Photomediated transformation of eremophilanes-I: photooxidation of 2β-angeloyloxy-10β-*H*-furanoeremophilane

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Abstract

The photochemical oxygenation reaction of 2β-angeloyloxy-10β-H-furanoeremophilane **(1)**, a sesquiterpene, was studied in benzene and methanol. Three photoproducts were isolated and characterized by IR ^{1}H-NMR, ^{13}C-NMR and mass spectral studies. Sesquiterpene itself was found to be singlet oxygen ($^1O_2$) sensitizer. Addition of rose bengal increased the rate of photooxidation whereas as DABCO was found to decrease the rate of photolysis proving the involvement of $^1O_2$ in these photoreactions. 2β-Angeloyloxy-8-hydroxy–10β-H-eremophilanolide **(4)** and 2β-angeloyloxy–7,8-epoxy-10β-*H*-eremophilanolide **(6)** were obtained as products in benzene. Photolysis in methanol gave a single product 2β-angeloyloxy-10β-*H*-8-methoxy-12-hydroperoxy-dihydro-furanoeremophilane **(7)**, which was further transformed into product **4**, **8** and **12**. Reaction was also carried out by adsorbing compound **(1)** on silica gel bound rose bengal, which yielded the products **4** and **6** with an increase in the rate of reaction.

Keywords: Photomediated transformation, singlet oxygen, furanoermophilane, sesquiterpenes

Introduction

For over a century, natural products have served as tools and leads for the developments of new drugs and several natural compounds from plants and animals kingdom are now useful drugs. Moreover, plenty of plant materials for their biologically active principles have proved to be of potential medicinal value.[1,2] Photochemistry of drugs is an area of vital importance in current medicinal chemistry, for establishing a relation to its phototoxicity, and a considerable amount of work has been done with synthetic drug molecule.[3-5]However, a significant and related work on photochemistry of medicinally or biologically active compounds from plants is sporadic.[6-9] Several natural plant extract containing terpenoids are widely used in agriculture and medicine.[10,11] Photochemical study is expected to through light on improving the stability of

these compounds into the biological formulations made from the natural plant extracts containing terpenoids. More over the significance of generation and reactions of $^1O_2$ with biomolecules in plants and living systems have been recognized .[12]

Furanoeremophilanes, a novel class of sesquiterpenes is the constituents of several medicinal plants[13-15] and is well known for their medicinal values[16-18] e.g. antioxidant and antiradical property, toxicity[19,20] and antifeedant[21] activity. We have initially investigated photooxidation of 2β- angeloyloxy-10β-*H*-furanoeremophilane[22] **(1)** in its reaction with singlet oxygen ($^1O_2$) in different reaction media.

The dye sensitized photooxygenation of furans has been the subject of extensive study.[23] Furan behaves as a typical 1,4-diene and undergoes [4π + 2π] cycloaddition[24] with dienophile ($^1O_2$) produced in situ by the photo-dye-sensitization. The reaction is thought to proceed by way of a cyclic peroxide formed by 1,4-addition of oxygen, which further transforms into oxygenation products. The secondary plant products are known to have a physiological role in that they protect the plant against damaging photodynamic reactions by quenching the excited singlet state of oxygen. The furan moiety in furanoeremophilanes may be susceptible to attack by $^1O_2$. Several eremophilanolides are known to occur naturally along with eremophilanes hence it is also of interest to study photooxygenation of eremophilanes in order to have knowledge of its parallel reaction with $^1O_2$ in plants.

