Ozonolysis of Bis-*endo*-diacylbicyclo[2.2.1]heptenes in Dichloromethane-Methanol

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Abstract:

Ozonolysis of bis-*endo*-diacylbicyclo[2.2.1]heptenes **3a-d** at -78 ℃ in dichloromethane-methanol gave the hydroperoxides **6a-d** in 70-80% yields. Ozonolysis of bis-*endo*-diacetylbicyclo[2.2.2]octene **15** and bis-*endo*-diacetyl-7-oxabicyclo-[2.2.1]heptene **16** under the same reaction conditions gave the hydroperoxides **17** and **18**, respectively. The intramolecular sequential nucleophilic addition of the carbonyl groups to the carbonyl oxide group was observed for the first time and was found to be faster than the intermolecular nucleophilic addition of a methanol molecule to the carbonyl oxide group. Ozonolysis of compound **23** in CH_2Cl_2-MeOH at -78 ℃ followed by reduction with Me_2S gave compounds **24** and **25**, in which the stereochemistry of the methoxyl groups was determined by X-ray analysis.

Introduction

Extensive investigation of the mechanism of alkene ozonolysis has confirmed the essential features of the pathway originally proposed by Criegee.[1] Apart from the long-established utility of ozonolysis in synthesis and structure determination, much of the current interest in this process centers on the factors affecting the direction of cleavage of the primary ozonide (PO) and the nature of the transient carbonyl oxide intermediate formed along with a carbonyl group by fragmentation of the PO.[2] Substituent effects on the regioselectivity of the PO fragmentation have been reported in cases in which the substituents are directly placed on the ozonation alkene bond.[3] The cleavage of the PO tends to occur along the path which results in the placement of electron-donating substituents on the carbonyl oxide fragment, while electron-withdrawing substituents are incorporated in the carbonyl product.

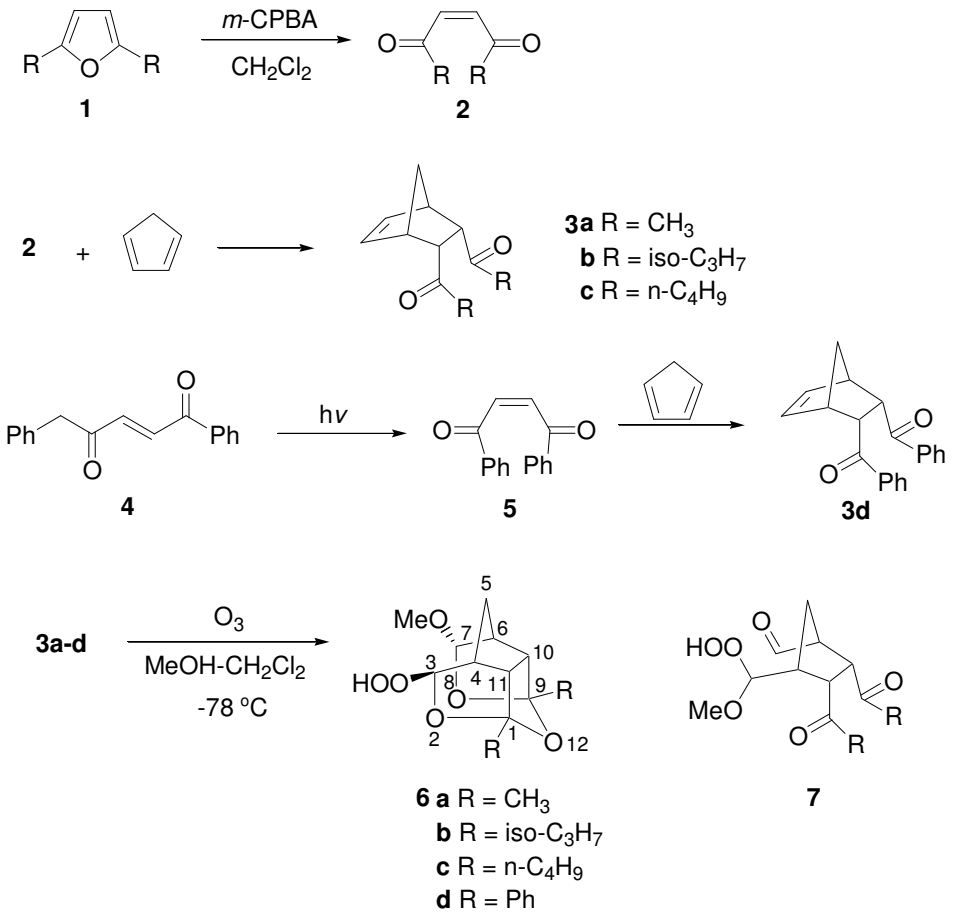
An intermolecular nucleophilic addition of a hydroxyl group to a carbonyl oxide, for instance, ozonolysis of an olefin in an alcohol, affords an α-alkoxy hydroperoxide and a carbonyl compound.[2] This reaction is usually used for the determination of the regiochemistry of carbonyl oxide formation from PO fragmentation because the product composition reflects the regioselectivity in the PO cleavage.[4] This reaction has also been utilized for the synthesis of terminally differentiated compounds.[5] Several years ago, we reported the observation of exclusive regioselective fragmentation of PO controlled by remote different carbonyl groups and stereoselective formation of final ozonides on ozonolysis of norbornene derivatives.[6] We also demonstrated that reaction of final ozonides with triethylamine could act as a method for determining the regiochemistry of carbonyl oxide formation from PO fragmentation. Later on, we reported the synthesis of new diacetal trioxa-cage compounds via an intramolecular nucleophilic addition of the hydroxyl group to the

carbonyl oxide which was generated by ozonolysis of the alkene bond.[7] In this paper we wish to report the observation for the first time of intramolecular sequential nucleophilic addition of carbonyl groups to the carbonyl oxide on ozonolysis of bis-*endo* diacylnorbornene derivatives in methanol-dichloromethane solution.

