The Reaction of Three Sesquiterpene Ethers with *m*-Chloroperbenzoic Acid

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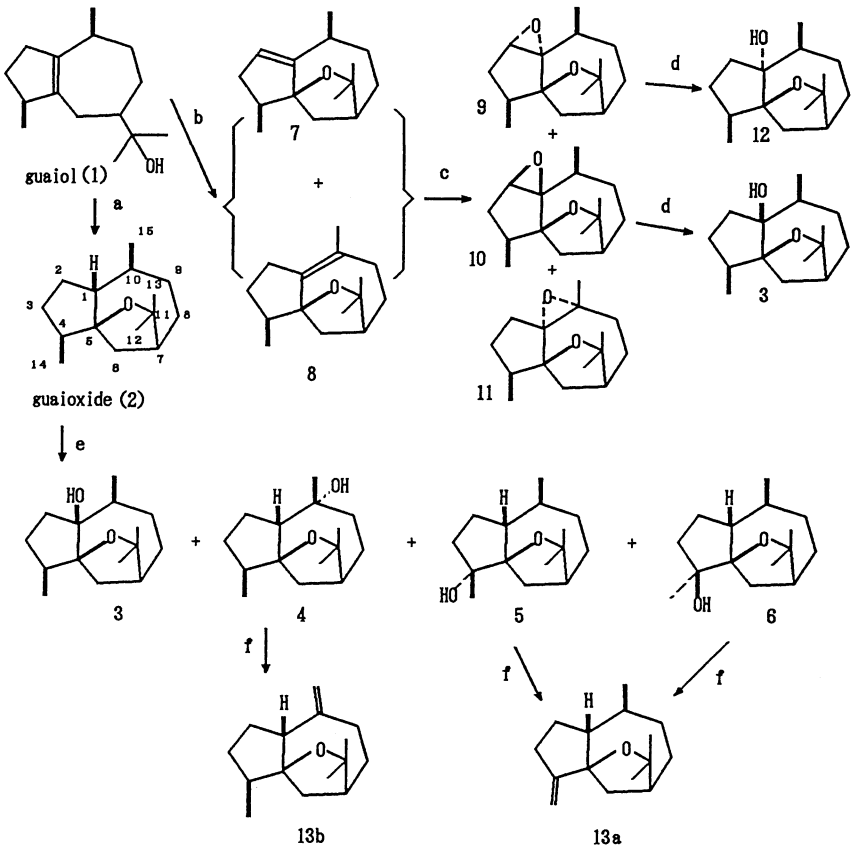
Three sesquiterpene ethers, guaioxide, a guaiane-type sesquiterpene ether (LB), and maalioxide have been subjected to reaction with *m*-chloroperbenzoic acid in chloroform under reflux. Guaioxide afforded four tertiary alcohols, while other two gave secondary alcohols. Structures of the products were determined by spectral data and chemical correlations.

Oxidation reactions at unactivated carbon atoms are difficult but very interesting and important. The known methods include microbial oxidation,[1] mammalian metabolism,[2] Barton reaction,[3] remote oxidation,[4] and dry ozonization.[5] In the previous papers, we reported the oxidation of natural products by *m*-chloroperbenzoic acid (*m*CPBA) yielding hydroxyl or carbonyl compounds as a result of functionalization of unactivated carbon atoms. Application of this method to mono-,[6] sesqui-,[7] and triterpenes,[8] and acyclic compounds[9] have been published and proved to be a convenient method for introduction of a hydroxyl group. Namely the method is very simple, safe, and applicable to a variety of compounds.

Guaioxide (**2**) is a tricyclic sesquiterpene ether isolated from guaiac wood oil and its microbial transformation has been reported.[10] Oxidation reactions by dry ozonization and by the metabolism using rabbits have been studied.[11] Radical brominations[12] have also been investigated. A guaiane-type sesquiterpene ether (a stereoisomer of **2**), LB (**14**), was isolated from the roots of a *Ligularia* genus by T. Takahashi and his group and its structure was determined by degradation.[13] Radical bromination of LB (**14**) using NBS has been studied by Hirota et al. as a method for functionalization of unactivated carbon atoms.[13] In connection with our recent study on oxidation reaction of natural and unnatural substances, three sesquiterpene ethers, guaioxide (**2**), LB (**14**), and maalioxide (**22**),[14] were subjected to *m*CPBA oxidation. We now describe the details of these reactions.



Scheme 1. a) H^+; b) $Pb(OAc)_4$; c) *m*CPBA; d) $LiAlH_4$; e) *m*CPBA/$CHCl_3$/reflux; f) $POCl_3$/Py.

