Pergamon

Tetrahedron, Vol. 53, No. 14, pp. 5217-5232, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00207-X

Syntheses of Bifunctional Compounds from Cycloalkenes via Ozonide Intermediates

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Abstract: The ozonolytic cleavage of cycloalkene in the presence of methyl pyruvate affords a tri-substituted ozonide. The resulted tri-substituted ozonide moiety contained three reactive centers (i.e. peroxide, ozonide ring proton and methoxycarbonyl group) which could be transformed to different functional groups under different conditions in good yields. It is a very efficient and versatile methodology to prepare the terminal differentiated compounds from symmetric cycloalkenes in two steps in high yields.

INTRODUCTION

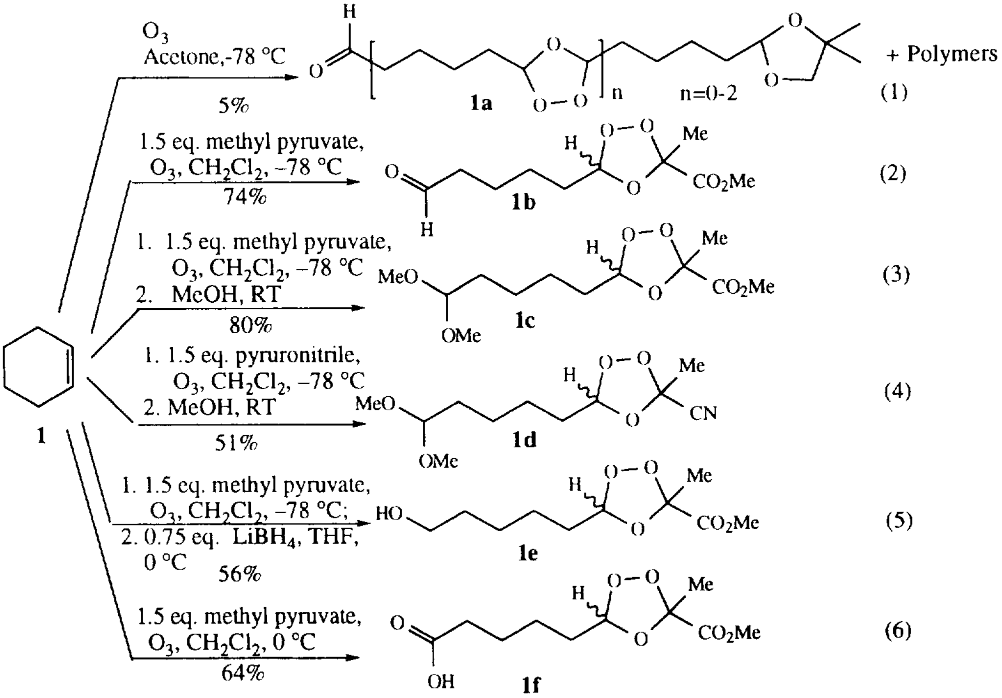
The ozonolysis of C_5 and C_6 cycloolefins in nonparticipating aprotic solvents is possible to obtain monomeric ozonides (about 70% for C_5 and 15% for C_6),[1] whereas for C_4, C_7, C_8 and others no monomeric ozonides is present in the reaction products because the intramolecular cycloaddition of carbonyl oxide with aldehyde is much slower than that of intermolecular process.[2] These polymeric ozonides were treated with acid or base to give bifunctional compounds albeit in modest yields.[1b] In order to avoid forming polymeric ozonides in the ozonolysis of cycloalkenes, Schreiber *et al.* used methanol to trap the carbonyl oxide intermediate to give an aldehyde tethered with an α-alkoxy hydroperoxide functionality, which could be further converted to the terminal differentiated compounds.[3] Odinokov *et al* used a mixture of sodium acetate in acetic acid to trap the carbonyl oxide intermediate generated from the partial ozonolysis of cyclooctadiene. The crude product was subsequently treated with methanolic acid to give the bifunctional compound in good yield.[4] Besten *et al.* performed ozonation of cyclopentene on water-containing silica gel to give 5-oxopentanoic acid in 80% yields.[5] All these approaches employed protic solvents to trap the carbonyl oxides to give α-alkoxy hydrogen peroxides intermediates.

We have reported that the E1cb mechanism is the overwhelming process in the reaction of bases and ozonides.[6] It is interesting to know whether it is possible to trap the carbonyl oxides with 1,3-dipolarophiles to give ozonide intermediate. We envisaged that the newly trapped ozonide moiety should be able to convert to different functional groups by base[6] or reducing agent.[7, 8] The 1,3-dipolarophiles, such as ketones[9], methyl formate[10], phenanthrene quinone[11] and 2-keto esters[11] have been employed to trap the carbonyl oxides to give tri- and tetra-substituted ozonides. The goal of these trapping experiments was simply to prepare the ozonides which are difficult to obtain by normal procedures.[12] In our early communication, we use methyl pyruvate as an 1,3-dipolarophiles to trap the carbonyl oxides generated from the ozonolysis of cycloalkenes. These ozonides were decomposed to give bifunctional compounds.[13] In this report, we want to describe the details of our approach and their applications in the preparation of terminally differentiated compounds.

RESULTS AND DISCUSSION

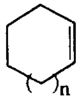
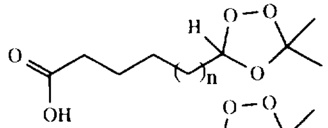
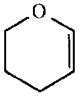
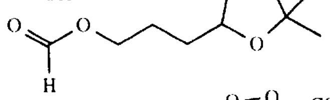
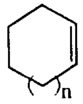
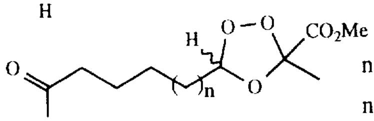
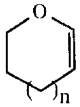
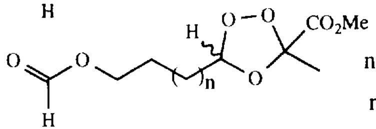
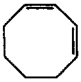
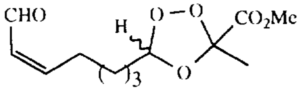
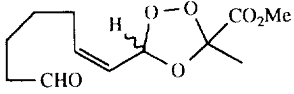
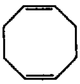
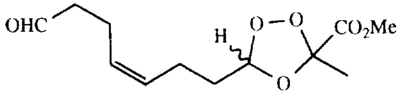
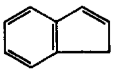
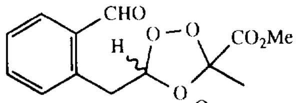
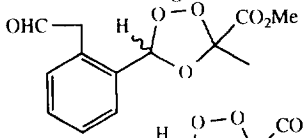
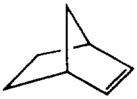
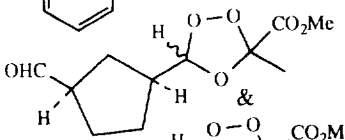
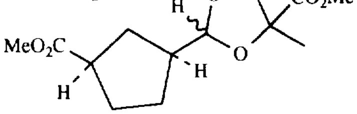
I. To Search a Good 1,3-Dipolarophile

The ozonolysis of cyclohexene (**1**) in acetone at -78 °C gave predominately the polymeric ozonides which are practically insoluble in CH_2Cl_2 and ethyl acetate. In this reaction, we obtained only about 5% yield of a mixture of aldehyde-ozonide **1a** which are soluble in CH_2Cl_2 (Eq. 1). The numbers of the ozonide unit in compound **1a** (n = 0-2) can be determined from the integration ratio (≈1/3-1) of aldehyde-H (δ 9.78 ppm, t, J = 1.5 Hz) to ozonide ring protons (δ 5.13-5.23 ppm, m). The ozonolysis of cyclohexene in CH_2Cl_2 in the presence of 1.5 mol equiv. of methyl pyruvate at -78 °C afforded ozonide-aldehyde **1b** in 74% yield as a mixture of two diastereomers in a ratio of 1:1 based on the ^{1}H-NMR integration of the ozonide ring protons appeared at δ 5.45 (t, J = 5.1 Hz) and 5.24 (t, J = 4.8 Hz) (Eq. 2). To the resulted mixtures obtained from Eq. 1 was added MeOH and the solution was then warmed up to room temperature, the acetal-ozonide **1c** was isolated in 80% yield (Eq. 3). The pyruronitrile was also employed in the ozonolytic reaction followed by addition of methanol to give the acetal-ozonide **1d** in 51% yield as a mixture of diastereomers (Eq. 4). The



aldehyde-ozonide **1b** obtained from Eq. 1 was directly treated with a solution of $LiBH_4$ in THF to give the alcohol-ozonide **1e** in 56% yield (Eq. 5). The hydride preferred to attack the aldehyde in the presence of ozonide moiety chemoselectively. If the ozonolysis of compound **1** was carried out at 0 °C instead of -78 °C,

Table 1: The ozonolysis of cycloalkenes in the presence of 1,3-dipolarophiles

Entry	Substrate	Conditions[a]	Product	Yield (%)
1	 n=1 **1**	A	 n=1 **1g**	40
2	n=3 **2**		n=3 **2a**	55
3	 **3**	A	 **3a**	51
4	 n=3 **2**	B	 n=3 **2b**	80
5	n=0 **4**		n=0 **4a**	50
6	 n=1 **3**	B	 n=1 **3b**	70
7	n=0 **5**		n=0 **5a**	30
8	 **6**	C	 **6a**	76
			 **6b**	–[b]
9	 **7**	B	 **7a**	65
10	 **8**	D	 **8a**	40
			 **8b**	–[b]
11	 **9**	E	 **9a** &	31
			 **9b**	40

[a] Condition **A**: O_3, Acetone, 0 °C; **B**: 1.5 eq. methyl pyruvate, O_3, CH_2Cl_2, -78 °C; **C**: 1.5 eq. methyl pyruvate, O_3, CH_2Cl_2, cat. Sudan 7B, -78 °C; **D**: 1. 1.5 eq. methyl pyruvate, O_3, EtOAc, -78 °C; **E**: (1) 1.5 eq. methyl pyruvate, O_3, EtOAc, -78 °C; (2) CH_2N_2. [b] They were not formed.

the acid–ozonide **1f** was formed in 64% yield (cf. Eq. 2 and 6). Apparently, the terminal aldehyde was further oxidized to carboxylic acid at 0 °C.

