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SYNTHESIS OF 3-HYDROPEROXY (OR HYDROXY)-SUBSTITUTED 1,2-DIOXANES AND 1,2-DIOXEPANES BY THE OZONOLYSIS OF UNSATURATED HYDROPEROXY ACETALS

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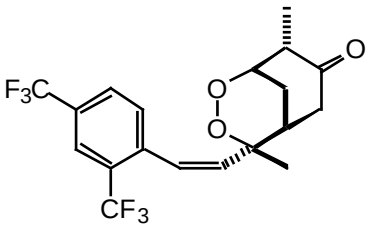
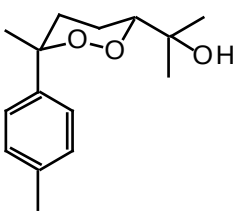
Abstract - Mono-ozonolysis of dienes in methanol gave in each case the corresponding unsaturated hydroperoxy acetals. The reaction of the hydroperoxides with ozone in the solvent system such as AcOH-CH_2Cl_2 resulted in the production of the corresponding hydroperoxy (or hydroxy)-substituted 1,2-dioxanes or 1,2-dioxepanes in good yield. By the treatment of the derived products with TMSOTf-Et_3SiH, replacement of the methoxy (or hydroxy) group by hydrogen was accomplished.

The discovery of pharmacologically active six- and seven-membered ring peroxides has placed a renewed interest for the development of new synthetic methods of cyclic peroxides having these structures.[1] In this respect, we[2] and Dussault[3] reported independently that the ozonolysis or the halonium ion-mediated cyclization of unsaturated hydroperoxy acetals, derived from capture of carbonyl oxide intermediates by unsaturated alcohols, are convenient methods for the synthesis of 1,2,4-trioxanes and 1,2,4-trioxepanes. Since 1,2-dioxane derivatives such as arteflene and yingzhaosu C are also known to show remarkable antimalarial activities,[4-6] we have examined the ozonolysis of the unsaturated hydroperoxy acetals, derived from trapping of unsaturated carbonyl oxides by methanol and have found that the reaction in the solvent system such as AcOH-CH_2Cl_2 is quite useful for the synthesis of the hydroperoxy (or hydroxy)-substituted 1,2-dioxanes and 1,2-dioxepanes. As an alternative way for the synthesis of the target compounds, the reaction of unsaturated ketones in methanol has been also examined.



arteflene



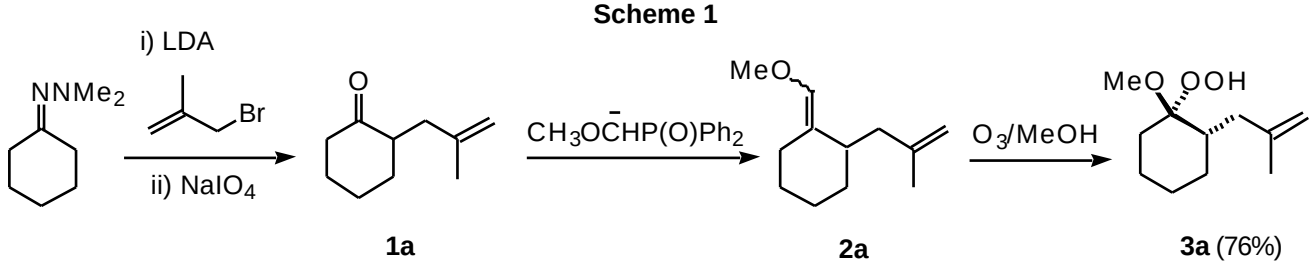
yingzhaosu C

RESULTS AND DISCUSSION

Preparation of Unsaturated Hydroperoxy Acetals

As reported before,[7] the preparation of unsaturated hydroperoxy acetals was conducted by the sequence illustrated in Scheme 1. The hydroperoxide (**3a**) obtained from the ozonolysis of **2a** in methanol was a single isomer, suggesting that capture of the 2-alkyl-substituted cyclohexanone *O*-oxide by methanol occurs from the less hindered face. The unsaturated hydroperoxy acetals (**3c**,**f**) were also isolated as the

Scheme 1



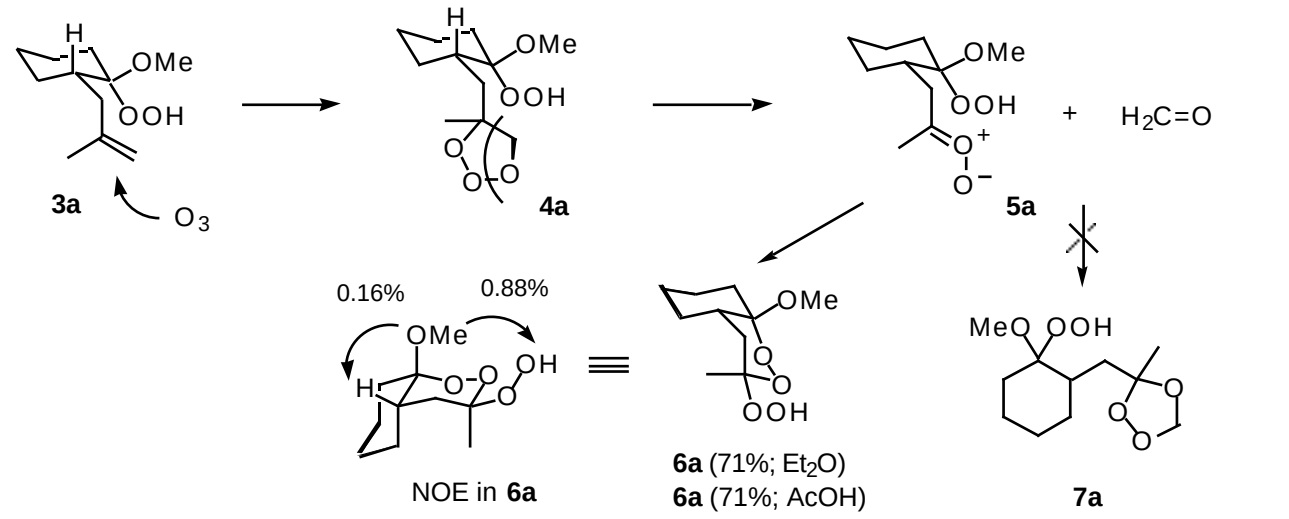
1a **2a** **3a** (76%)