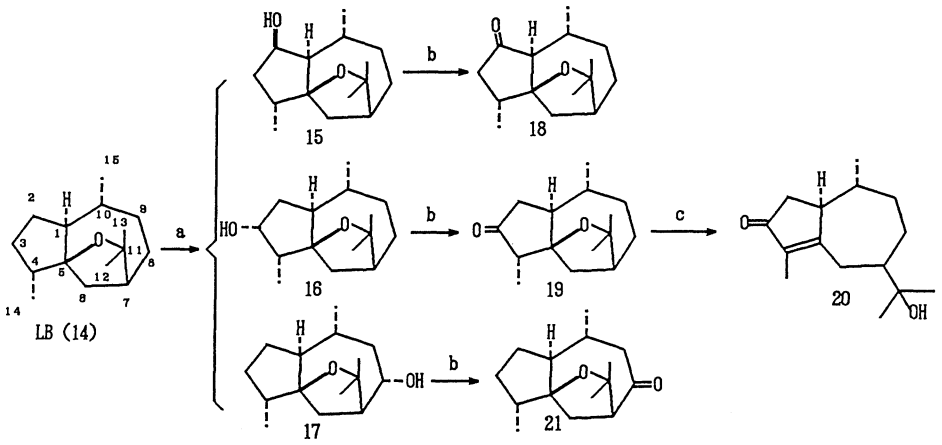
Results and Discussion

Oxidation of Guaioxide (2). Guaioxide (**2**) was treated with *m*CPBA in chloroform under reflux for 13 h to afford compounds **3**, **4**, and **5** after column chromatography. Careful purification by HPLC (Finepak Sil) yielded the fourth compound **6**. These four compounds were all tertiary alcohols (no proton attached to a carbon bearing the hydroxyl group was observed in the NMR spectra). Compound **3** had two secondary methyl groups, while the others had only one secondary methyl group. These facts suggest that compound **3** has a hydroxyl group at either C-1 or C-7 and others have at either C-4 or C-10, apart from their stereochemistry.

Since 7α-hydroxyguaioxide is known,[10] compound **3** is inferred to be 1-hydroxyguaioxide. To establish the stereochemistry at 1-position, both 1α- and 1β-hydroxyguaioxide, (**12**) and (**3**), were prepared from guaiol (**1**). Guaiol (**1**) was oxidized by lead tetraacetate according to the literature[15] to afford Δ^1-dehydroguaioxide (**7**) in addition to $\Delta^{1(10)}$-dehydroguaioxide (**8**), whose formation had not been reported so far.[15] The mixture was treated with *m*CPBA to afford three epoxides **9**—**11**, which were separated by silica-gel column chromatography. It was not easy to assign the stereochemistry of the epoxides **9** and **10** by the NMR spectra. However, the major epoxide **9** and the minor epoxide **10** were suggested tentatively to be 1α,2α-epoxyguaioxide and 1β,2β-epoxyguaioxide, respectively, since the β-face was sterically hindered. The fully substituted epoxide (**11**) was thus assigned to be 1α,10α-epoxyguaioxide by the same discussion. Each epoxide, **9** and **10**, was treated with $LiAlH_4$ to give the corresponding tertiary alcohol **12** and **3**, respectively. As expected, the yield of **12** from **9** was very low due to steric hindrance of the β-face, while that of **3** from **10** was very high. The spectral data of the oxidation product **3** were identical with those of the product, 1β-hydroxyguaioxide (**3**), synthesized in an alternative route.

Among the other three products, compound **5** showed the identical spectral data with those reported by microbial oxidation[10] and by dry ozonization.[11] Thus, the structure of **5** was determined to be 4α-hydroxyguaioxide. Since the extensive high-field NMR analysis of the other two alcohols, **4** and **6**, did not give the conclusive results, three alcohols, **4**, **5**, and **6**, were subjected to dehydration. The known alcohol **5** gave mainly the exo-olefin **13a** on dehydration with $POCl_3$ at 0 °C. Under the same reaction conditions, alcohol **4** afforded the other exo-olefin **13b**, while **6** yielded **13a**. Thus, the structures of **6** and **4** were assigned to be 4β-hydroxyguaioxide and 10α-hydroxyguaioxide, respectively, providing that the configuration of the 10-position was retained.[16]