We have shown that acetone is a poor reagent to trap the carbonyl oxide at -78 °C (Eq. 1). However, its reactivity was improved when the reaction temperature was raised to 0 °C where ozonide-acid **1g** was formed in 40% yield (entry 1, Table 1). Cyclooctene (**2**) or 3,4-dihydro-2*H*-pyran (**3**) was subjected to ozonolysis in acetone at 0 °C to give the trapped products (**2a** and **3a**) in modest yields (entries 2-3, Table 1). Based on these results, we found the relative efficiency of the carbonyl compounds to trap carbonyl oxide proceeds in the following order: methyl pyruvate > pyruronitrile > acetone. Since methyl pyruvate is also cheap and readily available, we decided to use it in our further studies.

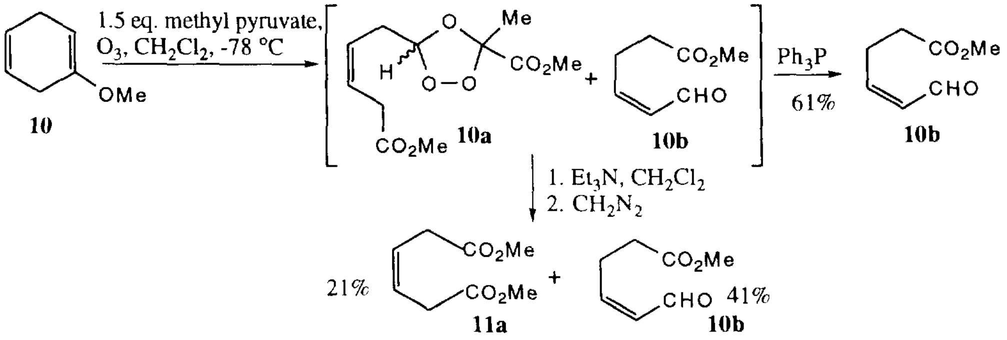
II. Ozonolytic Cleavage of Cycloalkenes in the Presence of Methyl Pyruvate

The methyl pyruvate is also an effective reagent to trap the carbonyl oxide generated from the ozonolysis of cyclooctene (**2**), cyclopentene (**4**), 3,4-dihydro-2*H*-pyran (**3**), and 2,3-dihydrofuran (**5**) at -78 °C, and their chemical yields ranged from 30-80% (Eq. 4-7, Table 1). Cyclopentene (**4**) and 2,3-dihydrofuran (**5**) might be carried away from the solution by the stream of ozone due to their volatility. This might be the reason to explain their poor chemical yields. To ensure that only one of the conjugated olefin was ozonized, the ozonolysis of 1,3-cyclooctadiene (**6**) was carried out in CH_2Cl_2 at -78 °C in the presence of Sudan red 7B, which turned from red to colorless when the first olefin has been consumed.[14] The *cis*-enal–ozonide **6a** was isolated as a mixture of diastereomers in 76% yield (Entry 8). The structure of compound (**6a**) could be unambiguously determined by ^1H NMR spectrum where the aldehyde absorption appeared as a doublet (δ 10.1 ppm, d, J = 10.1 Hz), ozonide ring proton absorption appeared as a triplet (δ 5.25 ppm, t, J = 4.8 Hz, 0.5 H from one diastereomer and δ 5.45 ppm, t, J = 5.1 Hz, 0.5 H from another diastereomer). Spectral analyses revealed that the structural isomer **6b** was not present. For the ozonolytic cleavage of nonconjugated cyclic diene, Sudan red 7B is not effective any more. By carefully bubbled the stoichiometric amount of O_3 in the presence of trapping agent at -78 °C, 1,5-cyclooctadiene (**7**) afforded (*E*)-enal–ozonide **7a** as a mixture of diastereomers in 65% yield (entry 9).

The efficiency to trap carbonyl oxide by methyl pyruvate in the ozonolytic cleavage of bicyclic alkenes, such as indene (**8**) and norbonylene (**9**), is solvent-dependent. It proceeded in the following order: ethyl acetate > dichloromethane > *n*-pentane. In ethyl acetate, indene (**8**) gave aryl aldehyde-ozonide **8a** in 40% yield in addition to the polymeric ozonides (entry 10). Spectral analyses revealed that the other structural isomer **8b** was not present. In the case of norbonylene (**9**), both the aldehyde-ozonide **9a** and acid-ozonide, which was treated with CH_2N_2 to give the corresponding methyl ester **9b**, were formed in 31% and 40% yields, respectively. The further oxidation of compound **9a** is unavoidable under our reaction condition (entry 11). Methyl pyruvate is not effective enough to trap the carbonyl oxide generated from dicyclopentadiene and only polymeric ozonides were formed. The further efforts are needed in order to look for a good 1,3-dipolarophile or a better reaction condition to trap the carbonyl oxide generated from the ozonolysis of bicyclic alkenes.

Under similar condition, 1-methoxy-1,4-cyclohexadiene (**10**) afforded an inseparable mixture of compounds (**10a**) and (**10b**). In order to determine their structures unambiguously, the mixtures were treated with Et_3N to decompose the ozonide ring. Under acidic workup, followed by treatment with CH_2N_2, we obtained 41% of enal-ester **10b** and 21% of diester **11a**. When the same mixtures were treated with Ph_3P, enal-ester **10b** was obtained in 61% yield. Presumably, the double bond isomerization occurred during the reduction of ozonide **10a** (Scheme 1).

Scheme 1



III. The Decomposition of the tri-substituted Ozonide by Different Reagents

Triphenylphosphine was known to attack the peroxide bond of the ozonide. In order to prepare the bifunctional compound, the acetal-ozonide **1c** was treated with Ph_3P to give 6,6'-dimethoxyhexanal (**12a**) in 88% yield (Scheme 2). Triethylamine is known to abstract the ozonide ring proton.[6] The 6,6-dimethoxyhexanoic acid (**12b**) was formed in 98% yield when compound **1c** was treated with Et_3N. Interestingly, reacting the acetal-ozonide **1c** with aqueous sodium hydroxide in THF produced the α,β-unsaturated aldehyde **12c** in 88% yield. This is consistent with that hydrolysis of the ester group occurred in the first place to give compound **12a** which was then underwent the aldol condensation (Scheme 2). The *E* configuration of the double bond of compound **12c** was confirmed by the 2D-NOESY technique. The tri-substituted ozonide on compound **1c** shown here serves as the masked functionalities of aldehyde and carboxylic acid. In addition, the carbomethoxy substituent of the trioxolane also serves as another reactive site to trigger the fragmentation of the ozonide. Therefore, the triple reactive sites in compound **1c** could be converted to different functional groups selectively by applying the different reaction conditions (Fig. 1).

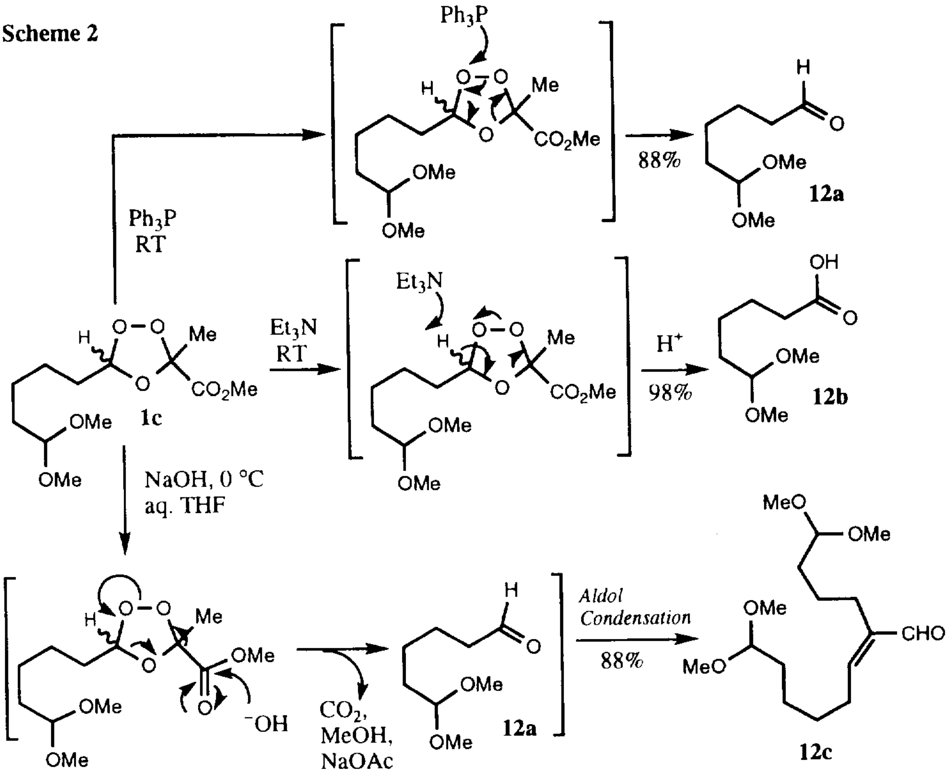
The tri-substituted ozonides tethered with aldehyde **1b**, alcohol **1e**, and acid **1f** can also be prepared from cyclohexene (**1**) in an one-flask operation (Eq. 2, 5 and 6). Each of these tri-substituted ozonides could also be converted to different products by treating with Ph_3P, Et_3N and aqueous NaOH, respectively. Their results were shown in Scheme 3. In other words, starting with cyclohexene, *via* two simple experimental operations, 10 different types of terminal differentiated compounds could be synthesized in high yields as shown in Scheme 3.