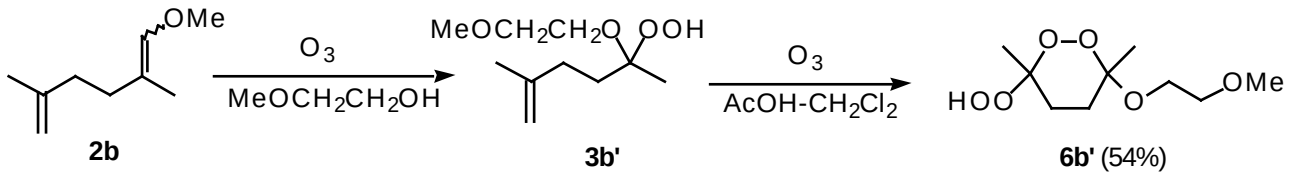
single isomers (Schemes 3 and 5).[7] In the case of the hydroperoxide (**3b'**), 2-methoxyethanol was used as the trapping agent of the carbonyl oxide intermediate (Scheme 2).[8]

Ozonolysis of Unsaturated Hydroperoxy Acetals

We conducted first the ozonolysis of the hydroperoxide (**3a**) in ether. The product was the dioxane (**6a**) (71%: a single isomer) (Scheme 2). No evidence was obtained for the formation of the ozonide (**7a**), derived from an intermolecular [3 + 2] cycloaddition of the carbonyl oxide intermediate (**5a**) with formaldehyde. In other words, the formation of the entropically favored dioxane is very fast. The reaction in AcOH-CH_2Cl_2 also gave the dioxane (**6a**) in moderate yield. The NOE measurement of **6a** suggested