Oxidation of LB (14). LB (**14**) was subjected to the reaction with *m*CPBA (1.2 equiv) in chloroform under reflux for 12 h. The products were separated by a combination of Sephadex LH-20 and silica-gel column chromatography to isolate three compounds **15**, **16**, and **17**, all of which were secondary alcohols (from the IR and NMR spectra, see Experimental). The first product **15** showed a molecular ion peak at *m/z* 238, suggesting the introduction of one hydroxyl group into LB (**14**). The proton attached to a carbon bearing the hydroxyl group appeared at δ 4.05 (m) and showed three cross peaks in its H-H COSY spectrum. The hydroxyl proton was observed at δ 3.49 as a doublet and was confirmed by the disappearance on addition of D_2O. As the NMR spectra of the compounds having a guaiane skeleton show characteristic signals of H-6α, H-6β, and H-7, the other protons are possible to trace starting from these protons in the COSY spectra. In this case, the H-6α was observed at δ 1.76 (1H, d), H-6β at δ 2.29 (1H, dd), and H-7 at δ 2.02 (1H, ddd), as the coupling constant between H-6α and H-7 is nearly zero. The methyl group attached at C-4 position [δ 0.90 (d, J=7.3 Hz)] was easily distinguished by observing NOE between H-6β. Thus both ends of the proton network of **15** were clearly assigned and other protons were traced on H-H COSY



Scheme 2. a) *m*CPBA/$CHCl_3$/reflux; b) Jones; c) Al_2O_3.

spectrum. Hence, the hydroxyl group was assigned at C-2 position. This conclusion was further confirmed by Jones oxidation of **15** to **18** (IR 1728 cm^{-1}) and the 2D NMR analysis of this ketone **18**. The stereochemistry was suggested by NOE difference experiments. When the proton at δ 4.05 was irradiated, NOE into 10α-methyl group was observed. NOE's into 12- and 13-methyl groups and 4β-proton were detected on irradiation of the hydroxyl proton at δ 3.49. Thus, the structure of **15** was established to be 2β-hydroxy-LB.

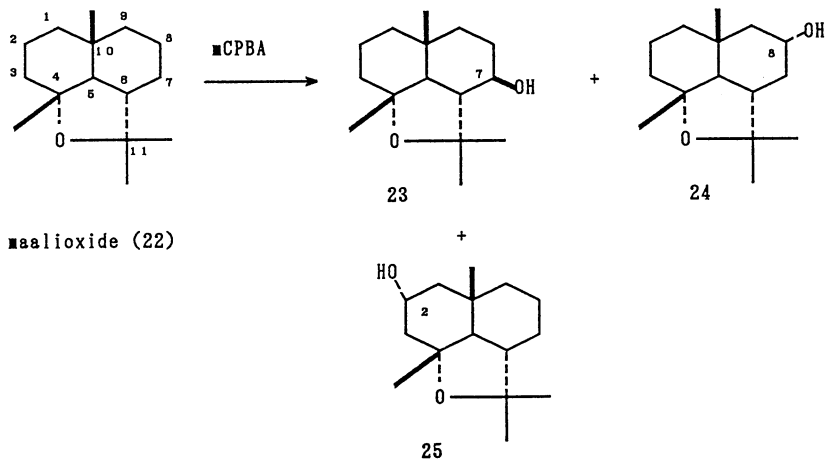
The second product **16** showed a molecular ion peak at *m/z* 238 and the presence of a hydroxyl group [3450 cm^{-1}; δ_H 3.73 (m); δ_C 78.4 (CH)]. As in the case of 2β-ol **15**, the position of the hydroxyl group was assigned at C-3 from the H-H COSY spectrum. Since the NOE difference spectra showed NOE into the H-4β on irradiation of the methine proton at δ 3.73 (m), the hydroxyl group at C-3 was α. The structure was further confirmed by conversion of **16** into the known enone **20**[13] through the ketone **19** [1) Jones oxidation; 2) alumina]. Thus the structure of **16** was established to be 3α-hydroxy-LB.

The last product **17** was also inferred as a secondary alcohol judging from the MS (*m/z* 238), ^{1}H NMR [δ 4.20 (dd)], ^{13}C NMR [δ 69.9 (CH)], and IR (3440 cm^{-1}) spectra. Although the protons at 6α-, 6β-, and 7 positions were characteristic, H-7 did not show the coupling with the proton attached to a carbon bearing the hydroxyl group. However, the methine proton at δ 4.20 (dd, H-8) coupled with two protons (H-9), which were further correlated to H-10. The position of hydroxyl group was suggested by oxidation of **17** into a ketone **21** (Jones oxidation), which exhibited the absorption at 1680 cm^{-1}, showing that the position of the carbonyl group was in the seven-membered ring. These results suggest that the hydroxyl group is at C-8 position. When the proton H-7 of **17** was irradiated, NOE into the 13-Me group was observed. On the other hand, when the 12-Me group was irradiated, NOE into H-8 was observed. These results indicate that compound **17** is 8α-hydroxy-LB.