CONCLUSIONS

From this report, we summarized our results as follows.

(1) The carbonyl oxide intermediates generated from the ozonolysis of cycloalkenes could be trapped by ketone functionality. We found their trapping capability order were $MeCOCO_2Me$ > MeCOCN > MeCOMe. Methyl pyruvate is less effective to the bicycloalkenes in comparison with that of monocycloalkenes as an 1,3-dipolarophile.

Scheme 2



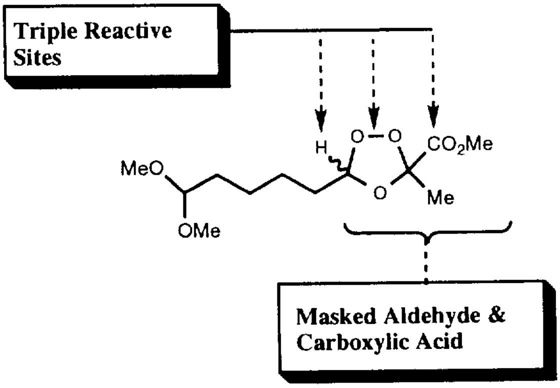
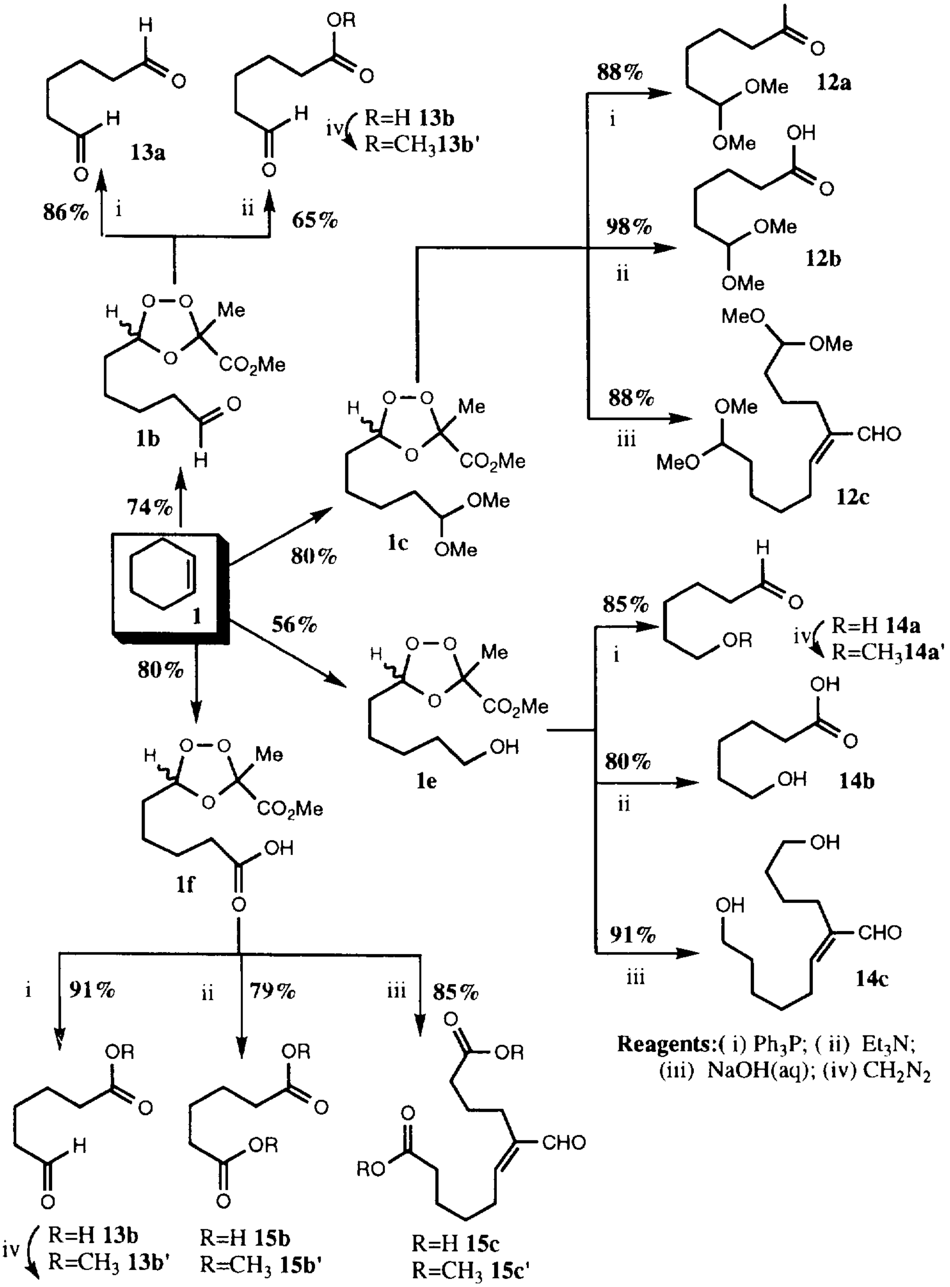


Fig 1: The tri-substituted ozonide contains triple reactive sites

Scheme 3



Reagents:(i) Ph_3P; (ii) Et_3N; (iii) NaOH(aq); (iv) CH_2N_2

(2) The resulted tri-substituted ozonide moiety contained three reactive centers (i.e. peroxide, ozonide ring proton and methoxycarbonyl groups) could be transformed to different functional groups under different conditions. Therefore, it is a very efficient and versatile methodology to prepare the terminal differentiated compounds from symmetric cycloalkenes in two steps.

EXPERIMENTAL SECTION

All reactions were carried out under nitrogen. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Ozone was prepared with a Fisher ozone generator (Model 501). Melting points were determined by using a Yanaco micro melting point apparatus and were uncorrected. The ^1H and ^{13}C-NMR spectra were recorded on a Bruker AC 200 spectrometer, and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). IR spectra were taken with a Perkin Elmer 882 spectrophotometer and only noteworthy absorptions were listed. Mass spectra were measured on a VG 70-250S mass spectrometer by electronic impact at 70 eV (unless otherwise indicated).

General Procedure for the Ozonolysis of Cycloalkenes in the Presence of Methyl Pyruvate:
5-(5-Methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)pentanal (1b): A two-necked flask is fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube and a magnetic stirring bar and is charged with cyclohexene (**1**) (160.1 mg, 1.95 mmol), methyl pyruvate (299.0 mg, 2.93 mmol) in 10 mL of CH_2Cl_2. The flask is cooled to -78 °C and ozone is bubbled through the solution. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharged. Removal of solvent afforded the crude product. The silica gel column chromatography by elution with EtOAc/hexane to give the tri-substituted ozonide **1b** (335.1 mg, 2.93 mmol; 74% yield) as a mixture of two diastereomers in a ratio of 1:1 as a colorless oil. TLC (EtOAc/Hexane=1/1) $R_f = 0.40$; ^1H-NMR ($CDCl_3$) δ 1.66 (s, 3H, $\text{-C}\underline{\text{H}}_3$), 1.42-1.81 (m, 6H), 2.48 (t, $J = 6.9$ Hz, 2H, $\text{-C}\underline{\text{H}}_2\text{-COOH}$), 3.80 (s, 3H, $\text{-CO}_2\text{C}\underline{\text{H}}_3$), 5.24 (t, $J = 4.8$ Hz, 0.5H, $\text{-OC}\underline{\text{H}}\text{RO-}$), 5.44 (t, $J = 5.1$ Hz, 0.5H, $\text{-OC}\underline{\text{H}}\text{RO-}$), 9.76 (s, 1H, $\underline{\text{H}}\text{C=O}$); ^{13}C-NMR ($CDCl_3$) δ 18.1 ($\underline{\text{C}}\text{H}_3$), 18.8, 21.1 (2°), 22.7 (2°), 29.0 ($\text{R}\underline{\text{C}}\text{H}_2(\text{CH}_2)_3\text{CHO}$), 32.1 ($\text{HCO}\underline{\text{C}}\text{H}_2$), 52.3 ($\text{-CO}_2\underline{\text{C}}\text{H}_3$), 52.4, 103.7 ($\text{-O}\underline{\text{C}}\text{CH}_3\text{RO-}$), 104.8 ($\text{-O}\underline{\text{C}}\text{HRO-}$), 168.0 ($\underline{\text{C}}\text{OOCH}_3$), 168.5, 201.6 ($\text{H}\underline{\text{C}}\text{OR}$); IR ($CH_2Cl_2$) ($\nu$, cm^{-1}): 2958 (C-H), 1753 (C=O), 1433, 1374, 1282, 1250.