Result and Discussion

Oxidation of 2,5-dialkylfurans **1a-c** with *m*-chloroperoxybenzoic acid (*m*-CPBA)[8] in dichloromethane at 0 ℃ gave the *cis*-enediones **2a-c**. Diels-Alder reaction of **2a-c** with cyclopentadiene at room temperature gave the *endo* products **3a-c** as the major products in 80-85% yields, respectively.[9] Photoisomerization of compound **4** (commercially available) via the *cis* isomer **5** followed by Diels-Alder reaction with cyclopentadiene gave compound **3d** in 70% yield (Scheme 1).[10] Ozonolysis of the *endo* adducts **3a-d** in the cosolvents of methanol and dichloromethane (1:1) at -78 ℃ gave the hydroperoxides **6a-d** in 70-80% yields, respectively. No detectable amount of compound **7** was obtained in each case. Thus, the intramolecular sequential nucleophilic addition of the carbonyl groups to the carbonyl oxide group is faster than the intermolecular nucleophilic addition of a methanol molecule to the carbonyl oxide group.

Scheme 1



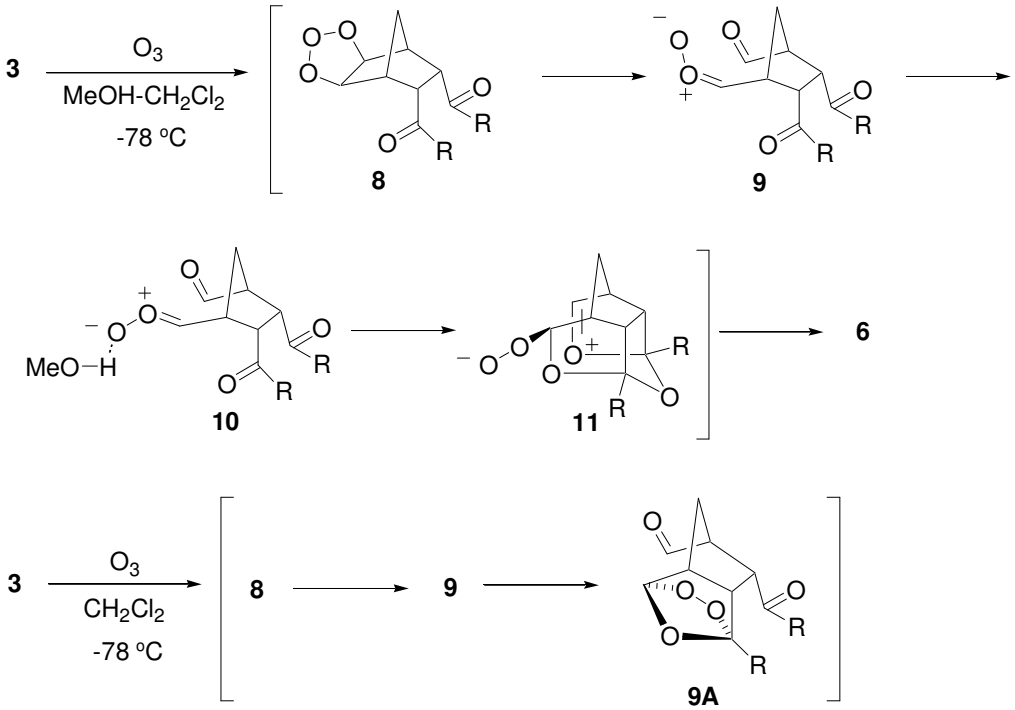
The structure of compounds **6a-d** was identified by their spectral data. The infrared (IR) spectra of **6a-d** showed strong absorptions at 3500-3200 cm^{-1} for the hydroperoxide hydroxyl group and at 1050 cm^{-1} for the ether C-O bonds and lacked any carbonyl absorption. The ^{1}H NMR spectrum of **6a** revealed a singlet at δ 8.70 for the hydroperoxide proton, a doublet at δ 5.46 for the hemiacetal proton on C_3, a doublet at δ 4.91 for the acetal proton on C_7, and a singlet at δ 3.35 for the methoxyl protons. The absorption at δ 2.08 (a singlet) for the methyl ketone protons of **3a** shifted to δ 1.63 and 1.58 for the angular methyl protons of **6a**. The ^{13}C NMR spectrum of **6a** lacked any carbonyl absorption and displayed two peaks at δ 113.63 and δ 110.97 for the two acetal carbons C_3 and C_7, two peaks at δ 119.80 and δ 119.66 for the two quarternary carbons C_1 and C_9, and one peak at δ 54.94 for the methoxyl

carbon. The IR spectra and ^{1}H and ^{13}C NMR spectra of **6b**, **6c**, and **6d** revealed that these compounds possess the same skeleton as **6a**. The coupling constants for the hemiacetal proton on C_3 (J = 2.4 Hz) and for the acetal proton on C_7 (J = 1.2 Hz) may imply that the protons on C_3 and C_7 are *trans* to the protons on C_4 and C_6, respectively. The stereochemistry of the hydroperoxide group and the methoxyl group of **6a-d** was also determined on the basis of NOE experiments of **6a**. Irradiating the hemiacetal proton on C_3 of **6a** (δ 5.46) gives 7.5% enhancement for the C_7 proton absorptions and 2.4% enhancement for the C_4 proton absorptions. Irradiating the acetal proton on C_7 of **6a** (δ 4.91) gives 7.3% enhancement for the C_3 proton absorptions and 2.0% enhancement for the C_6 proton absorptions.

A reaction mechanism was proposed for the formation of compounds **6a-d** by ozonolysis of **3a-d** in MeOH-CH_2Cl_2 cosolvents (Scheme 2). 1,3-Dipolar cycloaddition of an ozone molecule with the alkene bond of **3** via the *exo* face gave the 1,2,3-trioxolane **8**. A least-motion fragmentation[11] of the 1,2,3-trioxolane ring of the primary ozonide **8** leads to the syn-oriented carbonyl oxide **9**, followed by free rotation[2,4] of the carbonyl oxide group of **9** to give the intermediate **10** which is stabilized by hydrogen bonding with methanol molecule. Sequential intramolecular nucleophilic addition of the *endo* acyl groups and the newly-formed formyl group to the carbonyl oxide group gave the intermediate **11**. Intermolecular nucleophilic addition of a methanol molecule to the oxonium ion of **11** from the stereochemically less hindered convex face gave the observed products **6a-d**. Since products **6a-d**, instead of compounds **7a-d**, were obtained, the intramolecular sequential nucleophilic addition of the carbonyl groups to the carbonyl oxide group of **10** is faster than the intermolecular nucleophilic addition of a methanol molecule to the carbonyl oxide group of **10**. On the other hand, ozonolysis of **3** in dichloromethane in the absence of methanol gave the final ozonide **9A** via the intermediates **8** and **9**, which was