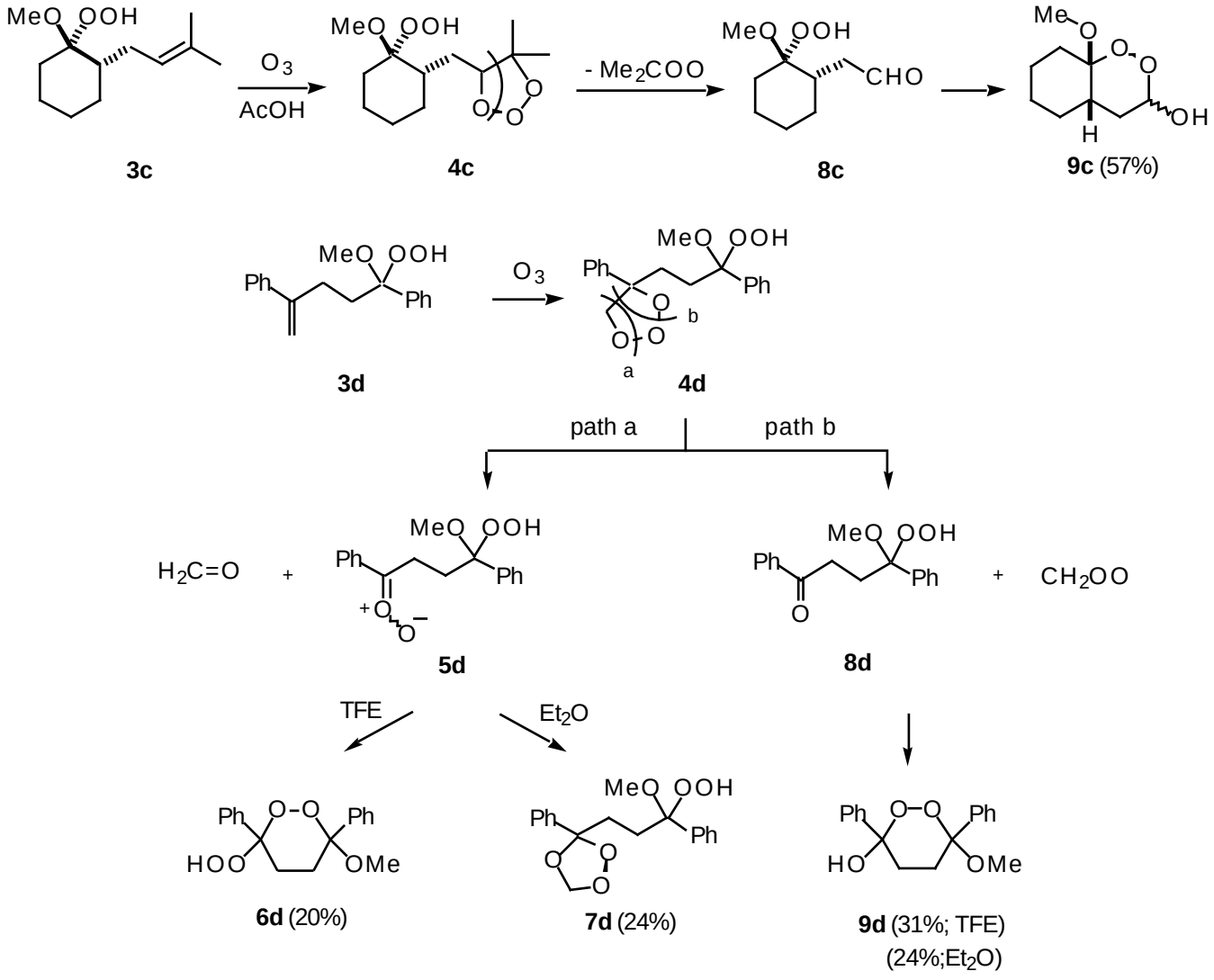
Scheme 2





that the hydroperoxy group is *cis* with both the methoxy group and the bridgehead hydrogen. From the hydroperoxide (**3b'**), the dioxane (**6b'**) was obtained in 54% yield (a 3:2 mixture of two isomers). Ozonolysis of the unsaturated hydroperoxide (**3c**) gave the hydroxy-substituted dioxane (**9c**) was the sole product (57%; a 3:2 mixture of two isomers) (Scheme 3). This is in marked contrast to the fact that only the hydroperoxy-substituted 1,2-dioxane (**6a**) was produced from the hydroperoxide (**3a**). This remarkable difference in behavior between two hydropeoxides (**3a**) and (**3c**) is rationalized in terms of the directive effect of the electron-donating methyl substituents on the cleavage of the primary ozonides (**4a**) and (**4c**).[9] Thus, the reaction of **3a** proceeds by the carbonyl oxide intermediate (**5a**), thereby providing the hydroperoxy-substituted 1,2-dioxane (**6a**) (Scheme 2). In the case of the primary ozonide (**4c**), however, the alternative mode of the cleavage yielding the keto hydroperoxide (**8c**) predominates and as a result, the hydroxy-substituted 1,2-dioxane (**9c**) is exclusively produced (Scheme 3). Since the ^{1}H NMR spectrum of the mixture of **9c** was quite complex, we failed to determine the stereochemistry.

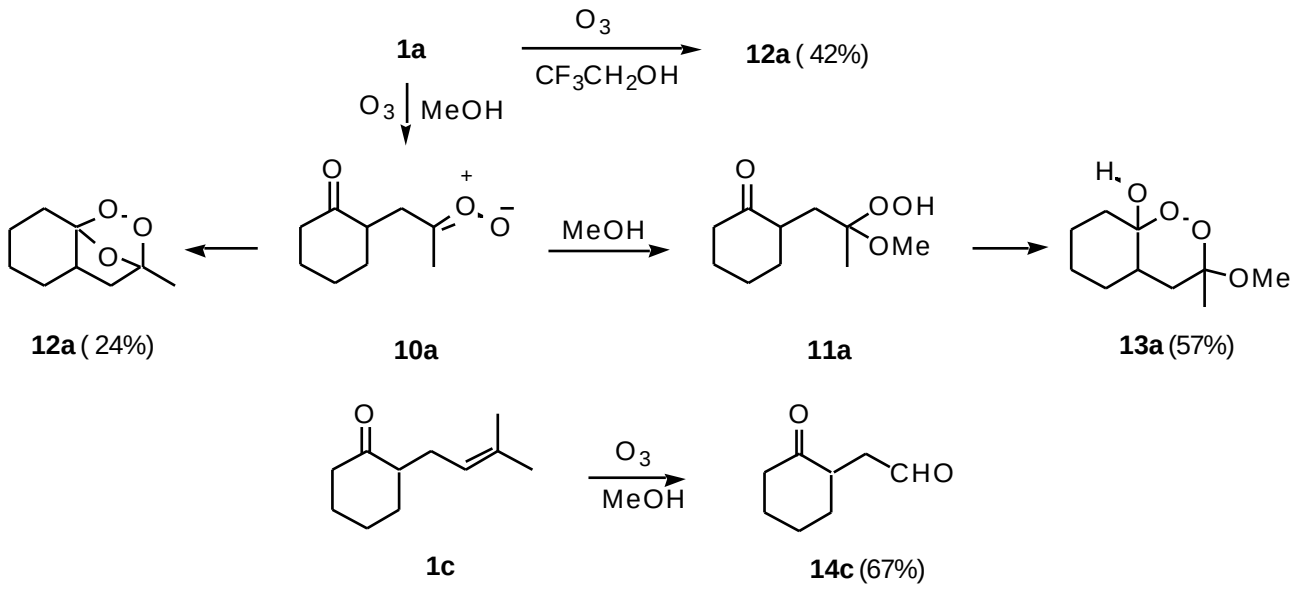
Scheme 3



The hydroperoxide (**3d**) seems to be a borderline case (Scheme 3). The ozonolysis of the hydroperoxide

(**3d**) in AcOH-CH_2Cl_2 gave only a complex mixture of unidentified products. When the same reaction was repeated in a less acidic solvent system, trifluoroethanol (TFE)-CH_2Cl_2, however, both the hydroperoxy- and hydroxy-substituted 1,2-dioxanes (**6d**) and (**9d**) were certainly obtained in yields of 20% and 31%, respectively (Scheme 3). The formation of both **6d** and **9d** implies that in the case of the primary ozonide (**4d**) two fission pathways contribute to a similar extent. Consistent with this, the reaction of **3d** in ether resulted in the formation of the ozonide (**7d**) (24%) together with the hydroxy-substituted 1,2-dioxane (**9d**) (24%). The 1,2-dioxane (**6d**) was found to be labile not only in a solvent such as $CDCl_3$ but also in the solid state; even in a refrigerator it decomposed into the unidentified products in less than one week. Thus, the stereochemistry of **6d**, although isolated as a single isomer, could not be determined. The same trend was observed for **9d**.