7-(5-Methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)heptanal (2b): TLC (EtOAc/Hexane=1/3) $R_f = 0.32$; Colorless oil; ^1H-NMR ($CDCl_3$) δ 1.33-1.79 (m, 10H), 1.66 (s, 3H, $\text{-C}\underline{\text{H}}_3$), 2.44 (t, $J = 8.1$ Hz, 2H, $\text{HOC}\underline{\text{H}}_2\text{R}$), 3.81 (s, 3H, $\text{-CO}_2\text{C}\underline{\text{H}}_3$), 5.23 (t, $J = 4.9$ Hz, 0.5H, $\text{-OC}\underline{\text{H}}\text{RO-}$), 5.43 (t, $J = 5.2$ Hz, 0.5H, $\text{-OC}\underline{\text{H}}\text{RO-}$), 9.76 (s, 1H, $\underline{\text{H}}\text{C=O}$); ^{13}C-NMR ($CDCl_3$) δ 18.5 ($\underline{\text{C}}\text{H}_3$), 19.3, 21.7 (2°), 23.2 (2°), 23.4, 28.6 (2°), 28.8, 29.5, 32.5 (2°), 43.6 ($\text{O=CH}\underline{\text{C}}\text{H}_2\text{R}$), 52.7 ($\text{-CO}_2\underline{\text{C}}\text{H}_3$), 52.8, 104.0 ($\text{-O}\underline{\text{C}}\text{CH}_3(\text{CO}_2\text{CH}_3)\text{O-}$), 105.3 ($\text{-O}\underline{\text{C}}\text{HRO-}$), 168.4 ($\underline{\text{C}}\text{OOCH}_3$), 168.4, 169.3 ($\underline{\text{C}}\text{OOCH}_3$), 202.4 ($\text{R}\underline{\text{C}}\text{HO}$); IR ($CH_2Cl_2$) ($\nu$, cm^{-1}): 2935 (C-H), 1753 (C=O), 1721 (C=O), 1435, 1375, 1283, 1191, 1132; MS (m/z) (60 eV, rel. intensity): 231 (M^+-29, 1), 201 (4), 200 (40), 191 (3), 189 (6), 173 (69), 172 (27), 130 (4), 119 (41), 113 (21), 97 (62), 55 (37), 43 (100).

3'-(5-methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)propyl formate (3b): TLC (EtOAc/Hexane=1/3) $R_f = 0.36$; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.68 (s, 3H, $-C\underline{H}_3$), 1.77-1.93 (m, 2H), 3.81 (s, 3H, $-CO_2C\underline{H}_3$), 3.82, 4.21 (t, J = 5.5 Hz, 2H, $HCO_2C\underline{H}_2R$), 5.30 (t, J = 4.1 Hz, 0.5H, $-OC\underline{H}RO-$), 5.51 (t, J = 5.2 Hz, 0.5H, $-OC\underline{H}RO-$), 8.07 (s, 1H, $RC\underline{H}O$); ^{13}C-NMR ($CDCl_3$) δ 18.5 ($\underline{C}H_3$), 19.0, 22.0 (2°), 22.6, 26.1 (2°), 29.5, 52.7 ($-CO_2\underline{C}H_3$), 52.8, 104.1, 104.2 ($-O\underline{C}CH_3(CO_2CH_3)O-$), 104.6, 104.7 ($-O\underline{C}HRO-$), 160.8 ($H\underline{C}O_2CH_2R$), 168.3 ($\underline{C}OOCH_3$), 168.8; IR ($CH_2Cl_2$) (v, cm $^{-1}$): 2956 (C-H), 1752 (C=O), 1720 (C=O), 1434, 1375, 1253, 1180; MS (m/z) (60 eV, rel. intensity): 219 (M^+-15, 4), 189 (M^+-45, 32), 175 (18), 161 (72), 147 (2), 128 (3), 119 (20), 87 (18), 71 (82), 59 (13), 43 (100).

4-(5-Methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)butanal (4a): TLC (EtOAc/Hexane=1/3) $R_f = 0.35$; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.66 (s, 3H, $-C\underline{H}_3$), 1.72-1.87 (m, 4H), 2.55 (dt, J = 4.9 and 2.4 Hz, 2H, $-RC\underline{H}_2OH$), 3.80 (s, 3H, $-CO_2C\underline{H}_3$), 5.26 (t, J = 4.3 Hz, 0.5H, $-OC\underline{H}RO-$), 5.47 (t, J = 2.2 Hz, 0.5H, $-OC\underline{H}RO-$), 9.76 (s, 1H, $\underline{H}C=O$); ^{13}C-NMR ($CDCl_3$) δ 15.7, 18.1 ($\underline{C}H_3$), 18.6, 28.4 (2°), 31.6 (2°), 42.5 ($HCO\underline{C}H_2$), 42.6, 52.3 ($-CO_2\underline{C}H_3$), 52.4, 103.7 ($-O\underline{C}CH_3RO-$), 104.6 ($-O\underline{C}HRO-$), 169.0 ($\underline{C}OOCH_3$), 168.4, 201.1 ($H\underline{C}OR$); IR (CH_2Cl_2) (v, cm $^{-1}$): 2957 (C-H), 1751, 1723 (C=O), 1436, 1375, 1255, 1190.

2'-(5-methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)ethyl formate (5a): TLC (EtOAc/Hexane=1/3) $R_f = 0.30$; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.69 (s, 3H, $-C\underline{H}_3$), 1.70, 2.06-2.25 (m, 2H, $HCO_2CH_2C\underline{H}_2-R$), 3.82 (s, 3H, $-CO_2C\underline{H}_3$), 4.31 (t, J = 6.3 Hz, 1H, $HCO_2C\underline{H}_2R$), 4.34 (t, J = 6.4 Hz, 1H, $HCO_2C\underline{H}_2R$), 5.39 (t, J = 4.7 Hz, 0.5H, $-OC\underline{H}RO-$), 5.65 (t, J = 5.2 Hz, 0.5H, $-OC\underline{H}RO-$), 8.05 (s, 1H, $\underline{H}C=O$); ^{13}C-NMR ($CDCl_3$) δ 18.4 ($\underline{C}H_3$), 18.6, 29.2 (2°), 32.6, 52.9 ($-CO_2\underline{C}H_3$), 58.6 ($HCO_2\underline{C}H_2R$), 58.7, 102.7 ($-O\underline{C}HRO-$), 102.8, 104.2 ($-O\underline{C}CH_3(CO_2CH_3)O-$), 104.3, 160.5 ($H\underline{C}O_2CH_2R$), 168.2 ($\underline{C}OOCH_3$), 168.6; IR ($CH_2Cl_2$) (v, cm $^{-1}$): 2939 (C-H), 1753 (C=O), 1724 (C=O), 1434, 1375, 1255, 1191, 1133; MS (m/z) (60 eV, rel. intensity): 219 (M^+-1, 4), 201 (1), 188 (5), 145 (100), 132 (53), 119 (19), 115 (15), 99 (30), 77 (10), 71 (31), 43 (100).

7-(5-Methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)-2(*Z*)-heptanal (6a): A mixture of 1,3-cyclooctadiene (**6**) (255.6 mg, 2.09 mmol), methyl pyruvate (319.6 mg, 3.13 mmol) , and sudan red 7B (2 mg) as a indicator in 10 mL of CH_2Cl_2 was subjected to the general ozonolytic procedure. The silica gel column chromatography by elution with EtOAc/hexane to give the tri-substituted ozonide **6a** (412.5 mg, 1.60 mmol; 76% yield) as a mixture of two diastereomers in a ratio of 1:1 as a colorless oil. TLC (EtOAc/Hexane=1/3) R_f = 0.41; ^{1}H-NMR ($CDCl_3$) δ 1.47-1.83 (m, 6H), 1.67 (s, 3H, $-C\underline{H}_3$), 2.65 (dt, J = 7.1 and 6.9 Hz, $RC\underline{H}_2CH=CH-CHO$), 5.25 (t, J = 4.8 Hz, 0.5H, $-OC\underline{H}RO-$), 5.45 (t, J = 5.1 Hz, 0.5H, $-OC\underline{H}RO-$), 5.98 (dtt, J = 10.4, 8.0 and 1.5 Hz, $RCH_2CH=C\underline{H}-CHO$), 6.63 (dt, J = 11.2 and 8.2 Hz, $RCH_2C\underline{H}=CH-CHO$), 10.1 (d, J = 8.0 Hz, 1H, $\underline{H}C=O$); ^{13}C-NMR ($CDCl_3$) δ 18.5 ($\underline{C}H_3$), 19.2 (2°), 23.0 (2°), 27.5 (2°), 27.6, 28.5 (2°), 28.6, 29.3 (2°), 32.4, 52.7 ($-CO_2\underline{C}H_3$), 52.8, 104.1 ($-O\underline{C}CH_3(CO_2CH_3)O-$), 105.1 ($O-\underline{C}HR-O$), 130.2 ($CH=\underline{C}HCHO$), 152.2 ($RCH_2\underline{C}H=CHCHO$), 168.3 ($\underline{C}OOCH_3$), 190.5 ($R\underline{C}HO$); IR ($CH_2Cl_2$) (v, cm $^{-1}$): 2956 (C-H), 1753 (C=O), 1419, 1374, 1254, 1190.

7-(5-Methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)-4(*Z*)-heptanal (7a): TLC (EtOAc/Hexane=1/3) $R_f = 0.53$; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.67 (s, 3H, $-C\underline{H}_3$), 1.77-1.91 (m, 6H), 3.81 (s, 3H, $-CO_2C\underline{H}_3$), 5.22-5.55 (m, 3H, $-OC\underline{H}RO-$), 9.77 (t, J = 1.3 Hz, 1H, $\underline{H}C=O$); ^{13}C-NMR

($CDCl_3$) δ 18.4 ($\underline{C}H_3$), 18.6, 19.0, 19.6 (2°), 21.3 (2°), 21.7, 29.3 (2°), 32.4, 43.2 ($R\underline{C}H_2CHO$), 52.6 (-$CO_2\underline{C}H_3$), 103.7 (-$O\underline{C}CH_3(CO_2CH_3)O$-), 103.9, 104.1, 104.2, 104.6 (O-$\underline{C}$HR-O), 104.7, 128.6 ($CH{=}\underline{C}H(CH_2)_2CHO$), 128.8 ($\underline{C}H{=}CH(CH_2)_2CHO$), 168.2 ($\underline{C}OOCH_3$), 168.8, 201.5 ($R\underline{C}HO$); IR ($CH_2Cl_2$) (v, cm^{-1}): 2957 (C-H), 1753 (C=O), 1433, 1375, 1254, 1191.