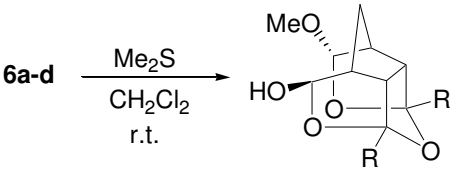
converted to the tetraoxa-cages by reduction with dimethyl sulfide.[9a]

Scheme 2

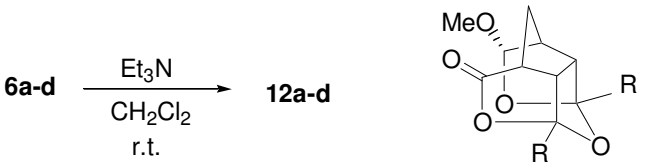


Reduction of **6a-d** with dimethyl sulfide in dichloromethane at room temperature gave compounds **12a-d** in 85-90% yields (Scheme 3). Treatment of **6a-d** with triethylamine in dichloromethane at room temperature gave the same products **12a-d** in 80-85% yields. No detectable amount of compounds **13a-d** was obtained. Thus, in reaction with compounds **6a-d**, triethylamine, like dimethyl sulfide, acts as a reducing reagent rather than as a base. On the other hand, in reaction with final ozonides, triethylamine acted as a base, different from dimethyl sulfide, to give different products.[5,9a] Ozonolysis of **3a-d** in the cosolvents of dichloromethane and methanol (1:1) at -78 ℃ followed by reduction with dimethyl sulfide gave compounds **14a-d** in 70-75% yields.

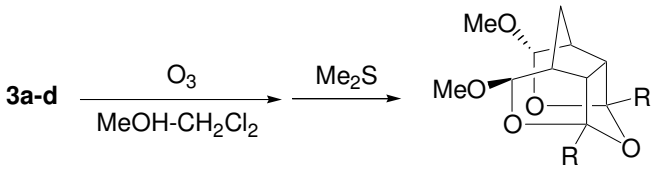
Scheme 3



12a-d



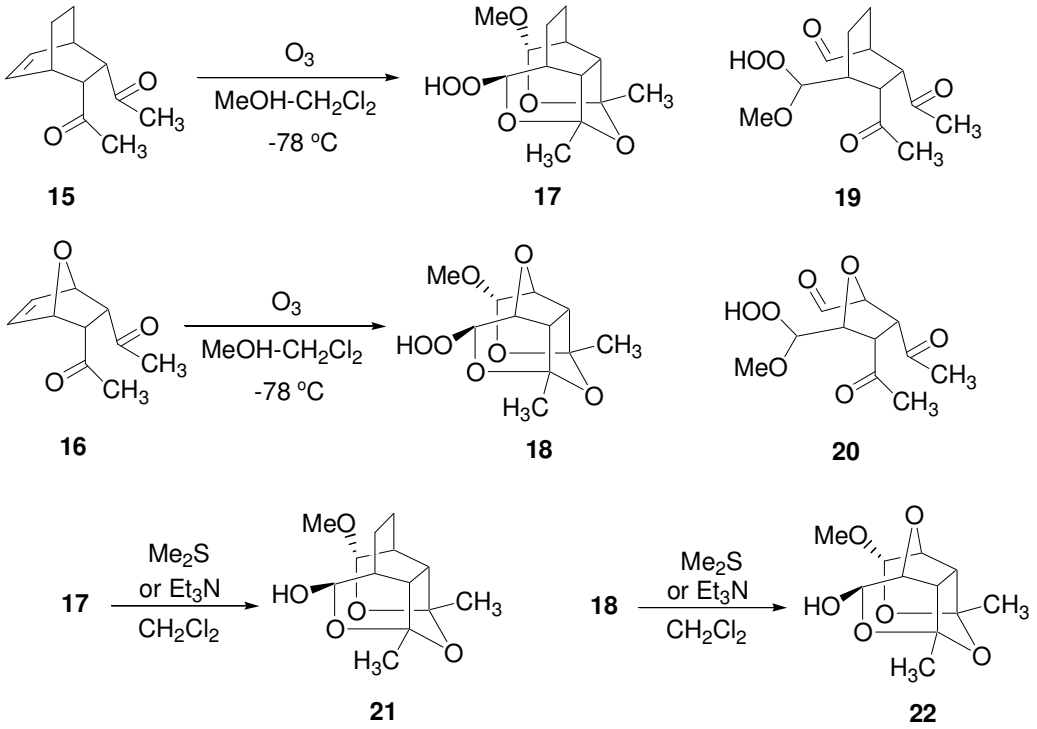
13



14a-d

To extend the intramolecular sequential nucleophilic addition of the carbonyl groups to the carbonyl oxide group, bis-*endo*-diacetylbicyclo[2.2.2]octane **15**[12] and bis-*endo*-diacetyl-7-oxabicyclo[2.2.1]heptane **16**[13] were prepared. Ozonolysis of **15** and **16** in CH_2Cl_2-MeOH (1:1) at -78 ℃ gave the hydroperoxides **17** and **18** in 70-80% yields, respectively. No detectable amount of compounds **19** and **20** was obtained (Scheme 4). Again, the intramolecular sequential nucleophilic addition of the carbonyl groups to the carbonyl oxide group is faster than the intermolecular nucleophilic addition of a methanol molecule to the carbonyl oxide group. Reduction of **17** and **18** with dimethyl sulfide or triethylamine at room temperature gave compounds **21** and **22**, respectively.