Oxidation of Maalioxide (22). A solution of maalioxide (**22**) in chloroform was heated at reflux with *m*CPBA for 12 h. The mixture was purified by column chromatography of Sephadex LH-20 followed by silica gel to afford alcohols **23**, **24**, and **25**, with recovered maalioxide (**22**). These three products all showed the absorption at 3400 cm^{-1} in their IR spectra and the molecular ion peak at *m/z* 238 in their mass spectra, suggesting that these three alcohols were all monohydroxy derivatives of maalioxide. As the ^{1}H and ^{13}C NMR spectra of **23** indicated the presence of a methine group [δ_H 3.62 (1H, td, *J*=10 and 4.4 Hz) and δ_C 72.8 (CH)], this alcohol must be secondary. The position of the hydroxyl group should be 7β (equatorial), since the methine proton appeared as triplet (10 Hz) of doublets (4.4 Hz) and only this position has three protons on adjacent carbons. Hence the structure of **23** was established to be 7β-hydroxymaalioxide.

The second product **24** is deduced to be also a secondary alcohol from its ^{1}H NMR [δ_H 3.87 (1H, tt, *J*=11 and 3.9 Hz)] and ^{13}C NMR [δ_C 68.6 (CH)] spectra. As this methine proton appeared as triplet (11 Hz) of triplets (3.9 Hz), the number of protons on adjacent carbons were four and the hydroxyl group was equatorial. These observations imply that the hydroxyl group is either on 2α or 8α (vide infra).

From the ^{1}H NMR [δ_H 3.96 (tt, *J*=11.2 and 4.6 Hz)] and ^{13}C NMR [δ_C 68.1 (CH)] specta of the last compound **25**, it was assigned to a secondary alcohol. Similar discussion on the coupling pattern of the proton attached to a carbon bearing the hydroxyl group led to the conclusion that the hydroxyl group is either on 2α or 8α. In order to determine the structures of **24** and **25**, either 2α- or 8α-hydroxymaalioxide, the NOE experiment was therefore performed. When the methine proton at δ 3.87 of **24** was irradiated, only one methyl signal appeared in the NOE difference



Scheme 3.

spectrum. On the other hand, when the proton at δ 3.96 of **25** was irradiated, NOE's into both methyl groups at C-4 and C-10 were observed. These observations clearly distinguished these two alcohols, as expected from the consideration of the model. From these results, the structures of **24** and **25** were determined to be 8α-hydroxymaalioxide and 2α-hydroxymaalioxide, respectively.

In the *m*CPBA oxidation reactions, the tertiary positions are easy to be oxidized giving hydroxylated compounds. In this case, however, the tertiary positions of LB (**14**) and maalioxide (**22**) were not attacked presumably because they were sterically hindered. Most of the methine protons of these compounds were β-oriented and close to the methyl groups or the epoxy bridge. The fact that all the products were equatorial alcohols was due to energetic preference and consistent with those observed before in the field of triterpenes.[8] On the contrary, guaioxide (**2**) has many α-protons, apart from the methyl groups or epoxy bridge. Thus, the introduction of the hydroxyl groups onto guaioxide occurred mainly from α-face. Actually 4α-alcohol **5** was the main product and it is noteworthy that this compound **5** was also the main product of the dry ozonization[11] or microbial oxidation,[10] suggesting this position was the least hindered and protruding.

Experimental

General. See Refs. 6—9.

Guaiol (1). Guaiol (**1**) was isolated from guaiac wood oil by recrystallization from acetone.

Guaioxide (2).[17] A solution of guaiol (**1**) (3 g) in acetic acid (10 ml) was treated with concd H_2SO_4 (0.1 ml) at room temperature for 10 h. After extraction with ether, the extracts (2.9 g) were purified by column chromatography over silica gel (120 g) which was eluted with benzene to afford guaioxide (**2**) (567 mg, 18.9%).