5-(5-Methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)pentanal dimethyl acetal (1c): A mixture of cyclohexene (**1**) (1.801 g, 21.96 mmol), methyl pyruvate (3.36 g, 32.94 mmol) in 100 mL of CH_2Cl_2 was subjected to the general ozonolytic procedure. MeOH was added right after the ozonolysis at -78 °C and the solution was then warmed up to room temperature. The reaction completed within 12 h. Removal of solvent afforded the crude product. The silica gel column chromatography by elution with EtOAc/hexane to give the tri-substituted ozonide **1c** (4.87 g, 17.53 mmol; 80% yield) as a mixture of two diastereomers in a ratio of 60:40 as a colorless oil. TLC (EtOAc/Hexane=1/1) $R_f = 0.66$; ^{1}H-NMR ($CDCl_3$) δ 1.38-1.83 (m, 8H), 1.67 (s, 3H, -$C\underline{H}_3$), 3.31 (s, 6H, $RCH(O\underline{C}H_3)_2$), 3.81 (s, 3H, -$CO_2C\underline{H}_3$), 4.35 (t, *J* = 5.5 Hz, 1H, -$RC\underline{H}(OCH_3)_2$-), 5.24 (t, *J* = 4.9 Hz, 0.6H, -$OC\underline{H}RO$-), 5.44 (t, *J* = 5.2 Hz, 0.4H,-$OC\underline{H}RO$-); ^{13}C-NMR ($CDCl_3$) δ 18.7 ($\underline{C}H_3$), 23.6 (2°), 24.3 (2 °), 27.9 (2°), 32.2 (2°), 52.7 (-$CO_2\underline{C}H_3$), 52.8, 104.3 (-$O\underline{C}CH_3(CO_2CH_3)O$-), 104.3 ($R\underline{C}H(OCH_3)_2$), 105.4 (-O-CHR-O), 169.1 ($\underline{C}OOCH_3$); IR (CH_2Cl_2) (v, cm^{-1}): 2954 (C-H), 1753 (C=O), 1435, 1374, 1287, 1192, 1137.

5-(5-Methyl-5-cyano-[1,2,4]trioxolan-3-yl)pentanal dimethyl acetal (1d): A mixture of cyclohexene (**1**) (200.1 mg, 2.44 mmol), pyrunonitrile (252.8 mg, 3.66 mmol) in 10 mL of CH_2Cl_2 was subjected to the general ozonolytic procedure. MeOH was added right after the ozonolysis at -78 °C and the solution was then warmed up to room temperature. The reaction completed within 8 h. Removal of solvent afforded the crude product. The silica gel column chromatography by elution with EtOAc/hexane to give the tri-substituted ozonide **1d** (305.6 mg, 1.25 mmol; 51% yield) as a mixture of two diastereomers in a ratio of 60:40 as a colorless oil. TLC (EtOAc/Hexane=1/1) $R_f = 0.61$; ^{1}H-NMR ($CDCl_3$) δ 1.41-1.71 (m, 8H), 1.85 (s, 3H, -$C\underline{H}_3$), 3.32 (s, 3H, -$OC\underline{H}_3$), 3.33 (s, 3H), 4.36 (t, *J* = 5.6 Hz, 1H, -$RC\underline{H}(OCH_3)_2$-), 5.24 (t, *J* = 4.8 Hz, 1H, -$OC\underline{H}RO$-); ^{13}C-NMR ($CDCl_3$) δ 20.8 ($\underline{C}H_3$), 23.1 (2°), 24.2 (2 °), 24.6, 29.6 (2°), 32.1, 32.3 (2°), 52.7 (-$CO_2\underline{C}H_3$), 98.1 ($R\underline{C}H(OCH_3)_2$), 104.3 (-$O\underline{C}CH_3(CN)O$-), 106.3 ($R\underline{C}H(OCH_3)_2$), 116.6 ($\underline{C}N$); IR (CH_2Cl_2) (v, cm^{-1}): 2954 (C-H), 2240 (-CN), 1442, 1172, 1191, 1069.

5-(5-Methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)pentanol (1e): A mixture of cyclohexene (**1**) (1.00 g, 12.21 mmol), methyl pyruvate (1.87 g, 18.31 mmol) in 60 mL of CH_2Cl_2 was subjected to the general ozonolytic procedure. The crude products were redissolved in 60 mL of THF. To this solution was added $LiBH_4$ (201.4 mg, 9.15 mmol; 0.75 mol equiv.) at 0 °C and stirred for 1 h. The reaction mixture was quenched by saturated aqueous ammonium chloride and extracted with dichloromethane. The extracts were washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane to give the desired product **1e** (1.59 g, 6.81 mmol; 56% yield) as a mixture of two diastereomers in a ratio of 70:30 as a colorless oil. TLC (EtOAc/Hexane=1/1) $R_f = 0.43$; ^{1}H-NMR ($CDCl_3$) δ 1.39-2.04 (m, 8H), 1.67 (s, 3H, -$C\underline{H}_3$), 3.64 (t, *J* = 6.2 Hz, 2H, $RC\underline{H}_2OH$), 3.81 (s, 3H, -$CO_2C\underline{H}_3$), 5.24 (t, *J* = 5.0 Hz, 0.7H, -$OC\underline{H}RO$-), 5.44 (t, *J* = 5.2 Hz, 0.3H,-$OC\underline{H}RO$-); ^{13}C-NMR ($CDCl_3$) δ 18.6 ($\underline{C}H_3$), 19.4, 23.5 (2°), 25.3 (2°), 25.5, 29.7 (2°), 32.3 (2°), 32.7 (2°), 52.8 (-$CO_2\underline{C}H_3$), 62.5 ($R\underline{C}H_2OH$), 104.1 (-$O\underline{C}CH_3(CO_2CH_3)O$-), 105.4 (-O-CHR-O), 168.6

($\underline{C}OOCH_3$), 169.2; IR (CH_2Cl_2) (v, cm $^{-1}$): 3618 (-OH), 2939 (C-H), 1753 (C=O), 1438, 1374, 1285, 1193; MS (m/z) (60 eV, rel. intensity): 219 (M^+-15, 8), 174 (M^+-60),1), 161 (31), 144 (2), 128 (4), 119 (19), 115 (11), 99 (82), 81 (50), 55 (19), 43 (100).

5-(5-Methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)pentanoic acid (1f): A mixture of cyclohexene (**1**) (150.1 mg, 1.83 mmol), methyl pyruvate (280.3 mg, 2.75 mmol) in 10 mL of CH_2Cl_2 was subjected to the general ozonolytic procedure at 0 °C. The silica gel column chromatography eluted with EtOAc/hexane give the tri-substituted ozonide **1f** (290.1 mg, 1.17 mmol; 64% yield) as a mixture of two diastereomers in a ratio of 60:40 as a colorless oil. TLC (EtOAc/Hexane=1/1) $R_f = 0.38$; ^{1}H-NMR ($CDCl_3$) δ 1.43-1.86 (m, 6H), 1.67 (s, 3H, $-C\underline{H}_3$), 2.38 (t, *J* = 7.3 Hz, 2H, $RC\underline{H}_2CO_2H$), 3.81 (s, 3H, $-CO_2C\underline{H}_3$), 5.24 (t, *J* = 4.9 Hz, 0.6H, $-OC\underline{H}RO-$), 5.45 (t, *J* = 5.0 Hz, 0.4H,$-OC\underline{H}RO-$); ^{13}C-NMR ($CDCl_3$) δ 18.6 ($\underline{C}H_3$), 19.3, 23.1 (2°), 24.2 (2 °), 24.3, 29.4 ($RC\underline{H}_2(CH_2)_3CHO$), 32.5, 33.7 ($RC\underline{H}_2CO_2H$), 52.9 ($-CO_2\underline{C}H_3$), 53.0, 104.2 ($-O\underline{C}CH_3(CO_2CH_3)O-$), 105.2 (-O-CHR-O), 168.6 ($\underline{C}OOCH_3$), 169.1, 179.4 ($-\underline{C}OOH$); IR (CH_2Cl_2) (v, cm $^{-1}$): 3550-2500 (-OH), 1753 (C=O), 1708 (C=O), 1434, 1375, 1287, 1192, 1135.

General Procedure for the Ozonolysis of Cycloalkenes in the Presence of Acetone:

7-(5,5-Dimethyl-[1,2,4]trioxolan-3-yl)heptanoic acid (2a): A two-necked flask is fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube and a magnetic stirring bar and is charged with cyclooctene (**2**) (162.4 mg, 1.48 mmol) in 7 mL of acetone. The flask is cooled to 0 °C and ozone is bubbled through the solution. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharged. Removal of solvent afforded the crude product which was purified by silica gel column chromatography to give the tri-substituted ozonide (**2a**) (188.7 mg, 0.81 mmol; 55% yield) as a colorless oil. TLC (EtOAc/Hexane=1/1) $R_f = 0.39$; ^{1}H-NMR ($CDCl_3$) δ 1.46 (s, 3H, $-C\underline{H}_3$), 1.48 (s, 3H, $-C\underline{H}_3$), 1.36-1.67 (m, 10H), 2.35 (t, *J* = 7.4 Hz, 2H, $-C\underline{H}_2-COOH$), 5.15 (t, *J* = 4.8 Hz, 1H, $-OC\underline{H}RO-$); ^{13}C-NMR ($CDCl_3$) δ 23.2 ($\underline{C}H_3$), 23.6 (2°), 24.4 (2°), 25.9 ($\underline{C}H_3$), 28.7 (2°C), 29.0 (2°), 30.1 (2°), 33.9 ($R\underline{C}H_2COOH$), 103.9 ($-O\underline{C}HRO-$), 108.6 ($-O\underline{C}(CH_3)_2O-$), 179.5 (C=O); IR ($CH_2Cl_2$) (v, cm $^{-1}$): 3550-2500 (-OH), 1707 (C=O), 1427, 1371, 1219, 1164, 1113.

