s, -CH_3), 1.76 (3H, d, *J*=1.0Hz, -CH_3), 1.84-2.01 (2H, m, -CH_2-), 2.04 (3H, s, -$COCH_3$), 2.51 (2H, t, *J*=7.3 Hz, -$COCH_2$-), 3.11 (2H, d, *J*=7.1 Hz, -CH_2-), 4.06 (2H, t, *J*=6.4Hz, -CH_2-OAc), 5.30 (1H, m, olefinic-H). Ms m/z: 198(M^+), 138, 129, 87, 43.

1-Acetoxy-7-methyl-4,4-[(2*R*,4*R*)-2,4-pentanedioxy]-6-octene (31): Compound **31** was obtained from **30** in 38% yield as a colorless oil, in a manner similar to that described for the preparation of **22**. $[\alpha]_D^{23}$ -15.2 (c 1.37, $CHCl_3$). IR(neat): 2920, 1740, 1670, 1440, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s, -CH_3), 1.20 (3H, s, -CH_3), 1.63 (3H, s, -CH_3), 1.65 (3H, s, -CH_3), 1.57-1.74 (6H, m, -CH_2-), 2.04 (3H, s, -$COCH_3$), 2.18-2.48 (2H, m, -CH_2-), 3.92-4.10 (4H, m, -CH_2-OAc; -OCH<), 5.13 (1H, t, *J*=7.9 Hz, olefinic-H). Ms m/z: 284(M^+), 224, 211, 69.

7-Methyl-4,4-[(2*R*,4*R*)-2,4-pentanedioxy]-6-octen-1-ol (32): Compound **32** was obtained from **31** in 91% yield as a colorless oil, in a manner similar to that described for the preparation of **23**. $[\alpha]_D^{22}$ -17.1 (c 1.46, $CHCl_3$). IR(neat): 3430, 2950, 1670, 1440, 1370, 1150, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, s, -CH_3), 1.21 (3H, s, -CH_3), 1.63 (3H, s, -CH_3), 1.71 (3H, s, -CH_3), 1.54-1.77 (6H, m, -CH_2-), 2.31-2.50 (3H, m, -OH, -CH_2-CH=), 3.62 (2H, s, -CH_2-OH), 3.96-4.11 (2H, m, -OCH<), 5.13 (1H, t, *J*=7.9 Hz, olefinic-H). Ms m/z: 242(M^+), 173, 136, 45.

7-Methyl-4,4-[(2*R*,4*R*)-2,4-pentanedioxy]-6-octen-1-al (10): Compound **10** was obtained from **32** in 55% yield as a colorless oil, in a manner similar to that described for the preparation of **1**. $[\alpha]_D^{24}$ -18.8 (c 0.26, $CHCl_3$). IR(neat): 2870, 2700, 1720, 1440, 1380, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s, -CH_3), 1.18 (3H, s, -CH_3), 1.51-1.66 (2H, m, -CH_2-),1.63 (3H, s, -CH_3), 1.72 (3H, s, -CH_3), 1.82-2.10 (2H, m, -CH_2-), 2.27-2.36 (2H, m, -CH_2-), 2.40-2.53 (2H, m, -CH_2-CHO), 3.89-4.41 (2H, m, -OCH<), 5.12 (1H, t, *J*=7.9 Hz, olefinic-H), 9.72 (1H, t, J=2.0 Hz, -CHO). Ms m/z: 240(M^+), 222, 201, 85.

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