Scheme 4

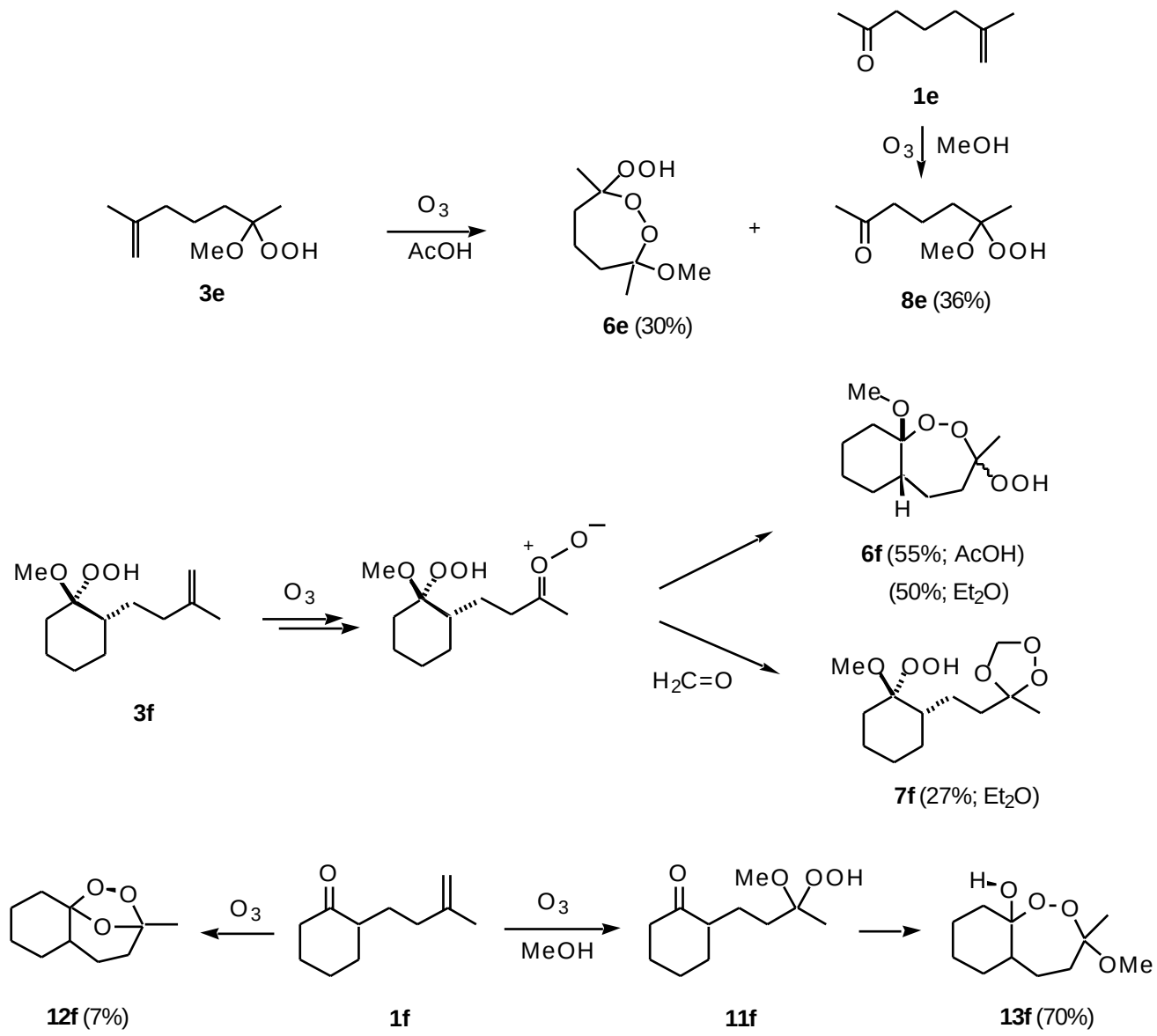


In connection with the easy formation of the hydroxy-substituted 1,2-dioxane (**9d**) from **3d**, it is well known that the γ-hydroperoxy-substituted ketones, if formed, are immediately transformed to the corresponding hydroxy-substituted 1,2-dioxanes by cyclization.[5a,b,g] Therefore, we then conducted the ozonolysis of the unsaturated ketones (**1a**,**c**)[10] in MeOH-CH_2Cl_2. Ozonolysis of **1a** gave, together with the ozonide (**12a**) (24%), the hydroxy-substituted 1,2-dioxane (**13a**) in 57% yield (a 3:1 mixture of two isomers which could be separated by column chromatography on silica gel) (Scheme 4). Because of the complex overlapping of the signals in ^{1}H NMR spectrum, we failed to determine the structure of the major isomer of **13a** by the HH, CH COSY and NOE measurements. In contrast to the reaction of **1a**, the reaction of the unsaturated ketone (**1c**) provided only the corresponding keto aldehyde (**14c**). These results demonstrate that in the ozonolysis of the keto olefins (**1a**,**c**) also, the substituent-dependent selectivity in cleavage of the primary ozonides is important in determining the structure of the products.

We next examined the synthesis of the 1,2-dioxepane derivatives from the hydroperoxides (**3e**,**f**) with a longer tether (Scheme 5). By the ozonolysis of the hydroperoxide (**3e**) in AcOH-CH_2Cl_2, the keto hydroperoxide (**8e**) (36%) was obtained together with the expected dioxepane (**6e**) (30% yield). In

contrast, the ozonolysis of the hydroperoxide (**3f**) gave only the corresponding dioxepane (**6f**) (55% yield; a 3:2 mixture of two isomers). It is interesting to note that the keto hydroperoxide (**8e**) did not cyclize to the corresponding dioxepane; ozonolysis of **1e** in methanol has been found to give **8e** in 90% yield.[11,12] In the case of the keto olefin (**1f**), however, treatment with ozone in methanol resulted in the formation of the hydroxy-substituted 1,2-dioxepane (**13f**) (70%; a 3:1 mixture of two isomers) together with the ozonide **12f** (7%). The remarkable difference in behavior between **8e** and **11f** demonstrates that the factor of entropy is important for the efficiency of cyclization of keto hydroperoxides.