Result and Discussion

Irradiation of furanoeremophilane **(1)** in benzene under continuous air bubbling with quartz filtered light from a medium pressure mercury lamp, and purification of the crude product by silica gel chromatography afforded compound **4** and **6**, identified as 2β-angeloyloxy-8-hydroxy – 10β-H-eremophilanolide and 2β-angeloyloxy–7,8-epoxy-10β-H-eremophilanolide, respectively. Both the 2β-angeloyloxy-10β-H-furanoeremophilane **(1)** and hydroxybutenolide **(4)** have been isolated from the same plant species and it has been indicated that **1** is probable natural artefact of **4**.[22]

The mechanism of formation of γ-hydroxybutenolide **(4)** and epoxylactone **(6)** is depicted in Scheme 1. [4π+2π] Cycloaddition of $^1O_2$ to furan moiety of **1** gives an unstable ozonide peroxide intermediate **(2)**, which by homolytic cleavage of O-O bond produces diradical intermediate **3**. Intermediate **3** on epoxycyclization followed by 1,2 – hydrogen shift gives compound **6**. In an alternative competitive path a 1,4-hydrogen migration in the intermediate **3** gives product **4** (Scheme 1). Cyclic peroxides are generally unstable; however in some cases stable peroxides have been isolated.[25] The participation of $^1O_2$ in this reaction was confirmed by studying the effect of DABCO (singlet oxygen scavenger) on the yield of photooxidation products. The drastic lowering of the yield of products in presence of DABCO confirms that $^1O_2$ is active oxidizing species in this photoreaction. Also no reaction was observed on conducting experiments under nitrogen atmosphere, which further support the fact.
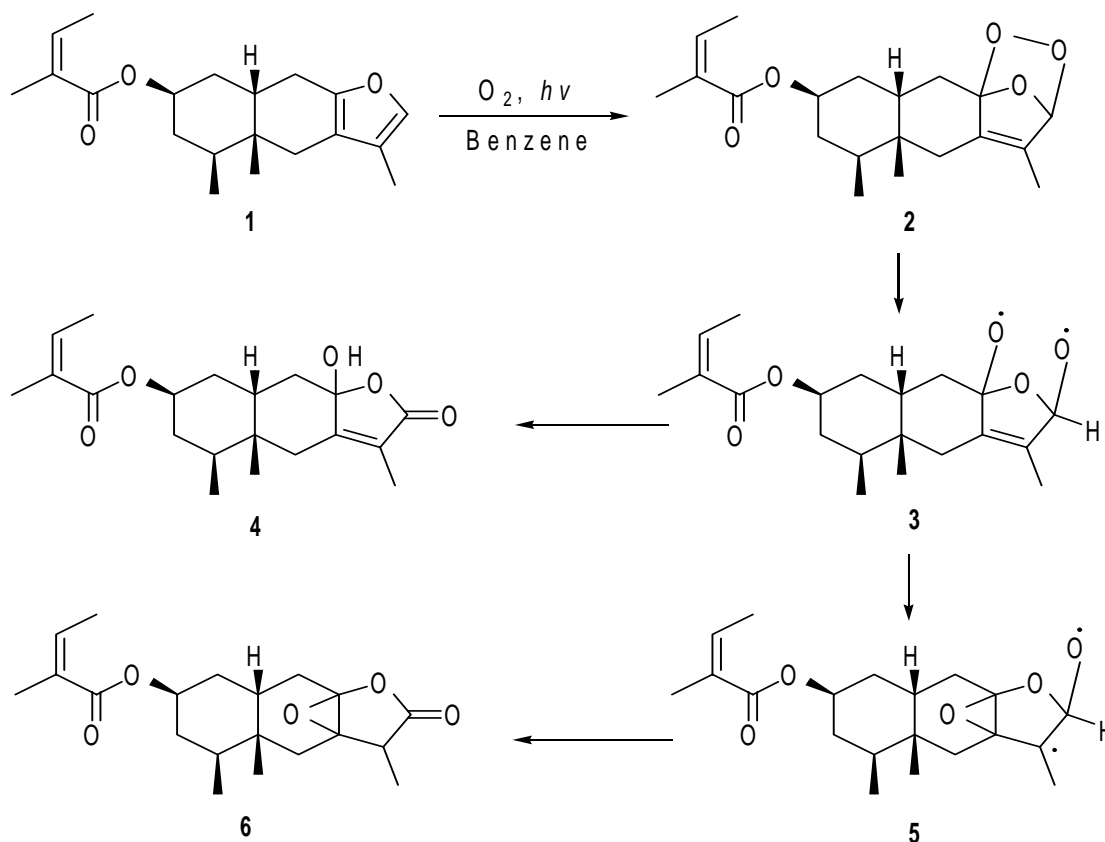
Scheme 1