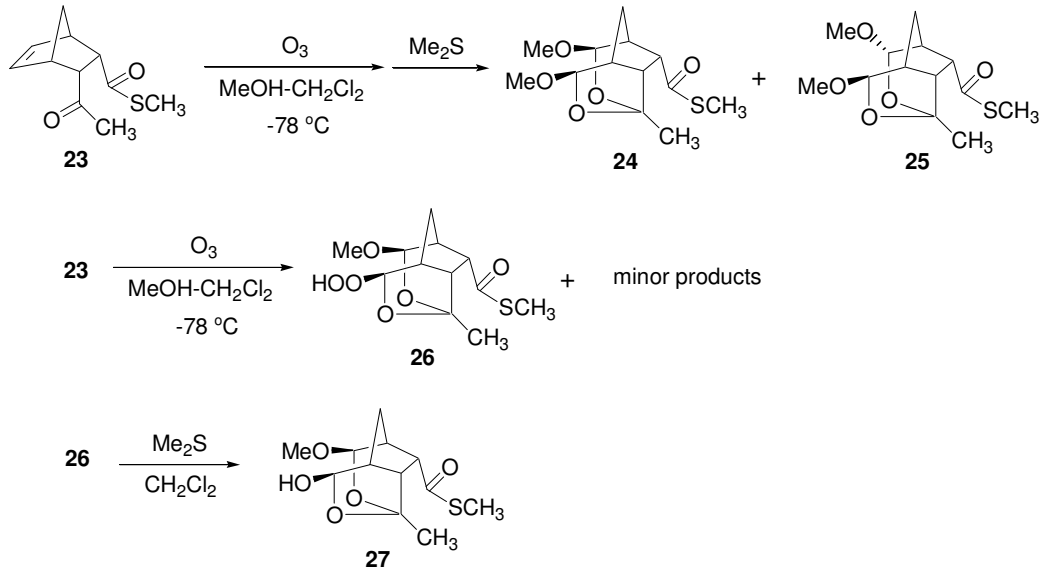
Scheme 4



To understand the feasibility of a thioester group on the sequential nucleophilic addition, compound **23** was prepared.[14] Ozonolysis of **23** in CH_2Cl_2-MeOH (1:1) at -78 ℃ followed by reduction with dimethyl sulfide gave compound **24** as the major product and compound **25** as the minor product (Scheme 5). The stereochemistry of the methoxyl groups of **24** and **25** was difficultly determined on the basis of H,H-COSY and NOESY experiments. The structures of **24** and **25** were finally determined by X-ray analysis, Figures 1 and 2. Ozonolysis of **23** in CH_2Cl_2-MeOH (1:1) at -78 ℃ without reduction gave compound **26** as the major product (65%) with unidentified minor products. In this ozonolysis reaction, the thioester group of **23** did not participate the intramolecular sequential nucleophilic addition. Reduction of compound **26** with dimethyl sulfide in CH_2Cl_2 gave the hemiacetal **27**. While the thioester group of compound **23** was replaced with an ester group, a similar result for the ozonolysis reaction was observed that the ester group did not participate the

intramolecular sequential nucleophilic addition.[15]

Scheme 5



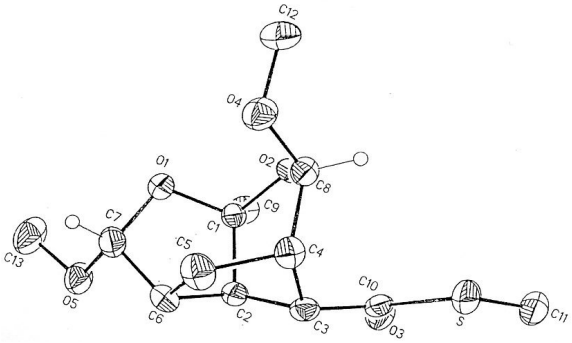


Figure 1. ORTEP diagram of **24**.

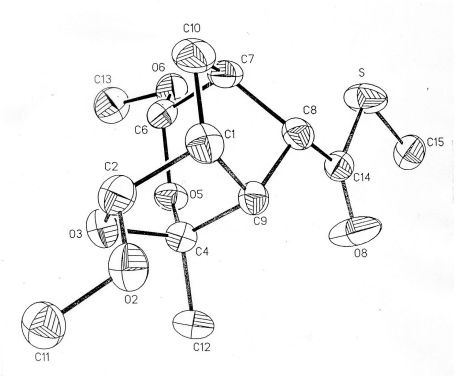


Figure 2. ORTEP diagram of **25**.

Conclusion

Ozonolysis of compounds **3a-d**, **15**, **16**, and **23** at -78 ℃ in dichloromethane-methanel solutions gave the hydroperoxides **6a-d**, **17**, **18**, and **26** in high yields, respectively. The intramolecular sequential nucleophilic addition of the carbonyl groups to the carbonyl oxide group was observed for the first time and was found to be faster than the intermolecular nucleophilic addition of a methanol molecule to the carbonyl oxide group. In the ozonolysis of compound **23**, the thioester group was found not to participate the sequential nucleophilic addition reaction. The structures and stereochemistry of the methoxyl groups of compounds **24** and **25** were determined by X-ray analysis.

Experimental Section

General. Melting points were determined in capillary tubes with a Laboratory Devices melting point apparatus and uncorrected. Infrared spectra were recorded in $CHCl_3$ solutions or on neat thin films between NaCl disks. ^1H NMR spectra were determined at 300 MHz, and ^{13}C NMR spectra were determined at 75 MHz on Fourier transform spectrometers. Chemical shifts are reported in ppm relative to TMS in the solvents specified. The multiplicities of ^{13}C signals were determined by DEPT techniques. High resolution mass values were obtained with a high resolution mass spectrometer at the Department of Chemistry, National Tsing Hua University. Elemental analyses were performed at the microanalysis laboratory of this department. X-ray analyses were carried out on a diffractometer at the Department of Chemistry, National Chung Hsing University. For thin-layer chromatography (TLC) analysis, precoated TLC plates (Kieselgel 60 F_{254}) were used, and column chromatography was done by using Kieselgel 60 (70-230 mesh) as the stationary phase. THF was distilled immediately prior to use from sodium benzophenone ketyl under nitrogen. CH_2Cl_2 was distilled from CaH_2 under nitrogen.

General procedure for the ozonolysis of 3a-d in the cosolvent of dichloromethane-methanol. Formation of the hydroperoxides 6a-d. The solution of **3a** (0.50 g, 2.8 mmol) in dichloromethane and methanol (volume 1:1) (40 mL) was cooled to -78 ℃, and ozone was bubbled through it at -78 ℃ until the solution turned light blue. The reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated, and the crude product was purified by flash column chromatography to give the hydroperoxide **6a** (0.45 g, 75%).