Scheme 5

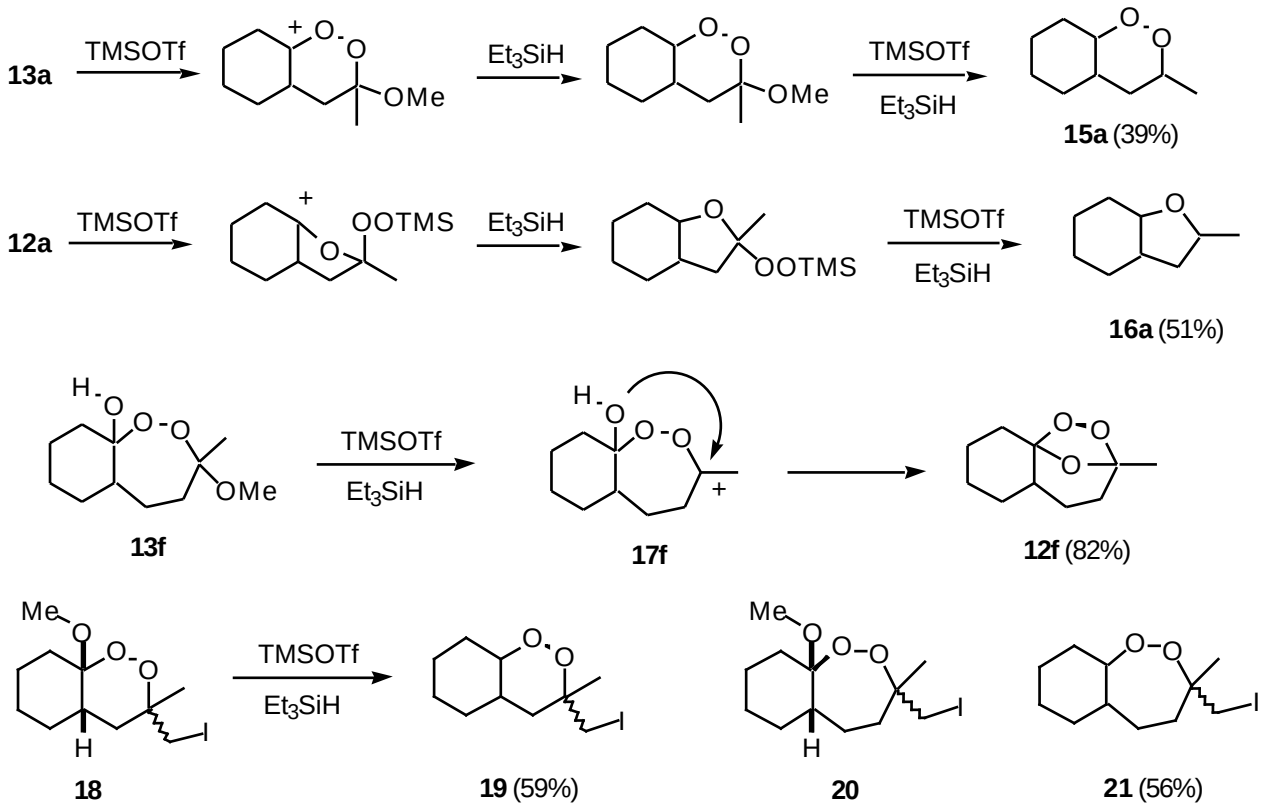


Reduction of 3-Hydroperoxy (or Hydroxy)-Substituted 1,2-Dioxanes and 1,2-Dioxepanes with TMSOTf-Et_3SiH

We next examined the possibility of transformation of the hydroperoxy (or hydroxy)-substituted 1,2-dioxane and dioxepane (Scheme 6). Treatment of **13a** with TMSOTf-Et_3SiH[13] gave the expected dioxane (**15a**) (39%; a single isomer). All our trial to determine the stereochemistry of **15a** by NMR

spectroscopy failed, because the signals overlapped in a complicated fashion. The reaction of the ozonide (**12a**) under the same conditions, however, resulted in the formation of the corresponding tetrahydrofuran (**16a**) (51%; a single isomer).[14] A possible mechanism of the transformation is illustrated in Scheme 6. In the case of the ozonide (**12a**), TMSOTf seems to induce cleavage of the C-O bond of the peroxide bridge rather than the ether bridge. Surprisingly, treatment of **13f** with a mixture of TMSOTf and Et_3SiH gave the novel tricyclic peroxide containing a 1,2,4-trioxolane structure in a high yield of 82%, suggesting that the intramolecular cyclization leading to **12f** is much faster than the hydride ion transfer from Et_3SiH to the carbocation center of **17f**. In contrast, treatment of the iodomethyl-substituted dioxepane (**20**), obtained from **3f** by the I^+-mediated cyclization,[7] with TMSOTf/Et_3SiH gave the expected dioxepane derivative (**21**) (56%). From **18**, the dioxane (**19**) was obtained in 59% yield (Scheme 6).

Scheme 6



EXPERIMENTAL

^1H (270 MHz) and ^{13}C NMR (67.5 MHz) spectra were obtained in $CDCl_3$ with $SiMe_4$ as standard. The method of ozonolysis was previously described.[15]

Caution: Since organic peroxides are potentially hazardous compounds, they must be handled with due care; avoid exposure to strong heat or light, or mechanical shock, or oxidizable organic materials, or transition metal ions.

Mono-ozonolysis of Dienes in MeOH-CH_2Cl_2

Ozonolysis of the vinyl ether (**2b**) is representative. To a solution of **2b** (340 mg, 2.5 mmol) in CH_2Cl_2 (25 mL) and 2-methoxyethanol (5 mL) was passed a slow stream of ozone (1 equiv.) at -70 °C. After adding ether (70 mL), the organic layer was washed with ice-cold 10% sodium bicarbonate, saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography on silica gel. Elution with ether-hexane (12:88) gave the unsaturated hydroperoxide (**3b'**) (51 mg, 10%).

2-(2-Methoxyethoxy)-5-methyl-5-hexen-2-yl hydroperoxide (3b')

A colorless oil, ^{1}H NMR δ 1.34 (s, 3 H), 1.7-2.2 (m, 4 H), 1.72 (s, 3 H), 3.34 (s, 3 H), 3.57 (t, *J* = 4.3 Hz, 2 H), 3.72 (t, *J* = 4.3 Hz, 2 H), 4.69 (s, 2 H), 10.27 (s, 1 H); ^{13}C NMR δ 19.70, 22.64, 32.15, 33.52, 58.92, 59.86, 72.89, 106.96, 109.65, 145.34.