5-(5,5-Dimethyl-[1,2,4]trioxolan-3-yl)pentanoic acid (1g): TLC (EtOAc/Hexane=1/3) $R_f = 0.15$; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.46 (s, 3H, $-C\underline{H}_3$), 1.48 (s, 3H, $-C\underline{H}_3$), 1.51-1.79 (m, 6H), 2.37 (t, *J* = 3.3 Hz, 2H, $-C\underline{H}_2-COOH$), 5.17 (t, *J* = 4.5 Hz, 1H, $-OC\underline{H}RO-$); ^{13}C-NMR ($CDCl_3$) δ 23.1 ($\underline{C}H_3$), 23.4 (2°), 23.5, 25.7 ($\underline{C}H_3$), 30.3 (2°), 30.6, 30.8, 31.9 (2°), 33.7 ($R\underline{C}H_2COOH$), 103.6 ($-O\underline{C}HRO-$), 103.8, 108.6 ($-O\underline{C}(CH_3)_2O-$), 179.5 (C=O); IR ($CH_2Cl_2$) (v, cm $^{-1}$): 3550-2500 (-OH), 1708 (C=O), 1372, 1333, 1219, 1116.

3'-(5,5-Dimethyl-[1,2,4]trioxolan-3-yl)propyl formate (3a): TLC (EtOAc/Hexane=1/3) $R_f = 0.43$; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.47 (s, 3H, $-C\underline{H}_3$), 1.49 (s, 3H, $-C\underline{H}_3$), 1.80-1.85 (m, 4H), 1.82 (dt, *J* = 7.1 and 2.7 Hz, 2H, $-C\underline{H}_2-COOH$), 5.22 (t, *J* = 1.5 Hz, 1H, $-OC\underline{H}RO-$), 8.06 (s, 1H, $\underline{H}COO$); ^{13}C-NMR ($CDCl_3$) δ 22.7 (2°), 23.2 ($\underline{C}H_3$), 25.6 ($\underline{C}H_3$), 27.5 (2°), 63.2 ($HCOO\underline{C}H_2$), 103.1 ($-O\underline{C}HRO-$), 108.8 ($-O\underline{C}(CH_3)_2O-$), 160.9 (C=O); IR ($CH_2Cl_2$) (v, cm $^{-1}$): 2937 (C-H), 1721 (C=O), 1447, 1372, 1339.

3-(2'-Formylbenzyl)-(5-methyl-5-methoxycarbonyl-[1,2,4]trioxolane (8a): A mixture of indene (**8**) (232.3 mg, 2 mmol), methyl pyruvate (306.3 mg, 3 mmol) in 9 mL of EtOAc was subjected to the general ozonolytic procedure. The crude product was chromatographed on a silica gel column by elution with EtOAc/hexane to give compound **8a** (106.4 mg, 0.8 mmol; 40% yield) as a colorless oil. TLC (EtOAc/Hexane=1/3) $R_f = 0.37$; ^{1}H-NMR ($CDCl_3$) δ 1.64, 1.65 (s, 3H), 2.32-3.60 (m, 2H, Ar-C$\underline{H}_2$-), 3.74 (s, 3H, -OC$\underline{H}_3$), 3.75, 3.77, 5.48 (t, *J* = 4.8 Hz, 0.8H, -OC$\underline{H}$RO-), 5.74 (t, *J* = 5.5 Hz, 0.2H, -OC$\underline{H}$RO-), 7.29-7.87 (m, 4H, Ph-H), 10.1 (s, RCHO); ^{13}C-NMR ($CDCl_3$) δ 18.4 ($\underline{C}H_3$), 18.5, 19.0, 33.3 (2°), 52.8 (-$CO_2\underline{C}H_3$), 52.9, 100.7 (-O$\underline{C}CH_3(CO_2CH_3)$O-), 104.4 (O-$\underline{C}$HR-O), 127.9, 132.9, 133.1, 133.3, 134.5, 135.7, 168.4 ($\underline{C}OOCH_3$), 168.8, 192.8 (R$\underline{C}$HO); IR (CH_2Cl_2) (v, cm $^{-1}$): 3051, 2956 (C-H), 1754 (C=O), 1693, 1419, 1375, 1256.

***cis*-1'-(5-Methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)-3'-formylcyclopentane (9a) and *cis*-1'-(5-Methyl-5-methoxycarbonyl-[1,2,4]trioxolan-3-yl)-3'-methoxycarbonylcyclopentane (9b)**: A mixture of norbonylene (**9**) (235.7 mg, 2.51 mmol), methyl pyruvate (383.6 mg, 3.76 mmol) in 9 mL of EtOAc was subjected to the general ozonolytic procedure. To the crude products in 5 mL of dichloromethane was added CH_2N_2 and the reaction mixture was concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane to give compound **9a** (189.6 mg, 0.78 mmol; 31% yield) and compound **9b** (260.8 mg, 1.00 mmol; 40% yield) as colorless oils. Compound **9a**: TLC (EtOAc/Hexane=1/3) $R_f = 0.36$; ^{1}H-NMR ($CDCl_3$) δ 1.58-2.34 (m, 7H), 1.68 (s, 3H, -CH_3), 2.73-2.86 (m, 1H), 3.68 (s, 3H, -OC$\underline{H}_3$), 3.82 (br s, 3H, OC$\underline{H}_3$), 5.15 (d, *J* = 5.4 Hz, 0.5H, -OC$\underline{H}$RO-), 5.34 (d, *J* = 6.5 Hz, 0.5H, -OC$\underline{H}$RO-); ^{13}C-NMR ($CDCl_3$) δ 18.4 ($\underline{C}H_3$), 18.5, 19.0, 33.3 (2°), 52.8 (-$CO_2\underline{C}H_3$), 52.9, 100.7 (-O$\underline{C}CH_3(CO_2CH_3)$O-), 104.4 (O-$\underline{C}$HR-O), 127.9, 132.9, 133.1, 133.3, 134.5, 135.7, 168.4 ($\underline{C}OOCH_3$), 168.8, 192.8 (R$\underline{C}$HO); IR (CH_2Cl_2) (v, cm $^{-1}$): 3051, 2956 (C-H), 1754 (C=O), 1693, 1419, 1375, 1256. Compound **9b**: ^{1}H-NMR ($CDCl_3$) δ 1.58-2.34 (m, 7H), 1.68 (s, 3H, -CH_3), 2.73-2.86 (m, 1H), 3.68 (s, 3H, -OC$\underline{H}_3$), 3.82 (br s, 3H, OC$\underline{H}_3$), 5.15 (d, *J* = 5.4 Hz, 0.5H, -OC$\underline{H}$RO-), 5.34 (d, *J* = 6.5 Hz, 0.5H, -OC$\underline{H}$RO-); ^{13}C-NMR ($CDCl_3$) δ 18.8 ($\underline{C}H_3$), 19.1, 26.1 (2°), 26.8, 26.9, 27.3, 29.2 (2°), 29.4, 29.6, 30.0, 31.1 (2°), 31.2, 31.6, 39.8 (3°), 42.5 (R$\underline{C}HCO_2$CH3), 42.6, 43.5, 43.8, 51.3 (-$CO_2\underline{C}H_3$), 51.7, 52.8, 53.0, 104.4 (-O$\underline{C}CH_3(CO_2CH_3)$O-), 107.8 (O-$\underline{C}$HR-O), 176.0 ($\underline{C}OOCH_3$); IR ($CH_2Cl_2$) (v, cm $^{-1}$): 3091, 3071, 1963, 1728 (C=O), 1474, 1033.

Methyl 6-oxo-4(*Z*)-hexenoate(10b): A mixture of 1-methoxy-1,4-cyclohexadiene (**10**) (220.1 mg, 2.00 mmol), methyl pyruvate (306.1 mg, 3.00 mmol) in 10 mL of CH_2Cl_2 was subjected to the general ozonolytic procedure. One mol equiv. of ozone is bubbled through the solution carefully. To the resulted solution was added Ph_3P (789.1 mg, 3 mmol) and stirred at room temperature for 2 h. Removal of solvent afforded the crude product. The silica gel column chromatography by elution with EtOAc/hexane to give the compound **10b** (170.1 mg, 0.69 mmol; 60% yield) as a pale yellow oil. TLC (EtOAc/Hexane=1/3) $R_f = 0.37$; ^{1}H-NMR ($CDCl_3$) δ 2.51-2.73 (m, 4H, CH=CHC$\underline{H}_2$C$\underline{H}_2$COOCH$_3$), 3.71 (s, 3H, -OCOC$\underline{H}_3$), 6.14 (ddt, *J* = 14.2, 7.7 and 1.0 Hz, 1H, -CH=C$\underline{H}$CHO), 6.87 (dt, *J* = 15.7 and 6.0 Hz, 1H, C$_H$=CHCHO), 9.52 (t, J = 7.7 Hz, 1H, RC$\underline{H}$O); ^{13}C-NMR ($CDCl_3$) δ 27.5 (R$\underline{C}H_2CH=CH2$), 31.9 (R$\underline{C}H_2CO_2CH_3$), 51.8 (-O$\underline{C}H_3$), 133.3 (CH=$\underline{C}$HCHO), 155.6 ($\underline{C}$H=CHCHO), 193.6 (R$\underline{C}$HO); IR (CH_2Cl_2) (v, cm $^{-1}$): 2928, 1730 (C=O), 1498, 1433, 1362, 1300; MS (m/z) (60 eV, rel. intensity): 142 (M^+, 5), 124 (17), 114 (42), 110 (42), 96 (7), 83 (100), 74 (23), 68 (22); HRMS calcd for $C_7H_{10}O_3$ (M^+), 142.0630, found 142.0624.