1,9-Dimethyl-3β-hydroperoxy-7α-methoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11}0.^{6,10}] dodecane 6a. White solid; mp 103-104 ℃; yield 75%; IR ($CHCl_3$) 3550-3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 1H), 5.46 (d, *J* = 2.4 Hz, 1H), 4.91 (d, *J* = 1.2 Hz, 1H), 3.35 (s, 3H), 3.25-3.22 (m, 2H), 2.79-2.73 (m, 2H), 2.39-2.30 (m, 1H), 2.14-2.08 (m, 1H), 1.63 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 119.80 (C), 119.66 (C), 113.63 (CH), 110.97 (CH), 59.90 (CH), 59.64 (CH), 54.94 (OCH_3), 52.26 (CH), 48.74 (CH), 36.50 (CH_2), 27.06 (CH_3), 26.94 (CH_3); LRMS *m/z* (rel int) 258 (M^+, 5), 153 (100); HRMS (EI) calcd for $C_{12}H_{18}O_6$ 258.1103, found 258.1108.

1,9-Diisopropyl-3β-hydroperoxy-7α-methoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11} 0.^{6,10}]dodecane 6b. White solid; mp 65-66 ℃; yield 80%; IR ($CHCl_3$) 3550-3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 5.54 (d, *J* = 2.7 Hz, 1H), 4.97 (d, *J* = 1.5 Hz, 1H), 3.39 (s, 3H), 3.29-3.25 (m, 2H), 2.70-2.58 (m, 2H), 2.31-2.27 (m, 2H), 2.05-1.95 (m, 2H), 1.08-0.91 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 123.85 (C), 123.82 (C), 113.58 (CH), 111.42 (CH), 56.64 (CH), 56.49 (CH), 55.53 (OCH_3), 52.09 (CH), 48.49 (CH), 37.35 (CH_2), 35.88 (CH), 35.73 (CH), 17.59 (CH_3), 17.51 (CH_3), 17.32 (CH_3), 17.10 (CH_3); LRMS *m/z* (rel int) 314 (M^+, 6), 209 (100); HRMS (EI) calcd for $C_{16}H_{26}O_6$ 314.1729, found 314.1726.

1,9-Di-*n*-butyl-3β-hydroperoxy-7α-methoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11}

0.^{6,10}]dodecane 6c. White solid; mp 70-71 ℃; yield 80%; IR ($CHCl_3$) 3550-3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 5.49 (d, *J* = 2.7 Hz, 1H), 4.92 (d, *J* = 1.5 Hz, 1H), 3.35 (s, 3H), 3.22-3.19 (m, 2H), 2.71-2.68 (m, 2H), 2.40-2.24 (m, 1H), 2.20-2.10 (m, 1H), 1.85-1.73 (m, 4H), 1.48-1.33 (m, 8H), 0.94-0.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 121.89 (C), 121.70 (C), 113.54 (CH), 111.12 (CH), 58.20 (CH), 58.06 (CH), 55.29 (OCH_3), 52.09 (CH), 48.48 (CH), 39.18 ($2CH_2$), 36.82 (CH_2), 26.42 (CH_2), 26.24 (CH_2), 22.75 ($2CH_2$), 14.01 ($2CH_3$); LRMS *m/z* (rel int) 342 (M^+, 12), 71 (100); HRMS (EI) calcd for $C_{18}H_{30}O_6$ 342.2042, found 342.2047.

1,9-Diphenyl-3β-hydroperoxy-7α-methoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11}0.^{6,10}] -dodecane 6d. White solid; mp 149-150 ℃; yield 70%; IR ($CHCl_3$) 3550-3300, 1600, 1100, 750, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.63-7.55 (m, 4H), 7.40-7.26 (m, 6H), 5.78 (d, *J* = 2.7 Hz, 1H), 5.24 (d, *J* = 1.8 Hz, 1H), 3.80-3.76 (m, 2H), 3.41 (s, 3H), 2.94-2.92 (m, 2H), 2.42-2.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 141.39 (C), 141.27 (C), 128.26 (2CH), 128.09 (2CH), 127.94 (2CH), 125.79 (2CH), 125.53 (2CH), 120.44 (2C), 114.19 (CH), 112.36 (CH), 62.13 (CH), 61.81 (CH), 55.99 (OCH_3), 52.44 (CH), 48.87 (CH), 36.71 (CH_2); LRMS *m/z* (rel int) 382 (M^+, 5), 277 (100); HRMS (EI) calcd for $C_{22}H_{22}O_6$ 382.1416, found 382.1413.

General procedure for the reduction of 6a-d with dimethyl sulfide. To a solution of **6a** (0.30 g, 1.16 mmol) in dichloromethane (20 mL) was added excess dimethyl sulfide (0.50 g) at 0 ℃. The reaction mixture was stirred at room temperature for 1 h. The solvent and excess dimethyl sulfide was evaporated, and the crude product was purified by flash column chromatography to give the hemiacetal product **12a** (0.27 g, 85%).

1,9-Dimethyl-3β-hydroxy-7α-methoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11}0.^{6,10}]do-decane 12a. White solid; mp 102-103 ℃; yield 85%; IR ($CHCl_3$) 3500, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.39 (d, *J* = 3.0 Hz, 1H), 4.88 (s, 1H), 4.01 (d, *J* = 3.9

Hz, 1H), 3.29 (s, 3H), 3.25-3.14 (m, 2H), 2.74-2.67 (m, 2H), 2.29-2.18 (m, 1H), 2.04-1.90 (m, 1H), 1.55 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 119.54 (C), 118.99 (C), 111.00 (CH), 104.13 (CH), 60.04 (CH), 59.05 (CH), 54.59 (OCH_3), 53.72 (CH), 52.61 (CH), 35.48 (CH_2), 27.64 (CH_3), 27.44 (CH_3); LRMS *m/z* (rel int) 242 (M^+, 3), 153 (100); HRMS (EI) calcd for $C_{12}H_{18}O_5$ 242.1154, found 242.1158; Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.53; H, 7.52.