Ozonolysis of Unsaturated Hydroperoxy Acetals (3a,b',c-f) in AcOH-CH_2Cl_2

The reaction of the hydroperoxide (**3a**) is representative. A solution of **3a** (260 mg, 1.3 mmol) in acetic acid (5 mL)-CH_2Cl_2 (25 mL) was cooled to -70 °C, and ozone (1.5 equiv.) was bubbled through it at -70 °C. Aqueous 10% $NaHCO_3$ was added, and the mixture was extracted with ether (70 mL), washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel. Elution with ether-hexane (1:9) gave the hydroperoxy-substituted 1,2-dioxane (**6a**) (200 mg, 71%).

1-Methoxy-4-methyl-2,3-dioxabicyclo[4.4.0]decan-4-yl hydroperoxide (6a)

A colorless oil, ^{1}H NMR δ 1.2-1.8 (m, 10 H), 1.8-1.9 (m, 1 H), 1.42 (s, 3 H), 3.29 (s, 3 H), 8.90 (s, 1 H); ^{13}C NMR δ 19.50, 21.76, 22.52, 27.10, 27.82, 32.92, 34.52, 48.47, 104.21, 109.04. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03: H, 8.31. Found: C, 54.58: H, 8.17. Irradiation of the methoxy proton resulted in the small enhancement of the signals of the OOH and the hydrogen at C-6 [δ 1.8-1.9 (m)]. No enhancement of the methyl signal [δ 1.42 (s)] was observed by the irradiation.

6-(2-Methoxyethoxy)-3,6-dimethyl-1,2-dioxan-3-yl hydroperoxide (6b')

A colorless oil (a 3:2 mixture of two isomers), ^{1}H NMR δ 1.31 (s, major) + 1.43 (s) + 1.44 (s, major) + 1.48 (s) (6 H), 1.5-2.2 (m, 4 H), 3.38 (s) + 3.40 (s, major) (3 H), 3.4-3.8 (m, 4 H), 8.36 (s, major) + 9.04 (s) (1 H); ^{13}C NMR δ 19.70, 19.89, 20.16, 20.43, 26.38, 27.53, 29.53, 30.98, 58.94, 59.01, 60.72, 61.13, 71.92 (2C), 102.41, 102.97, 106.92, 107.35. Anal. Calcd for $C_9H_{18}O_6$: C, 48.64: H, 8.16. Found: C, 48.85: H, 8.17.

4-Hydroxy-1-methoxy-2,3-dioxabicyclo[4.4.0]decane (9c)

A colorless oil (a 3:2 mixture of two isomers), ^{1}H NMR δ 1.1-2.2 (m, 11 H), 3.33 (s, 3 H), 3.57 (d, *J* = 3.9 Hz, major) + 3.87 (d, *J* = 7.3 Hz) (1 H), 5.3-5.4 (m, 1 H); ^{13}C NMR δ 21.96 (CH_2), 22.73 (CH_2), 24.28 (CH_2), 27.42 (CH_2), 28.16 (CH_2), 28.70 (CH_2), 29.87 (CH_2), 30.87 (CH_2), 32.85 (CH_2), 34.25 (CH), 37.61 (CH), 48.23 (CH_3), 48.57 (CH_3), 94.30 (CH), 97.40 (CH), 101.58 (C), 104.65 (C). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43: H, 8.57. Found: C, 57.71: H, 8.48.

7-Methoxy-3,7-dimethyl-1,2-dioxepan-3-yl hydroperoxide (6e)

A colorless oil (a 1:1 mixture of two isomers), ^{1}H NMR δ 1.26 (s) + 1.41 (s) + 1.43 (s) + 1.47 (s) (6 H), 1.6-2.0 (m, 6 H), 3.34 (s) + 3.35 (s, 3 H), 8.39 (s) + 8.60 (s) (1 H); ^{13}C NMR δ 18.28 (CH_2), 18.58 (CH_2), 18.96 (CH_3), 19.46 (CH_3), 19.70 (CH_3), 20.04 (CH_3), 35.35 (CH_2), 38.87 (CH_2), 40.09 (CH_2),

49.24 (CH_3), 49.92 (CH_3), 107.60 (C), 108.36 (C), 111.81 (C), 112.47 (C). Anal. Calcd for $C_8H_{16}O_5$: C, 49.99: H, 8.39. Found: C, 50.03: H, 8.38.

6-Hydroperoxy-6-methoxy-2-heptanone (8e)

A colorless oil, ^{1}H NMR δ 1.2-2.0 (m, 4 H), 1.24 (s, 3 H), 2.09 (s, 3 H), 2.3-2.5 (m, 2 H), 3.26 (s, 3 H), 8.34 (br s, 1 H); ^{13}C NMR δ 17.81, 18.39, 29.92, 34.36, 42.93, 48.84, 106.56, 209.61. Anal. Calcd for $C_8H_{16}O_4$: C, 54.53: H, 9.15. Found: C, 54.47: H, 9.32.

1-Methoxy-4-methyl-2,3-dioxabicyclo[5.4.0]undecan-4-yl hydroperoxide (6f)

A colorless oil (a 3:2 mixture of two isomers), ^{1}H NMR δ 1.2-2.4 (m, 13 H), 1.40 (s, major) + 1.44 (s) (3 H), 3.28 (s) + 3.31 (s, major) (3 H), 8.45 (s) + 8.74 (s, major) (1 H); ^{13}C NMR δ 19.52 (CH_3), 19.61 (CH_3), 20.65 (CH_2), 22.21 (CH_2), 22.73 (CH_2), 24.49 (CH_2), 24.57 (CH_2), 24.91 (CH_2), 25.11 (CH_2), 28.97 (CH_2), 30.55 (CH_2), 33.28 (CH_2), 35.06 (CH_2), 39.43 (CH), 48.16 (CH_3), 49.24 (CH_3), 108.12 (C), 109.31 (C), 111.41 (C), 112.17 (C). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88: H, 8.68. Found: C, 56.91: H, 8.62.