Reaction of Guaioxide (2) with *m*CPBA. A solution of guaioxide (**2**) (479 mg) in chloroform (50 ml) was treated with *m*CPBA (1.06 g, 2 equiv.) under reflux for 13 h. The mixture was concentrated and filtered. The filtrate was directly subjected to column chromatography on silica gel (benzene : AcOEt gradient) to give recovered guaioxide (**2**) (230 mg), 1β-ol **3** (6.5 mg, 2.4%[18]), 10α-ol **4** (8 mg, 3.0%.[18]), a mixture of **4** and **6** (ca. 5 mg), 4α-ol **5** (26.5 mg, 9.9%[18]). The mixture fraction was further purified by HPLC (JASCO Fine pak SIL; 10% EtOAc-hexane) to give 4β-ol **6** (2 mg, 0.7%[18]). 1β-Hydroxyguaioxide (**3**): IR (CCl_4) 3550 and 3450 cm^{-1}; ^{1}H NMR δ=0.93 (3H, d, J=6.6 Hz), 0.97 (3H, d, J=7.1 Hz), 1.22 (3H, s,), 1.34 (3H, s), and 3.41 (1H, s, -OH); ^{13}C NMR δ=22.9 (CH_3), 23.0 (CH_3), 23.1 (CH_3), 26.8 (CH_2), 30.6 (CH_2), 31.6 (CH_3), 33.2 (CH_2), 33.7 (CH_2), 35.1 (CH_2), 38.7 (CH), 46.6 (CH), 53.7 (CH), 80.7 (C), 81.6 (C), and 93.6 (C); MS 238 (M^+), 223, 220, 205 (base), 182, and 139; HRMS: Found: m/z 238.1909 (M^+). Calcd for $C_{15}H_{26}O_2$: M, 238.1933. 10α-Hydroxyguaioxide (**4**): IR ($CHCl_3$) 3600 and 3450 cm^{-1}; ^{1}H NMR δ=0.97 (3H, d, J=6.8 Hz), 1.15 (3H, s), 1.22 (3H, s), and 1.35 (3H, s); ^{13}C NMR δ=15.7 (CH_3), 23.0 (CH_2), 23.7 (CH_3), 25.4 (CH_2), 30.4 (CH_3), 31.7 (CH_2), 34.0 (CH_3), 38.3 (CH_2), 40.4 (CH_2), 44.9 (CH), 46.0 (CH), 58.2 (CH), 73.0 (C), 82.1 (C), and 91.1 (C); MS m/z 238 (M^+), 223, and 205 (base); HRMS: Found: m/z 238.1944 (M^+). Calcd for $C_{15}H_{26}O_2$: M, 238.1933. 4α-Hydroxyguaioxide (**5**)[10,11]: IR 3600 cm^{-1}; ^{1}H NMR δ=0.87 (3H, d, J=6.1 Hz), 1.19 (3H, s), 1.308 (3H, s), and 1.315 (3H, s); ^{13}C NMR δ=22.5 (CH_3), 23.0 (CH_3), 24.8 (CH_3), 24.8 (CH_2), 30.7 (CH_2), 31.1 (CH_3), 31.4 (CH_2), 33.5 (CH_2), 34.9 (CH_2), 40.0 (CH), 45.5 (CH), 52.1 (CH), 78.8 (C), 81.6 (C), and 93.0 (C); MS m/z 238 (M^+), 223, 205 (base), 162, and 95. 4β-Hydroxyguaioxide (**6**): IR ($CHCl_3$) 3500 and 3400 cm^{-1}, ^{1}H NMR δ=0.91 (3H, d, J=6.6 Hz), 1.19 (3H, s), 1.22 (3H, s), and 1.32 (3H, s); ^{13}C NMR δ=22.9 (CH_3), 23.0 (CH_3), 23.1 (CH_3), 26.8 (CH_2), 30.5 (CH_2), 31.6 (CH_3), 33.2 (CH_2), 33.6 (CH_2), 35.0 (CH_2), 38.7 (CH), 46.5 (CH), 53.6 (CH), 80.7 (C), 81.7 (C), and 93.6 (C); MS m/z 238 (M^+), 223, 205, 162, and 95 (base); HRMS: Found: m/z 238.1960 (M^+). Calcd for $C_{15}H_{26}O_2$: M, 238.1933.

Cyclization of Guaiol (1). A solution of guaiol (**1**) (500 mg) in acetic acid (10 ml) was treated with $Pb(OAc)_4$ (1.67 g, 1 equiv.) at room temperature for 24 h. Aqueous Na_2SO_3 was added and the mixture was extracted with ether. The residue was purified by column chromatography over silica gel (25 g) (benzene : EtOAc gradient) to afford a mixture of Δ^1-dehydroguaioxide (**7**) and $\Delta^{1(10)}$-dehydroguaioxide (**8**) (32.7 mg).