1,9-Diisopropyl-3β-hydroxy-7α-methoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11}0.^{6,10}]-dodecane 12b. White solid; mp 70-71 ℃; yield 90%; IR ($CHCl_3$) 3500, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (d, *J* = 3.9 Hz, 1H), 4.96 (s, 1H), 3.33 (s, 3H), 3.28-3.25 (m, 2H), 2.84 (d, *J* = 3.9 Hz, 1H), 2.74-2.50 (m, 2H), 2.26-2.22 (m, 2H), 2.04-1.93 (m, 2H), 1.08-0.88 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 123.72 (C), 122.36 (C), 111.76 (CH), 104.14 (CH), 57.48 (CH), 56.18 (CH), 55.28 (OCH_3), 53.69 (CH), 52.40 (CH), 36.75 (CH_2), 36.12 (CH), 35.80 (CH), 17.70 (CH_3), 17.45 ($2CH_3$), 17.08 (CH_3); LRMS *m/z* (rel int) 298 (M^+, 3), 223 (100); HRMS (EI) calcd for $C_{16}H_{26}O_5$ 298.1780, found 298.1786; Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.45; H, 8.83.

1,9-Di-*n*-butyl-3β-hydroxy-7α-methoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11}0.^{6,10}]-dodecane 12c. White solid; mp 75-76 ℃; yield 90%; IR ($CHCl_3$) 3500, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (d, *J* = 3.9 Hz, 1H), 4.93 (s, 1H), 3.79 (d, *J* = 3.9 Hz, 1H), 3.33 (s, 3H), 3.27-3.17 (m, 2H), 2.78-2.58 (m, 2H), 2.31-2.05 (m, 2H), 1.83-1.62 (m, 4H), 1.45-1.30 (m, 8H), 0.91 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 121.45 (C), 120.69 (C), 111.22 (CH), 104.01 (CH), 58.56 (CH), 57.55 (CH), 54.89 (OCH_3), 53.56 (CH), 52.32 (CH), 39.66 (CH_2), 39.44 (CH_2), 35.91 (CH_2), 26.37 (CH_2), 26.17 (CH_2), 22.77 ($2CH_2$), 14.01 (CH_3), 13.98 (CH_3); LRMS *m/z* (rel int) 326 (M^+, 5), 237 (100); HRMS (EI) calcd for $C_{18}H_{30}O_5$ 326.2093, found 326.2095; Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.27; H, 9.28.

1,9-Diphenyl-3β-hydroxy-7α-methoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11}0.^{6,10}]dodecane 12d. White solid; mp 155-156 ℃; yield 85%; IR ($CHCl_3$) 3500, 1600, 1100, 750, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63-7.59 (m, 4H), 7.39-7.28 (m, 6H), 5.80 (d, *J* = 3.9 Hz, 1H), 5.23 (s, 1H), 3.89 (d, *J* = 3.9 Hz, 1H), 3.79-3.74 (m, 2H), 3.34 (s, 3H), 2.93-2.85 (m, 2H), 2.35-2.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 142.03 (C), 141.77 (C), 128.12 (2CH), 128.06 (2CH), 128.03 (2CH), 126.01 (2CH), 125.90 (2CH), 120.62 (C), 119.60 (C), 112.71 (CH), 105.35 (CH), 63.32 (CH), 61.63 (CH), 55.66 (OCH_3), 53.79 (CH), 52.79 (CH), 36.43 (CH_2); LRMS *m/z* (rel int) 366 (M^+, 3), 203 (100); HRMS (EI) calcd for $C_{22}H_{22}O_5$ 366.1467, found 366.1463; Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 72.16; H, 6.09.

General procedure for the reaction of 6a-d with triethylamine. To a solution of **6a** (0.30 g, 1.16 mmol) in dichloromethane (20 mL) was added excess triethylamine (0.60 g) at 0 ℃. The reaction mixture was stirred at room temperature for 1 h. The solvent and excess triethylamine was evaporated, and the crude product was purified by flash column chromatography to give the hemiacetal product **12a** (0.27 g, 85%). No detectable amount of the lactone **13a** was obtained.

General procedure for the ozonolysis of 3a-d. Formation of the diacetals 14a-d. The solution of **3a** (0.50 g, 2.8 mmol) in dichloromethane and methanol (volume 1:1) (40 mL) was cooled to -78 ℃, and ozone was bubbled through it at -78 ℃ until the solution turned light blue. To this solution was added dimethyl sulfide (0.52 g, 8.4 mmol) at -78. ℃ The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated, and the crude product was purified by column chromatography to give the diacetal **14a** (0.46 g, 70%).

1,9-Dimethyl-3,7-dimethoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11}0.^{6,10}]dodecane 14a. White solid; mp 100-101 ℃; yield 70%; IR ($CHCl_3$) 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (d, *J* = 1.8 Hz, 2H), 3.36 (s, 6H), 3.24-3.21 (m, 2H), 2.74-2.71 (m, 2H),

2.39-2.28 (m, 1H), 2.05-1.95 (m, 1H), 1.57 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 119.56 (2C), 111.00 (2CH), 59.61 (2CH), 54.92 ($2OCH_3$), 52.62 (2CH), 36.10 (CH_2), 27.31 ($2CH_3$); LRMS *m/z* (rel int) 256 (M^+, 14), 117 (100); HRMS (EI) calcd for $C_{13}H_{20}O_5$ 256.1311, found 256.1317; Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.95; H, 7.89.

1,9-Diisopropyl-3,7-dimethoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11}0.^{6,10}]dodecane 14b. White solid; mp 80-81 ℃; yield 75%; IR ($CHCl_3$) 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (d, *J* = 2.4 Hz, 2H), 3.34 (s, 6H), 3.24-3.21 (m, 2H), 2.64-2.53 (m, 2H), 2.30-2.19 (m, 2H), 1.95-1.91 (m, 2H), 1.08-0.89 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 123.70 (2C), 111.60 (2CH), 56.87 (2CH), 55.62 ($2OCH_3$), 52.54 (2CH), 36.03 (CH_2), 35.96 (2CH), 17.64 ($2CH_3$), 17.30 ($2CH_3$); LRMS *m/z* (rel int) 312 (M^+, 4), 194 (100); HRMS (EI) calcd for $C_{17}H_{28}O_5$ 312.1937, found 312.1931; Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.39; H, 9.07.