The ^{1}H-NMR and ^{13}C-NMR spectrum of compound **4** were similar to those of **1** except for the furan signals. The extra carbonyl resonance at δ 177.4 ppm indicated an additional lactone carbonyl compared to that of parent compound. This was confirmed by the presence of IR bands at 1765, 1715 and 1650 cm^{-1}. The absence of C/H NMR signals due to furan moiety indicated that the furan ring had been the site of attack. ^{13}C-NMR signals at δ 110 ppm (carbon having no proton), indicated that the carbon must be attached to two oxygen atoms. Further, δ 2.48 and 2.23, the H-9 signal in compound **1** changes to δ 1.80 and 1.55 ppm, suggesting that double bond between C_7-C_8 in **1** is shifted to C_7-C_{11} in **4**, and the carbon connected to two oxygen atoms must be adjacent to β carbon of the α, β-unsaturated ketone system. The presence of other carbon signals at 177.4, 156.3, 125.9 and 11.6 ppm along with an IR band at 3620 cm^{-1} indicated that the furan ring has been modified to a γ-hydroxybutenolide moiety. The compound was thus assigned structure as **4** with a molecular formula $C_{20}H_{28}O_5$ (M$^+$, 349).

The spectral data of photoproduct **6** was almost identical to that of starting compound **1**, except for the values corresponding to an epoxide at C_7-C_8 and an epoxylactone in place of furan ring. This is evidenced by the following changes in the methylene carbon signals: δ 2.60, 2.35 ppm (C-6) and δ 2.48, 2.23 ppm (C-9), changed to δ 1.58, 133 ppm (C-6) and δ 1.89, 1.64 ppm

(C-9) suggesting that the change has occurred at C_7-C_8. Further ^{13}C-NMR value at δ 59.3 ppm (C-7) and 93.3 ppm (C-8), suggested that initially sp^2 hybridized carbon changed to quaternary carbon. The compound **6** showed a singlet at δ 2.78 ppm attached to C-11 at δ 47.8 ppm, which was not present in the in starting compound. This suggested that both the double bonds of furan ring were utilized in epoxide and lactone formation. ^{13}C-NMR exhibited signal due to lactone carbonyl at δ 177.4 ppm, which is supported by the IR bands at 1765 cm^{-1} (lactone) and 1715 cm-1 (α, β-unsaturated ester).

Photooxygenation of **1** in methanol gave a compound identified as a crystalline hydroperoxide whose properties require that it should have structure **7**. The compound has absorption bands at 3514 cm^{-1} (-OOH) and 1250 cm^{-1} (C-O) but none in –C=O region indicating it to be a hydroperoxide. Its ^{1}H-NMR spectrum has significant signals at δ 8.16 (1H, OOH, exch.) and δ 3.24 (3H, OCH$_3$) consistent with structure **1**. The microanalysis of this compound corresponds to molecular formula $C_{21}H_{32}O_6$. A quantitative Zeisel determination indicated the presence of one OMe group and the result of quantitative peroxide and active hydrogen determinations were consistent with the presence of one O-O and one OH group. When **1** was irradiated in presence of [P$_{si}$]–rose bengal[26] in methanol under bubbling oxygen a mixture of products **4** and **6** was obtained. It was found that upon standing the reaction mixture and so also on addition of dil HCl in the reaction mixture, the product **6** (epoxy lactone) converted into hydroxy butenolide **4** (Scheme 2). The comparative yields of the photoproducts (**4**, **6** and **7**) under different reaction conditions are given in Table 1.