Epoxidation of the Mixture of 7 and 8. To a solution of the mixture of **7** and **8** (86.2 mg) in chloroform (3 ml) was added *m*CPBA (144.9 mg, 1.5 equiv.). The mixture was treated with aqueous Na_2SO_3 and the residue was purified by column chromatography over silica gel (benzene : EtOAc gradient) to give 1α,2α-epoxyguaioxide (**9**) (73.6 mg), 1β,2β-epoxyguaioxide (**10**) (2.8 mg), and 1α,10α-epoxyguaioxide (**11**) (5 mg). **9**: ^{1}H NMR δ=0.90 (3H, d, J=7.6 Hz), 0.91 (3H, d, J=7.6 Hz), 1.16 (3H, s), 1.40 (3H, s), and 3.50 (1H, s); ^{13}C NMR δ=12.8 (CH_3), 18.6 (CH_3), 23.1 (CH_3), 30.6 (CH_2), 31.1 (CH_3), 31.2 (CH_2), 34.0 (CH), 34.9 (CH_2), 35.0 (CH_2), 35.1 (CH), 44.3 (CH), 61.5 (CH), 80.8 (C), 83.0 (C), and 89.8 (C); MS m/z 236 (M^+), 221, 192, 137, 55 (base), and 43; HRMS Found: m/z 236.1746 (M^+). Calcd for $C_{15}H_{24}O_2$: M, 236.1774. **10**: ^{1}H NMR δ=0.73 (3H, d, J=7.0 Hz), 1.02 (3H, d, J=7.0 Hz), 1.17 (3H, s), 1.38 (3H, s), and 3.19 (1H, d, J=1.5 Hz); ^{13}C NMR δ=17.4 (CH_3), 18.8 (CH_3), 22.8 (CH_3), 29.9 (CH_3), 30.7 (CH_2), 31.3 (CH_2), 31.9 (CH), 34.3 (CH_2), 42.1 (CH_2), 43.3 (CH), 45.1 (CH), 59.6 (CH), 68.2 (C), 82.9 (C), and 90.2 (C); MS m/z 236 (M^+), 221, 203, 179, 124 (base), 109, and 43; HRMS: Found: m/z 236.1743 (M^+). Calcd for $C_{15}H_{24}O_2$: M, 236.1774. **11**: ^{1}H NMR δ=1.01 (3H, d, J=7 Hz), 1.23 (6H, s), and 1.25 (3H, s); ^{13}C NMR δ=13.3 (CH_3), 21.6 (CH_2), 27.1 (CH_3), 28.1 (CH_2), 28.4 (CH_2), 28.8 (CH_2), 28.9 (CH_3), 30.7 (CH_3), 32.5 (CH_2), 36.1 (CH), 40.9 (CH), 67.0 (C), 71.2 (C), 72.9 (C), and 75.0 (C); MS m/z 236 (M^+), 221, 203, 179, 161 (base), 124, 109, and 43; HRMS Found: m/z 236.1743 (M^+). Calcd for $C_{15}H_{24}O_2$: M, 236.1774.

Reduction of 9. A solution of **9** (30 mg) in THF (3 ml) was treated with $LiAlH_4$ (24 mg) under reflux for 10 h. Ether saturated with water was added and the mixture was worked up as usual to afford **12** (3 mg) after purification by column chromatography (benzene : EtOAc gradient). IR ($CHCl_3$) 3400 cm^{-1}; ^{1}H NMR δ=0.95 (3H, d, J=7 Hz), 1.05 (3H, d, J=7 Hz), 1.17 (3H, s), and 1.34 (3H, s); MS m/z 238 (M^+), 223, 220, 205, and 43 (base); HRMS Found: m/z 238.1912 (M^+). Calcd for $C_{15}H_{26}O_2$: M, 238.1933.

Reduction of 10. A solution of **10** (2 mg) in THF was

also reduced as described above to afford **3** (1.5 mg). The spectral data of this product were identical with those of the *m*CPBA oxidation product of guaioxide (**2**).