1,9-Di-*n*-butyl-3,7-dimethoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11}0.^{6,10}]dodecane 14c. White solid; mp 75-76 ℃; yield 75%; IR ($CHCl_3$) 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91 (d, *J* = 2.4 Hz, 2H), 3.35 (s, 6H), 3.20-3.17 (m, 2H), 2.71-2.65 (m, 2H), 2.31-2.26 (m, 1H), 2.07-2.02 (m, 1H), 1.85-1.67 (m, 4H), 1.51-1.26 (m, 8H), 0.91 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 121.58 (2C), 111.09 (2CH), 58.09 (2CH), 55.18 ($2OCH_3$), 52.41 (2CH), 39.59 ($2CH_2$), 36.50 (CH_2), 26.22 ($2CH_2$), 22.78 ($2CH_2$), 13.98 ($2CH_3$); LRMS *m/z* (rel int) 340 (M^+, 8), 195 (100); HRMS (EI) calcd for $C_{19}H_{32}O_5$ 340.2249, found 340.2245; Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 67.05; H, 9.51.

1,9-Diphenyl-3,7-dimethoxy-2,8,12-trioxatetracyclo[7.2.1.0.^{4,11}0.^{6,10}]dodecane 14d. White solid; mp 112-113 ℃; yield 75%; IR ($CHCl_3$) 1600, 1100, 750, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.58 (m, 4H), 7.37-7.30 (m, 6H), 5.25 (d, *J* = 2.4 Hz, 2H), 3.78-3.75 (m, 2H), 3.41 (s, 6H), 2.94-2.89 (m, 2H), 2.39-2.35 (m, 2H); ^{13}C NMR

(75 MHz, $CDCl_3$, DEPT) δ 141.83 (2C), 128.04 (4CH), 127.99 (4CH), 125.91 (2CH), 120.47 (2C), 112.55 (2CH), 62.32 (2CH), 55.93 ($2OCH_3$), 52.79 (2CH), 36.97 (CH_2); LRMS *m/z* (rel int) 380 (M^+, 3), 198 (100); HRMS (EI) calcd for $C_{23}H_{24}O_5$ 380.1623, found 380.1628; Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.64; H, 6.39.

Ozonolysis of compounds 15 and 16 in CH_2Cl_2-MeOH. The same reaction conditions of ozonolysis of **3a-d** were applied for the ozonolysis of compounds **15** and **16** in the cosolvents of dichloromethane-methanol to give the hydroperoxides **17** and **18**, respectively.

1,10-Dimethyl-3β-hydroperoxy-8α-methoxy-2,9,13-trioxatetracyclo[8.2.1.0.^{4,12} 0.^{7,11}]tridecane 17. White solid; mp 106-107 ℃; yield 70%; IR ($CHCl_3$) 3600-3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 5.39 (d, *J* = 2.4 Hz, 1H), 4.81 (d, *J* = 2.1 Hz, 1H), 3.55-3.48 (m, 2H), 3.35 (s, 3H), 2.80-2.72 (m, 2H), 2.48-2.34 (m, 2H), 1.73-1.67 (m, 2H), 1.63 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 121.29 (C), 121.08 (C), 113.25 (CH), 111.29 (CH), 55.14 (OCH_3), 45.84 (CH), 45.09 (CH), 41.38 (CH), 37.99 (CH), 28.16 (CH_3), 28.06 (CH_3), 21.68 (CH_2), 21.07 (CH_2); LRMS *m/z* (rel int) 272 (M^+, 3), 91 (100); HRMS (EI) calcd for $C_{13}H_{20}O_6$ 272.1259, found 272.1256.

1,9-Dimethyl-3β-hydroperoxy-7α-methoxy-2,5,8,12-tetraoxatetracyclo[7.2.1.0.^{4,11} 0.^{6,10}]dodecane 18. White solid; mp 85-86 ℃; yield 80%; IR ($CHCl_3$) 3600-3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 5.57 (s, 1H), 5.03 (s, 1H), 4.70-4.67 (m, 1H), 4.59-4.57 (m, 1H), 3.48-3.46 (m, 2H), 3.34 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 121.82 (C), 121.02 (C), 111.57 (CH), 108.39 (CH), 90.45 (CH), 88.04 (CH), 59.39 (CH), 59.24 (CH), 54.29 (OCH_3), 27.40 (CH_3), 27.24 (CH_3); LRMS *m/z* (rel int) 260 (M^+, 5), 113 (100); HRMS (EI) calcd for $C_{11}H_{16}O_7$ 260.0896, found 260.0894.

Reduction of compounds 17 and 18 with dimethyl sulfide or triethylamine. The same reaction conditions of the reduction of **6a-d** with dimethyl sulfide or triethylamine were applied for the reduction of compounds **17** and **18** to give the hemiacetals **21** and **22**, respectively.

1,10-dimethyl-3β-hydroxy-8α-methoxy-2,9,13-trioxatetracyclo[8.2.1.0.^{4,12}0.^{7,11}]tridecane 21. White solid; mp 112-113 ℃; 80% yield; IR ($CHCl_3$) 3500, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (d, *J* = 2.4 Hz, 1H), 4.81 (s, 1H), 3.32 (s, 3H), 2.78-2.75 (m, 2H), 2.43-2.40 (m, 2H), 1.69-1.49 (m, 10H), 1.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 120.30 (C), 120.00 (C), 110.69 (CH), 104.52 (CH), 54.91 (OCH_3), 45.79 (CH), 45.27 (CH), 42.10 (CH), 41.37 (CH), 28.34 (CH_3), 28.08 (CH_3), 21.70 (CH_2), 20.53 (CH_2); LRMS *m/z* (rel int) 256 (M^+, 5), 69 (100); HRMS (EI) calcd for $C_{13}H_{20}O_5$ 256.1310, found 256.1315; Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.96; H, 7.91.