Ozonolysis of the Unsaturated Hydroperoxy Acetal (3c) in CF_3CH_2OH-CH_2Cl_2

A solution of **3d** (230 mg, 0.81 mmol) in trifluoroethanol (TFE)-CH_2Cl_2 (1:2 v/v; 25 mL) was cooled to 0 °C, and ozone (1.5 equiv.) was bubbled through it at 0 °C. Aqueous 10% $NaHCO_3$ was added, and the mixture was extracted with ether, washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel. Elution with ether-hexane (1:9) gave the hydroperoxy-substituted dioxane (**6d**) (55 mg, 20%). Subsequent elution with ether-hexane (12:88) gave the hydroxy-substituted dioxane (**9d**) (76 mg, 31%).

4-Methoxy-1,4-diphenyl-2,3-dioxanyl hydroperoxide (6d)

A white powder, mp 152-153 °C (ether-hexane), ^{1}H NMR δ 1.9-2.3 (m, 4 H), 3.36 (s, 3 H), 7.3-7.6 (m, 10 H), 8.49 (s, 1 H); ^{13}C NMR δ 28.77, 31.79, 50.73, 103.99, 108.07, 125.84, 128.46, 128.61, 128.81, 137.84, 138.54. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54: H, 6.00. Found: C, 67.48: H, 5.84.

3-Hydroxy-6-methoxy-3,6-diphenyl-1,2-dioxane (9d)

A white powder, mp 127-128 °C (ether-hexane), ^{1}H NMR δ 1.9-2.6 (m, 4 H), 3.32 (s, 3 H), 7.3-7.7 (m, 10 H); ^{13}C NMR δ 30.60, 31.92, 50.62, 100.05, 102.77, 125.41, 125.73, 126.56, 128.45, 128.54, 128.59, 129.00, 139.33, 141.26. Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31: H, 6.34. Found: C, 71.59: H, 5.92.

Ozonolysis of the Unsaturated Hydroperoxy Acetals 3 in Ether

The reaction of **3d** is representative. A solution of **3d** (250 mg, 1.1 mmol) in ether (30 mL) was cooled to -70 °C, and ozone (1.5 equiv.) was bubbled through it at -70 °C. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel. Elution with ether-hexane (12:88) gave the hydroxy-substituted dioxane (**9d**) (85 mg, 24%). Subsequent elution with ether-hexane (16:84) gave the ozonide (**7d**) (85 mg, 24%).

1-Methoxy-1-phenyl-3-(3-phenyl-1,2,4-trioxolan-3-yl)propyl hydroperoxide (7d)

A white powder (a 2:1 mixture of two isomers), mp 117-124 °C (ethyl acetate), ^{1}H NMR δ 1.8-2.2 (m, 4 H), 3.22 (s, major) + 3.23 (s) (3 H), 5.12 (s, 1 H), 5.20 (s, 1 H), 7.2-7.4 (m, 10 H), 7.9 (br s, 1 H); ^{13}C NMR δ 29.78 (CH_2), 29.83 (CH_2), 31.48 (CH_2), 49.44 (CH_3), 49.49 (CH_3), 94.70 (CH_2), 107.94 (C),

109.56 (C), 125.30 (CH), 126.36 (CH), 128.19 (CH), 128.30 (CH), 128.34 (CH), 128.55 (CH), 137.75 (C), 137.81 (C), 139.77 (C), 139.80 (C). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05: H, 6.07. Found: C, 64.82: H, 5.94.

1-Methoxy-2-[(3-methyl-1,2,4-trioxolan-3-yl)ethyl]cyclohexyl hydroperoxide (7f)

An oil; ^{1}H NMR δ 1.5-2.0 (m, 13 H), 1.46 (s, 3 H), 3.31 (s, 3 H), 5.09 (s, 1 H), 5.15 (s, 1 H), 7.96 (s, 1 H). Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95: H, 8.45. Found: C, 55.18: H, 8.36.

Ozonolysis of the Unsaturated Ketone (1) in Methanol

The reaction of **1a** is representative. A solution of **1a** (228 mg, 1.5 mmol) in MeOH-CH_2Cl_2 (1:4 v/v; 25 mL) was cooled to -70 °C, and ozone (1.2 equiv.) was bubbled through it at -70 °C. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel. Elution with ether-hexane (1:9) gave the ozonide (**12a**) (60 mg, 24%). Elution with ether-hexane (14:86) gave the hydroxy-substituted dioxane (**13a**) (major isomer; 130 mg, 43%). Subsequent elution with ether-hexane (18:82) gave the minor isomer of (**13a**) (41 mg, 14%).

8-Methyl-9,10,11-trioxatricyclo[6.2.1.0^{1,6}]undecane (12a)

A colorless oil, ^{1}H NMR δ 0.9-2.3 (m, 11 H), 1.67 (s, 3 H); ^{13}C NMR δ 15.09 (CH_3), 23.22 (CH_2), 24.08 (CH_2), 24.76 (CH_2), 32.98 (CH_2), 42.30 (CH), 42.55 (CH_2), 110.89, 110.93. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51: H, 8.29. Found: C, 63.45: H, 7.96.

1-Hydroxy-4-methoxy-4-methyl-2,3-dioxabicyclo[4.4.0]decane (13a: major isomer)

A while powder, mp 97-98 °C (ether-hexane), ^{1}H NMR δ 1.2-2.2 (m, 11H), 1.23 (s, 3 H), 2.84 (s, 1 H), 3.28 (s, 3 H); ^{13}C NMR δ 20.83, 23.13, 25.48, 28.00, 33.84, 35.01, 36.28, 49.08, 99.84, 102.64. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39: H, 8.97. Found: C, 59.33: H, 8.92.

1,2-Dioxane (13a) (minor isomer)

A white powder, mp 118-120 °C (ether-hexane), ^{1}H NMR δ 1.2-2.0 (m, 11 H), 1.30 (s, 3 H), 3.20 (s, 1 H), 3.30 (s, 3 H); ^{13}C NMR δ 19.66, 22.43, 22.17, 28.23, 33.48, 35.98, 36.14, 48.95, 101.35 , 103.81. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39: H, 8.97. Found: C, 59.24: H, 8.87.