Reaction of LB (14) with *m*CPBA. A solution of LB (**14**) (80.6 mg) in chloroform (3 ml) was treated with *m*CPBA (101.2 mg, 1.2 equlv.) under reflux for 12 h. The mixture was concentrated and filtered. The filtrate was directly subjected to column chromatography on Sephadex LH-20 ($CHCl_3$: MeOH=1 : 1) and then silica gel (hexane : AcOEt gradient) to give recovered LB (**14**) (46.8 mg), 2β-ol **15** (3.3 mg, 9.1%[18]), 3α-ol **16** (5.0 mg, 13.8%[18]), and 8α-ol **17** (3.3 mg, 9.1%[18]). **15**: IR 3450 cm^{-1}; ^1H NMR δ=0.90 (3H, d, J=7.3 Hz, 1.02 (3H, d, J=6.8 Hz), 1.18 (3H, s), 1.26 (3H, s), 3.49 (1H, d, J=11.5 Hz), and 4.05 (1H, dt, J=11.5 and 5.8 Hz); ^{13}C NMR δ=20.1 (CH_3), 22.1 (CH_3), 24.5 (CH_3), 25.8 (CH_2), 28.2 (CH), 31.4 (CH_3), 32.7 (CH_2), 33.4 (CH_2), 43.3 (CH), 43.4 (CH_2), 44.1 (CH), 56.9 (CH), 73.9 (CH), 84.3 (C), and 96.2 (C); MS m/z 238 (M^+), 223, 220, and 43; HRMS Found: m/z 238.1893 (M^+). Calcd for $C_{15}H_{26}O_2$: M, 238.1933. **16**: IR 3450 cm^{-1}; ^1H NMR δ=0.86 (3H, d, J=6.6 Hz), 0.87 (3H, d, J=7.6 Hz), 1.19 (3H, s), 1.25 (3H, s), and 3.73 (1H, m); ^{13}C NMR δ=15.1 (CH_3), 22.2 (CH_3), 24.6 (CH_3), 25.6 (CH_2), 31.0 (CH_3), 33.5 (CH), 33.7 (CH_2), 33.9 (CH_2), 40.1 (CH_2), 43.7 (CH), 53.7 (CH), 54.6 (CH), 78.4 (CH), 83.3 (C), and 94.9 (C); MS m/z 238 (M^+), 223, 220, and 95; HRMS Found: m/z 238.1890 (M^+). Calcd for $C_{15}H_{26}O_2$: M, 238.1933. **17**: IR 3580 cm^{-1}; ^1H NMR δ=0.92 (6H, d, J=7.1 Hz), 1.24 (3H, s), 1.31 (3H, s), and 4.20 (1H, dd, J=16.4 and 6.4 Hz); ^{13}C NMR δ=20.0 (CH_3), 22.4 (CH_3), 24.5 (CH_3), 28.0 (CH_2), 29.8 (CH), 30.4 (CH_2), 31.2 (CH_2), 31.8 (CH_3), 43.8 (CH_2), 44.8 (CH), 54.1 (CH), 54.6 (CH), 69.9 (CH), 81.5 (C), and 94.4 (C); MS m/z 238 (M^+), 223, 205, and 137; HRMS: Found: m/z 238.1969 (M^+). Calcd for $C_{15}H_{26}O_2$: M, 238.1933.

Oxidation of 2β-ol 15. A solution of 2β-ol **15** (1.9 mg) in acetone (0.4 ml) was treated with Jones reagent (3 drops) at 0 °C for 1 h. Usual work up and chromatography over silica gel (hexane : EtOAc gradient) gave 2-oxo-LB **18** (0.3 mg). IR 1728 cm^{-1}; ^1H NMR δ=1.09 (3H, d, J=7.3 Hz), 1.20 (3H, d, J=6.1 Hz), 1.21 (3H, s), and 2.63 (1H, dd, J=18.8 and 8.8 Hz); ^{13}C NMR δ=21.1 (CH_3), 24.6 (CH_3), 25.2 (CH_3), 29.2 (CH_2), 29.7 (CH_2), 30.9 (CH_3), 34.1 (CH_2), 34.6 (CH_2), 40.0 (CH), 44.4 (CH), 45.1 (CH_2), 60.3 (CH), 83.1 (C), 92.2 (C), and 214.0 (C); MS m/z 236 (M^+), 221, 203, and 137; HRMS Found: m/z 236.1778 (M^+). Calcd for $C_{15}H_{24}O_2$: M, 236.1776.

Oxidation of 3α-ol 16. A solution of 3α-ol **16** (1.7 mg) in acetone (0.3 ml) was treated with Jones reagent (3 drops) at 0 °C for 1 h. Usual work up and chromatography over silica gel (hexane ; EtOAc gradient) gave 3-oxo-LB **19** (0.9 mg). IR 1730 cm^{-1}; ^1H NMR δ=0.91 (3H, d, J=6.7 Hz), 1.05 (3H, d, J=7.7 Hz), 1.18 (3H, s), and 1.26 (3H, s),; ^{13}C NMR δ=13.5 (CH_3), 22.3 (CH_3), 24.4 (CH_3), 25.3 (CH_2), 30.8 (CH_3), 33.2 (CH), 33.6 (CH_2×2), 42.1 (CH_2), 44.3 (CH), 51.7 (CH), 55.9 CH), 83.4 (C), 90.9 (C), and 214.4 (C); MS m/z 236 (M^+), 221, and 203; HRMS Found: m/z 236.1775 (M^+). Calcd for $C_{15}H_{24}O_2$: M, 236.1776.