1,9-dimethyl-3β-hydroxy-7α-methoxy-2,5,8,12-tetraoxatetracyclo[7.2.1.0.^{4,11}0.^{6,10}]-dodecane 22. White solid; mp 141-142 ℃; yield 75%; IR ($CHCl_3$) 3500, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.52 (d, *J* = 2.4 Hz, 1H), 5.01 (s, 1H), 4.58 (d, *J* = 6.0 Hz, 1H), 4.54 (d, *J* = 6.0 Hz, 1H), 3.54-3.41 (m, 2H), 3.33 (s, 3H), 3.10 (s, 1H), 1.65 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 121.74 (C), 121.36 (C), 108.27 (CH), 102.23 (CH), 91.12 (CH), 90.48 (CH), 59.35 (CH), 59.15 (CH), 54.29 (OCH_3), 28.15 (CH_3), 27.74 (CH_3); LRMS *m/z* (rel int) 244 (M^+, 10), 231 (100); HRMS (EI) calcd for $C_{11}H_{16}O_6$ 244.0946, found 244.0942; Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.12; H, 6.62.

Ozonolysis of compound 23 in dichloromethane-methanol followed by reduction with dimethyl sulfide. The same reaction conditions for the ozonolysis of **3a-d** to form the diacetals **14a-d** were applied for the ozonolysis of **23** to give the major product **24** (74%) and the minor product **25** (11%).

4-Methyl-2β,6β-dimethoxy-8α-methylthiocarboxyl-3,5-dioxatricyclo[5.2.1.0.^{4,9}]-decane 24. White solid; mp 79-80 ℃; IR ($CHCl_3$) 1680, 1125, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.09 (d, *J* = 5.7 Hz, 1H), 4.78 (s, 1H), 3.42 (s, 3H), 3.31 (s, 3H), 3.16-3.13 (m, 1H), 2.93-2.80 (m, 2H), 2.57-2.51 (m, 1H), 2.34 (s, 3H), 2.13-2.04 (m, 1H), 1.80-1.73 (m, 1H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 196.93 (COS), 109.37 (C), 108.21 (CH), 99.29 (CH), 55.99 (OCH_3), 55.38 (CH), 54.10 (OCH_3), 48.33 (CH), 46.17 (CH), 39.39 (CH), 29.27 (CH_3), 26.16 (CH_2), 11.24 (SCH_3); LRMS *m/z* (rel int) 288 (M^+, 16), 241 (62), 153 (100); HRMS (EI) calcd for $C_{13}H_{20}O_5S$ 288.1031, found 288.1036.

4-Methyl-2β,6α-dimethoxy-8α-methylthiocarboxyl-3,5-dioxatricyclo[5.2.1.0.^{4,9}]-decane 25. White solid; mp 85-86 ℃; IR ($CHCl_3$) 1680, 1125, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (s, 1H), 4.47 (s, 1H), 3.44 (s, 3H), 3.33 (s, 3H), 3.12-3.09 (m, 1H), 2.87-2.84 (m, 1H), 2.71-2.67 (m, 1H), 2.62-2.54 (m, 1H), 2.34 (s, 3H), 2.18-2.02 (m, 1H), 1.72 (s, 3H), 1.52-1.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 197.16 (COS), 107.91 (C), 107.42 (CH), 104.18 (CH), 57.07 (OCH_3), 55.91 (CH), 54.13 (OCH_3), 47.86 (CH), 46.70 (CH), 42.94 (CH), 32.98 (CH_2), 28.40 (CH_3), 11.47 (SCH_3); LRMS *m/z* (rel int) 288 (M^+, 11), 241 (49), 153 (100); HRMS (EI) calcd for $C_{13}H_{20}O_5S$ 288.1031, found 288.1033.

Ozonolysis of compounds 23 in dichloromethane-methanol. The same reaction conditions for the ozonolysis of **3a-d** to form the hydroperoxides **6a-d** were applied for the ozonolysis of **23** to give compound **26** as the major product with unidentified minor products.

4-Methyl-2β-hydroperoxy-6β-methoxy-8α-methylthiocarboxyl-3,5-dioxatricyclo-[5.2.1.0.^{4,9}]decane 26. White solid; mp 90-91 ℃; IR ($CHCl_3$) 3500-3200, 1680, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 5.34 (s, 1H), 5.12 (d, *J* = 5.4 Hz, 1H), 3.41 (s, 3H), 3.16-3.11 (m, 1H), 2.91-2.85 (m, 2H), 2.68-2.63 (m, 1H), 2.35 (s,

3H), 2.22-2.16 (m, 1H), 1.83-1.78 (m, 1H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 196.84 (COS), 111.54 (CH), 110.26 (C), 98.88 (CH), 56.07 (CH), 55.23 (OCH_3), 48.57 (CH), 43.51 (CH), 39.35 (CH), 28.64 (CH_3), 27.23 (CH_2), 11.34 (SCH_3); LRMS *m/z* (rel int) 290 (M^+, 2), 211 (100); HRMS (EI) calcd for $C_{12}H_{18}O_6S$ 290.0824, found 290.0829.

Reduction of compound 26 with dimethyl sulfide. The same reaction conditions for the reduction of **6a-d** with dimethyl sulfide were applied for the reduction of compound **26** to give compound **27**.

4-Methyl-2β-hydroxy-6β-methoxy-8α-methylthiocarboxyl-3,5-dioxatricyclo[5.2.1.0.^{4,9}]decane 27. White solid; mp 113-114 ℃; IR ($CHCl_3$) 3500-3200, 1680, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (s, 1H), 5.08 (d, *J* = 5.7 Hz, 1H), 4.04 (brs, 1H), 3.38 (s, 3H), 3.26-3.23 (m, 1H), 2.74-2.82 (m, 2H), 2.62-2.54 (m, 1H), 2.34 (s, 3H), 2.13-2.08 (m, 1H), 1.81-1.69 (m, 1H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 196.92 (COS), 109.44 (C), 102.06 (CH), 98.94 (CH), 55.97 (CH), 54.99 (OCH_3), 48.19 (CH), 46.88 (CH), 39.30 (CH), 29.51 (CH_3), 26.36 (CH_2), 11.20 (SCH_3); LRMS *m/z* (rel int) 274 (M^+, 10), 227 (100); HRMS (EI) calcd for $C_{12}H_{18}O_5S$ 274.0875, found 274.0868.

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Ozonolysis of Bis-*endo*-diacylbicyclo[2.2.1]heptenes in Dichloromethane-Methanol