9-Methyl-10,11,12-trioxatricyclo[7.2.1.0^{1,6}]undecane (12f)

An oil; ^{1}H NMR δ 1.2-1.9 (m, 13 H), 1.50 (s, 3 H); ^{13}C NMR δ 21.21, 23.61, 24.08, 24.84, 30.42, 32.42, 34.09, 39.91, 107.94, 109.26. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19: H, 8.75. Found: C, 65.38: H, 8.65.

1-Hydroxy-4-methoxy-4-methyl-2,3-dioxabicyclo[5.4.0]dodecane (13f)

A white powder (a 3:1 mixture of two isomers), mp 76-79 °C (ether-hexane); ^{1}H NMR δ 1.2-2.1 (m, 13 H), 1.27 (s) + 1.30 (s) (3 H), 3.34 (s) + 3.38 (s) (3 H), 3.60 (s) + 3.61 (s) (1 H); ^{13}C NMR δ 19.86, 22.86, 25.20, 25.57, 30.62, 34.92, 40.61, 49.04, 51.20, 104.33, 107.69. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09: H, 9.32. Found: C, 61.23: H, 9.24.

2-(Formylmethyl)cyclohexanone (14c)

An oil; ^{1}H NMR δ 1.2-2.0 (m, 4 H), 2.0-2.4 (m, 5 H), 2.8-3.0 (m, 2 H), 9.80 (s, 1 H); ^{13}C NMR δ 25.14, 27.66, 33.95, 41.67, 43.54, 45.37, 200.79, 210.82. HRMS [$(M + H)^+$] *m/z* Calcd for $C_8H_{12}O_2$ 140.0837, Found 140.0838.

Reaction of the Hydroxy-substituted 1,2-Dioxanes with TMSOTf-Et_3SiH

The reaction of **13a** is representative. To a solution of **13a** (472 mg, 2.3 mmol) in CH_2Cl_2 (30 mL) were added Et_3SiH (1.2 g, 10.1 mmol) and then TMSOTf (1.1 g, 5.1 mmol) in 10 min and the mixture was stirred at -70 ℃ for 1 h under nitrogen atmosphere. The mixture was poured into aqueous 10 % $NaHCO_3$ and extracted with ether. The organic layer was washed with saturated brined and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was separated by column chromatography on silica gel. Elution with ether-hexane (5:95) gave the 1,2-dioxane (**15a**) (141 mg, 39%).

4-Methyl-2,3-dioxabicyclo[4.4.0]decane (15a)

A colorless oil, ^{1}H NMR δ 0.9-1.8 (m, 11 H), 1.03 (d, *J* = 6.27 Hz, 3 H), 3.6-3.7 (m, 1 H), 4.2-4.3 (m, 1 H); ^{13}C NMR δ 18.89 (CH_3), 24.84 (CH_2), 25.38 (CH_2), 28.61 (CH_2), 30.44 (CH_2), 38.30 (CH_2), 40.72 (CH), 78.44 (CH), 78.44 (CH), 85.28 (CH); HRMS (M^+) *m/z* calcd for $C_9H_{16}O_2$ 156.1150, Found 156.1167.

Reaction of the Ozonide (12a), Dioxane (18) or Dioxepane (20) with TMSOTf-Et_3SiH

The reaction of **12a** is representative. To a solution of **12a** (380 mg, 2.2 mmol) in CH_2Cl_2 (30 mL) were added Et_3SiH (1.1 g, 9.7 mmol) and then TMSOTf (1.1 g, 4.8 mmol) in 10 min and the mixture was stirred at -70 ℃ for 1 h under nitrogen atmosphere. After treated as above, the residue was separated by column chromatography on silica gel. Elution with ether-hexane (5:95) gave the tetrahydrofuran (**16a**) (157 mg, 51%).

3-Methyl-2-oxabicyclo[4.3.0]nonane (16a)

A colorless oil, ^{1}H NMR δ 1.30 (d, *J* = 5.94 Hz, 3 H), 1.20-2.13 (m, 11 H), 3.75-3.78 (m, 1 H), 4.00 (dt, *J* = 1.65 and 4.95 Hz, 1 H); ^{13}C NMR δ 21.21, 22.84, 24.06, 28.70, 29.20, 38.13, 39.36, 74.07, 77.40; HRMS (M^+) *m/z* calcd for $C_9H_{16}O$: 140.1201, Found: 140.1202.

4-Iodomethyl-4-methyl-2,3-dioxabicyclo[5.4.0]undecane (21)

An oil; ^{1}H NMR δ 1.21 (s, 3 H), 1.3-2.2 (m, 13 H), 3.36 (d, *J* = 10.1 Hz, 1 H), 3.48 (d, *J* = 10.1 Hz, 1 H), 4.2-4.3 (m, 1 H); ^{13}C NMR δ 16.35, 21.64, 24.03, 25.02, 26.51, 28.02, 29.63, 32.19, 38.24, 82.71, 84.58; HRMS (M^+) *m/z* calcd for $C_{11}H_{19}IO_2$: 310.0430, Found: 310.0443; Anal. Calcd for $C_{11}H_{19}IO_2$: C, 42.60; H, 6.17. Found: C, 43.29; H, 6.25.

4-Iodomethyl-4-methyl-2,3-dioxabicyclo[4.4.0]decane (19)

An oil; ^{1}H δ 1.26 (s, 3 H), 1.1-2.0 (m, 10 H), 2.1-2.2 (m, 1 H), 3.58 (d, *J* = 10.1 Hz, 1 H), 3.64 (d, *J* = 10.1 Hz, 1 H), 3.7-3.8 (m, 1 H); ^{13}C NMR δ 12.26, 24.92, 25.39, 26.56, 28.54, 30.42, 36.77, 37.54, 79.98, 85.43; HRMS (M^+) *m/z* calcd for $C_{10}H_{17}IO_2$: 296.0274, Found: 296.0271.

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