Isomerization of 3-Oxo LB 19.[13] A solution of 3-oxo LB (**19**) (0.9 mg) in ether (1 ml) was absorbed on alumina (2.5 g) and eluted with ether (80 ml) after 5 h. Purification over silica-gel column chromatography (hexane : EtOAc gradient) afforded an enone **20** (0.2 mg). UV (MeOH) λ_{max} =242 nm (ε=1.09×10^4); IR 3400 and 1680 cm^{-1}; ^1H NMR δ=1.04 (3H, d, J=6.3 Hz), 1.23 (3H, s), 1.26 (3H, s), and 1.68 (3H, d, J=1.5 Hz); MS m/z 236 (M^+), 218, 203, and 59.

Oxidation of 8α-ol 17. A solution of 8α-ol **17** (1.5 mg) in acetone (0.3 ml) was treated with Jones reagent (3 drops) at 0 °C for 1 h. Usual work up and chromatography over silica gel (hexane : EtOAc gradient) gave 8-oxo-LB **21** (0.4 mg). IR 1680 cm^{-1}; ^1H NMR δ=0.96 (3H, d, J=6.6 Hz), 0.97 (3H, d, J=7.6 Hz), 1.24 (3H, s), and 1.25 (3H, s); ^{13}C NMR δ=19.5 (CH_3), 22.0 (CH), 25.3 (CH_3), 28.5 (CH_2), 30.4 (CH_2), 30.7 (CH), 31.0 (CH_3), 34.4 (CH_2), 45.2 (CH), 51.6 (CH_2), 54.3 (CH), 61.1 (CH), 83.2 (C), 95.2 (C), and 202.0 (C); MS m/z 236 (M^+), 221, 208, and 137; HRMS Found: m/z 236.1805 (M^+). Calcd for $C_{15}H_{24}O_2$: M, 236.1776.

Reaction of Maalioxide (22) with *m*CPBA. A solution of maalioxide (**22**) (151 mg) in chloroform (10 ml) was heated at reflux with *m*CPBA (211 mg, 1.2 equiv.) for 12 h. The mixture was concentrated and filtered. The filtrate was directly subjected to column chromatography on Sephadex LH-20 ($CHCl_3$-MeOH) and then silica gel (benzene-AcOEt). Further purification by preparative TLC gave 7β-hydroxymaalioxide (**23**) (1 mg, 1.2%[18]), 8α-hydroxymaalioxide (**24**) (1.2 mg, 1.5%[18]), and 2α-hydroxymaalioxide (**25**) (1.6 mg, 2.0%[18]) in addition to recovered maalioxide (**22**) (76 mg).

7β-Hydroxymaalioxide (**23**); IR ($CHCl_3$): 3400 cm^{-1}; ^1H NMR: δ=0.92 (3H, s), 1.14 (3H, s), 1.21 (3H, s), 1.43 (3H, s), 3.62 (1H, td, J=10 and 4.4 Hz), and 3.68 (1H, s); MS m/z 238 (M^+), 223, and 205; HRMS Found: m/z 238.1933 (M^+), Calcd for $C_{15}H_{26}O_2$: M, 238.1933.

8α-Hydroxymaalioxide (**24**); IR ($CHCl_3$): 3400 cm^{-1}; ^1H NMR: δ=0.92 (3H, s), 1.07 (3H, s), 1.12 (3H, s), 1.33 (3H, s), 3.67 (1H, s), and 3.87 (1H, tt, J=11 and 3.9 Hz); MS m/z 238 (M^+), 223, 205, and 195; HRMS Found: m/z 238.1935 (M^+), Calcd for $C_{15}H_{26}O_2$: M, 238.1933.

2α-Hydroxymaalioxide (**25**); IR ($CHCl_3$): 3400 cm^{-1}; ^1H NMR: δ=0.93 (3H, s), 1.06 (3H, s), 1.15 (3H, s), 1.33 (3H, s), and 3.96 (1H, tt, J=11.2 and 4.6 Hz); MS m/z 238 (M^+), 223, 205, and 147; HRMS Found: m/z 238.1931 (M^+), Calcd for $C_{15}H_{26}O_2$, M, 238.1933.

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