Methyl 6-oxo-4(*Z*)-hexenoate (10b) and Dimethyl 3(*Z*)-hexenedioate (11a): A mixture of 1-methoxy-1,4-cyclohexadiene (**10**) (200.1 mg, 1.82 mmol), methyl pyruvate (278.3 mg, 2.73 mmol) in 9 mL of

CH_2Cl_2 was subjected to the general ozonolytic procedure. One mol equiv. of ozone is bubbled through the solution. An inseparable mixture of compounds **10a** and **10b** were obtained. To a mixture of **10a** and **10b** in CH_2Cl_2 was added Et_3N (202.1 mg, 4.96 mmol) and stirred at room temperature for 2 h. The reaction mixture was quenched by 1N HCl and extracted with CH_2Cl_2. The extracts were washed with water and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. To the crude products in 5 mL of CH_2Cl_2 was added CH_2N_2 and the reaction mixture was concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane to give compound **11b** (98.3 mg, 0.69 mmol, 41% yield) and compound **11a** (62.7 mg, 0.37 mmol; 20% yield) as pale yellow oils. Compound **11a:** TLC (EtOAc/Hexane=1/3) $R_f = 0.46$; ^{1}H-NMR ($CDCl_3$) δ 3.12 (d, J = 5.3 Hz, 2H, $RC\underline{H}_2CO_2CH_3$), 3.70 (s, 6H, $RCOOC\underline{H}_3$), 5.82 (dt, J = 4.5 and 0.7 Hz, 2H, -CH=CH-); ^{13}C- NMR ($CDCl_3$) δ 232.8 ($R\underline{C}H_2COOCH_3$), 51.9 ($-COO\underline{C}H_3$), 124.4 (-CH=CH-), 171.6 $R\underline{C}OOCH_3$); IR (CH_2Cl_2) (v, cm $^{-1}$): 2939, 1739 (C=O), 1435, 1374, 1252; MS (m/z) (60 eV, rel. intensity): 172 (M^+, 2), 157 (1), 140 (87), 127 (3), 108 (70), 97 (7), 81 (8), 71 (100); HRMS calcd for $C_8H_{12}O_4$ (M^+), 172.0736, found 172.0734.

General Procedure for the Reaction of Tri-substituted Ozonides with Ph_3P

6,6-Dimethoxyhexanal (12a): To the 8 mL of dichloromethane solution of ozonide **1c** (447.0 mg, 1.61 mmol) was added triphenylphosphine (631.9 mg, 4.41 mmol) at room temperature and stirred at this temperature for 4 h. The reaction mixture was concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane to give compound **12a** (336.4 mg, 1.42 mmol; 88% yield) as a colorless oil. TLC (EtOAc/Hexane=1/3) $R_f = 0.43$; ^{1}H-NMR ($CDCl_3$) δ 1.34-1.74 (m, 6H), 2.45 (dt, J = 8.1 and 1.7 Hz, 2H, $RC\underline{H}_2CHO$), 3.32 (s, 6H, $RCH(OC\underline{H}_3)_2$), 4.36 (t, J = 5.7 Hz, 1H, $RC\underline{H}C(OCH_3)_2$), 9.77 (t, J = 1.7 Hz, 1H, $RC\underline{H}O$); ^{13}C-NMR ($CDCl_3$) δ 21.9 (2°), 24.2 (2°), 32.3, 43.8 ($R\underline{C}H_2CHO$), 52.8 ($-O\underline{C}H_3$), 104.3 ($R\underline{C}H(OCH_3)_2$), 202.5 ($R\underline{C}HO$); IR (CH_2Cl_2) (v, cm $^{-1}$): 2950, 1721 (C=O), 1452, 1384, 1255, 1187; MS (m/z) (60 eV, rel. intensity): 159 (M^+-1, 1), 144 (1), 129 (10), 111 (2), 97 (9), 84 (7), 75 (100), 69 (12); HRMS calcd for $C_8H_{15}O_3$ (M^+-1), 159.1021, found 159.1023.

1,6-Hexanedial (Adipaldehyde) (13a): TLC (EtOAc/Hexane=1/3) $R_f = 0.63$; ^{1}H-NMR ($CDCl_3$) δ 1.60-1.76 (m, 4H), 2.43-2.55 (m, 4H), 9.77 (t, J = 1.6 Hz, 1H, $RC\underline{H}O$); ^{13}C-NMR ($CDCl_3$) δ 21.3 (2°), 43.3 ($R\underline{C}H_2CHO$), 201.8 ($R\underline{C}HO$); IR (CH_2Cl_2) (v, cm $^{-1}$): 2940, 2887, 2827, 1720 (C=O), 1388, 1371, 1239; This aldehyde oxidises readily and should be kept in a sealed tube under nitrogen.

6-Acetoxyhexanal (14a'): To the 4 mL of dichloromethane solution of ozonide **1e** (134.2 mg, 0.57 mmol) was added triphenylphosphine (225.4 mg, 0.86 mmol) at room temperature and stirred at this temperature for 4 h. It is difficult to separate 6-hydroxyhexanal (**14a**) from triphenylphosphine oxide due to the close polarity. To the reaction mixtures were added acetic anhydride (64.4 mg, 0.63 mmol) and triethylamine (63.6 mg, 0.63 mmol) and stirred for 1 h. The reaction mixture was concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane to give compound **14a'** (80.8 mg, 0.51 mmol; 88% yield) as a colorless oil. TLC (EtOAc/Hexane=1/1) $R_f = 0.63$; ^{1}H-NMR ($CDCl_3$) δ 1.35-1.48 (m, 6H), 2.04 (s, 3H, $-OCOC\underline{H}_3$), 2.47 (dt, J = 8.0 and 1.6 Hz, 2H, $RC\underline{H}_2CHO$), 4.06 (d, J = 7.2 Hz, 2H, $RC\underline{H}_2OCOCH_3$), 9.77 (t, J = 2.4 Hz, 1H, $RC\underline{H}O$); ^{13}C-NMR ($CDCl_3$) δ 20.8 ($\underline{C}H_3$), 21.5 (2°), 25.3 (2°), 28.2 (2°), 43.5 ($R\underline{C}H_2CHO$), 64.0 ($-O\underline{C}H_2-$), 170.9 ($\underline{C}OCH_3$), 202.1 ($R\underline{C}HO$); IR (CH_2Cl_2) (v, cm $^{-1}$): 2943, 1719 (C=O), 1456, 1385, 1364, 1231;

MS (m/z) (60 eV, rel. intensity): 159 (M^++1, 2), 135 (88), 115 (39), 98 (40), 84 (36), 70 (25), 61 (100); HRMS calcd for $C_8H_{14}O_3$ (M^+), 158.0943, found 158.0951.

Methyl 6-oxohexanoate (15a'): TLC (EtOAc/Hexane=1/1) R_f = 0.75; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 62-1.74 (m, 6H), 2.30-2.50 (m, 4H, $-C\underline{H}_2CHO$ and $-C\underline{H}_2CO_2CH_3$), 3.67 (s, 3H, $-COOC\underline{H}_3$), 9.77 (t, J = 1.6 Hz, 1H, $RC\underline{H}O$); ^{13}C-NMR ($CDCl_3$) δ 21.4 (2°), 24.3 (2°), 33.6 ($R\underline{C}H_2COOCH_3$), 43.4 ($R\underline{C}H_2CHO$), 51.5 ($COO\underline{C}H_3$), 173.6 ($\underline{C}OOCH_3$), 202.0 ($R\underline{C}HO$); IR (CH_2Cl_2) (v, cm $^{-1}$): 2943, 1735, 1719 (C=O), 1455, 1383, 1363, 1230; MS (m/z) (60 eV, rel. intensity): 144 (M^+, 2), 143 (10), 126 (12), 113 (32), 87 (100), 81 (19), 74 (58), 67 (35); HRMS calcd for $C_7H_{11}O_3$ (M^+-1), 143.0708, found 143.0710.

General Procedure for the Reaction of Tri-substituted Ozonides with Et_3N

6,6-Dimethoxyhexanoic acid (12b): To the 8 mL of dichloromethane solution of ozonide **1c** (438.1 mg, 1.58 mmol) was added triethylamine (175.0 mg, 1.73 mmol) at room temperature and stirred at this temperature for 1 h. The reaction mixture was quenched by 1N hydrogen chloride at 0 °C and extracted with dichloromethane. The extracts were washed with water and brine. The organic layer was dried (Na_2SO_4) filtered and concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane to give compound **12b** (271.6 mg, 1.54 mmol; 98% yield). TLC (EtOAc/Hexane=1/1) R_f = 0.67; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.32-1.74 (m, 6H), 2.37 (dt, J = 7.3 Hz, 2H, $RC\underline{H}_2COOH$), 3.32 (s, 6H, $OC\underline{H}_3$), 4.38 (t, J = 5.5 Hz, 2H, $RC\underline{H}(OCH_3)_2$); ^{13}C-NMR ($CDCl_3$) δ 24.0 (2°), 24.4 (2°), 32.1 ($RCH(O\underline{C}H_3)_2$), 33.9 ($R\underline{C}H_2CO_2H$), 52.7 ($RCH(O\underline{C}H_3)_2$), 104.3 ($R\underline{C}H(OCH_3)_2$), 179.3 ($R\underline{C}OOH$); IR (CH_2Cl_2) (v, cm $^{-1}$): 3550-2500 (-OH), 1706 (C=O), 1408, 1384, 1255, 1190, 1125; MS (m/z) (60 eV, rel. intensity): 175 (M^+-1, 2), 145 (13), 127 (3), 113 (25), 95 (5), 84 (10), 75 (100), 67 (20); HRMS calcd for $C_8H_{16}O_4$ (M^+-1), 175.0970, found 175.0961.

Methyl 6-oxohexanoate (13b'): To the 8 mL of dichloromethane solution of ozonide **1b** (240.1 mg, 1.03 mmol) was added triethylamine (115.0 mg, 1.14 mmol) at room temperature and stirred at this temperature for 1 h. The reaction mixture was quenched by 1N hydrogen chloride at 0 °C and extracted with dichloromethane. The extracts were washed with water and brine. The organic layer was dried (Na_2SO_4) filtered and concentrated. The crude product (**13b**) in 5 mL of CH_2Cl_2 was then treated with CH_2N_2. The reaction mixtures were concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane to give compound **13b'** (96.9 mg, 0.67 mmol; 65% yield). TLC (EtOAc/Hexane=1/1) R_f = 0.75; Pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 1.62-1.74 (m, 6H), 2.30-2.50 (m, 4H, $CHOC\underline{H}_2(CH_2)_2C\underline{H}_2CO_2Me$), 3.67 (s, 3H, $COOC\underline{H}_3$), 9.77 (t, J = 1.6 Hz, 1H, $RC\underline{H}O$); ^{13}C-NMR ($CDCl_3$) δ 21.4 (2°), 24.3 (2°), 33.6 ($R\underline{C}H_2COOMe$), 43.4 ($R\underline{C}H_2CHO$), 51.5 ($COO\underline{C}H_3$), 173.6 ($R\underline{C}OOMe$), 202.0 ($R\underline{C}HO$); MS (m/z) (60 eV, rel. intensity): 144 (M^+, 2), 143 (10), 126 (12), 113 (32), 101 (61), 87 (100), 81 (19), 74 (58), 67 (35); HRMS calcd for $C_7H_{11}O_3$ (M^+-1), 143.0708, found 143.0710.

6-Hydroxyhexanoic acid (14b): TLC (EtOAc/Hexane=1/1) R_f = 0.06; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.25-1.73 (m, 6H), 2.35 (t, J = 7.3 Hz, 2H, $RC\underline{H}_2CO_2H$), 3.63 (td, J = 6.8 and 6.5 Hz, 2H, $RC\underline{H}_2OH$), 6.91 (br, 2H, $-O\underline{H}$); ^{13}C- NMR ($CDCl_3$) δ 24.4 (2°), 25.1 (2°), 32.0 (2°), 33.9 ($R\underline{C}H_2COOH$), 62.4 ($-\underline{C}H_2-OH$), 179.0 $R\underline{C}OOH$); IR (CH_2Cl_2) (v, cm $^{-1}$): 3550-2500 (-OH), 1702 (C=O), 1397, 1254, 1069; MS (m/z)

(60 eV, rel. intensity): 114 (M$^+$-18, 16), 102 (4), 84 (100), 73 (16), 68 (9), 61 (1); HRMS calcd for $C_6H_{10}O_2$ (M$^+$-18), 114.0681, found 114.0683.

Diethyl hexanedioate (15b'): TLC (EtOAc/Hexane=1/1) R_f = 0.73; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.61-1.70 (m, 4H), 2.29-2.39 (m, 2H, $RC\underline{H}_2COOCH_3$), 3.67 (s, 6H, $RCH_2COOC\underline{H}_3$); ^{13}C-NMR ($CDCl_3$) δ 24.4 ($\underline{C}H_3$), 33.6 (2°), 51.5 (-O$\underline{C}H_3$), 173.7 (C=O); MS (m/z) (60 eV, rel. intensity): 175 (M$^+$+1, 1), 143 (77), 114 (100), 101 (90), 83 (31), 74 (60), 61 (2); HRMS calcd for $C_8H_{14}O_4$ (M$^+$), 174.0892, found 174.0886.

General Procedure for the Reaction of Tri-substituted Ozonides with with aqueous NaOH

(4',4'-Dimethoxybutyl)-8,8-dimethoxyoct-2(*E*)-enal (12c): To the 7 mL of THF solution of ozonide **1c** (438.1 mg, 1.58 mmol) was added 1N aqueous NaOH (5.8 mL, 5.8 mmol) at room temperature and stirred at this temperature for 16 h. The reaction mixture was quenched by 1N hydrogen chloride at 0 °C and extracted with dichloromethane. The extracts were washed with water and brine. The organic layer was dried (Na_2SO_4) filtered and concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane to give compound **12c** (191.2 mg, 0.63 mmol; 88% yield). TLC (EtOAc/Hexane=1/1) R_f = 0.62; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.36-1.69 (m, 10H), 2.22-2.42 (m, 4H), 3.31 (s, 6H, $OC\underline{H}_3$), 3.32 (s, 6H, $OC\underline{H}_3$), 4.34 (t, *J* = 5.7 Hz, 1H, $RC\underline{H}(OCH_3)_2$), 4.38 (t, *J* = 5.4 Hz, 1H, $RC\underline{H}(OCH_3)_2$), 6.46 (t, *J* = 7.4 Hz, 1H, -$\underline{C}H$=CHCHO), 9.36 (s, $RC\underline{H}O$); ^{13}C-NMR ($CDCl_3$) δ 23.7 ($\underline{C}H_3$), 24.4 (2°), 28.5 (2°), 32.3, 52.7 (-O$\underline{C}H_3$), 104.3 (-O$\underline{C}H(OCH_3)_2$), 143.4 (CH=$\underline{C}$RCHO), 155.1 (-$\underline{C}$H=C-), 195.0 (R$\underline{C}$HO); IR (CH_2Cl_2) (ν, cm^{-1}): 2951, 1687 (C=O), 1438, 1384, 1245, 1187, 1125; MS (m/z) (60 eV, rel. intensity): 301 (M$^+$-1, 1), 270 (1), 239 (2), 207 (8), 147 (14), 75 (100), 71 (24); HRMS calcd for $C_{16}H_{29}O_5$ (M$^+$-1) 301.2015, found 301.2022. Calc. for $C_{16}H_{30}O_5$: C, 63.54; H, 10.00%. Found: C, 63.39; H, 10.23%.

2-(4'-Hydroxybutyl)-8-hydroxy-oct-2(*E*)-enal (14c): TLC (EtOAc/Hexane=1/1) R_f = 0.1; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.37-1.63 (m, 10H), 2.23-2.45 (m, 4H, allylic hydrogens), 2.59 (br, 2H, -OH), 3.63 (t, *J* = 6.1 Hz, 2H, $RC\underline{H}_2OH$), 3.64 (t, *J* = 6.2 Hz, 1H, $RC\underline{H}_2OH$), 6.49 (t, *J* = 7.4 Hz, 1H, -$\underline{C}$H=CHCHO), 9.35 (s, $RC\underline{H}O$); ^{13}C-NMR ($CDCl_3$) δ 23.5 (2°), 24.8 (2°), 25.2 (2°), 32.2, 62.2 ($RC\underline{H}_2OH$), 62.3 ($RC\underline{H}_2OH$), 143.5 (-CH=$\underline{C}$RCHO), 155.6 (-$\underline{C}$H=CRCHO), 195.4 (R$\underline{C}$HO); IR (CH_2Cl_2) (ν, cm^{-1}): 3650-3200 (-OH), 2938, 1672 (C=O), 1452, 1372, 1280; MS (m/z) (60 eV, rel. intensity): 214 (M$^+$, 2), 196 (18), 178 (10), 149 (32), 137 (100), 127 (47), 111 (27), 93 (95), 81 (78), 67 (51); HRMS calcd for $C_{12}H_{22}O_3$ (M$^+$) 214.1569, found. 214.1570. Calc. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35%. Found: C, 67.41; H, 10.45%.

Dimethyl 5-formylundec-5(*E*)-enedioate (15c'): TLC (EtOAc/Hexane=1/1) R_f = 0.63; Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.46-1.75 (m, 6H), 2.20-2.41 (m, 8H), 3.63 (s, 6H, $OC\underline{H}_3$), 3.64 (s, 6H, $OC\underline{H}_3$), 6.44 (t, *J* = 7.4 Hz, 1H, -$\underline{C}$H=CRCHO), 9.33 (s, $RC\underline{H}O$); ^{13}C-NMR ($CDCl_3$) δ 23.2 (2°), 23.7 (2°), 24.5 (2°), 28.0 (2°), 28.5, 33.5 (2°), 33.6 (2°), 51.4 (-O$\underline{C}H_3$), 143.0 (CH=$\underline{C}$RCHO), 154.8 (-$\underline{C}$H=CRCHO), 173.6 (-$\underline{C}OOCH_3$), 194.7 (R$\underline{C}$HO); IR (CH_2Cl_2) (ν, cm^{-1}): 2923, 1728 (C=O), 1430, 1371, 1278, 1234; MS (m/z) (60 eV, rel. intensity): 270 (M$^+$, 7), 238 (13), 221 (15), 210 (30), 193 (10), 178 (31), 161 (15), 129 (31), 113 (45), 101 (58), 87 (100), 69 (77); HRMS calcd for $C_{14}H_{22}O_5$ (M$^+$) 270.1467, found 270.1454.

Acknowledgments. We are grateful to National Science Council, Academia Sinica and National Chung-Cheng University , the Republic of China for the financial supports.

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(*Received in China* 22 *October* 1996; *revised* 4 *December* 1996; *accepted* 6 *February* 1997)