Table 1. Yields of the reaction products, in photooxygenation reaction of **(1)** under different reaction conditions

| Solvent	Photoproduct(s)	Yields of products (mg)^b
Benzene	**4 + 6**	58.23 (38.48+19.75)
Methanol	**7**	37.20
[P$_{Si}$]-rose bengal/methanol	**4 + 6**	58.28 (45.08+13.20)

^{b}Yields of the products after isolation and purification.
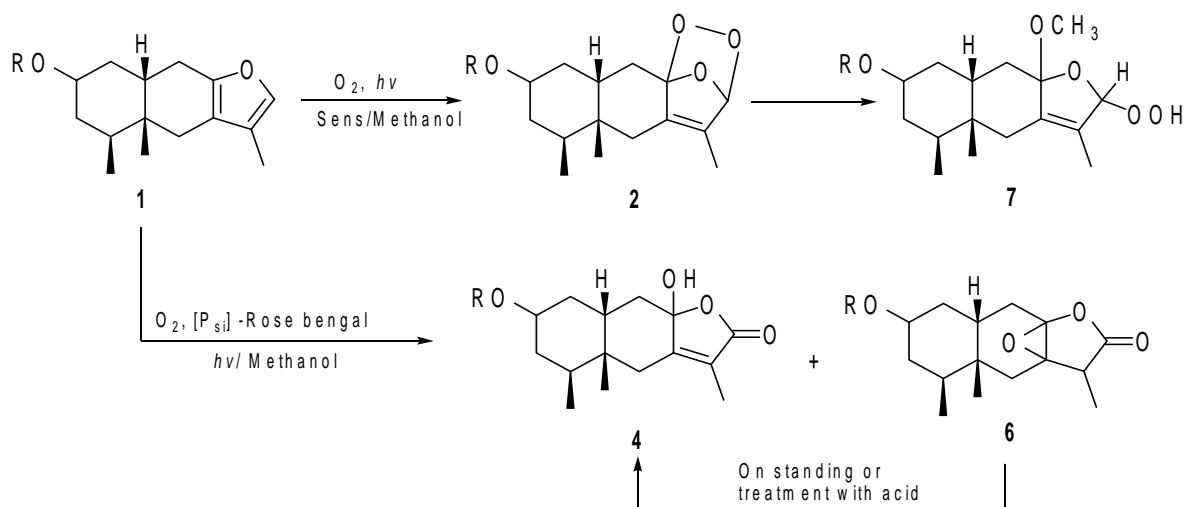
Scheme 2

Treatment of methoxy hydroperoxide **7** with methanolic HCl gave a product identified as **4**. Whereas pyrolysis of **7** produced **8**. (Scheme 3) The structure of **8** was readily established by its spectral and chemical properties. In the IR, the compound absorbs at 1779 cm^{-1}, characteristics of γ-oxygenated α,β-unsaturated-γ-lactone functionality. In the UV as well, absorption characteristics of this chromophore occurred at λ_{max} 216 nm. The NMR spectrum clearly showed the presence of a –OMe group δ 3.24 (3H) and an allylic Me δ 1.71 (3H). The presence of the OMe group was confirmed by a quantitative zeisel determination; microanalysis required the formula $C_{21}H_{30}O_5$. Reduction of **7** with triphenylphosphine in ether gave a product, which was identified as **12**. Its formation could be realized via unstable hemiacetal **10** (Scheme 3).

Compound **12** was found to have the empirical formula $C_{20}H_{28}O_4$. Its IR absorption at 1779 cm^{-1} and UV λ_{max} 217 nm are characteristic of an α, β-unsaturated γ-lactone. The NMR spectrum showed the presence of an allylic Me group, δ 1.93 (3H, t); the single proton in the lactone ring appears as the quartet centered at δ 4.91 (1H, J=6 and 11 Hz). The compound was identified as 2β-angeloyloxy -10β-H-eremophilanolide **12**.
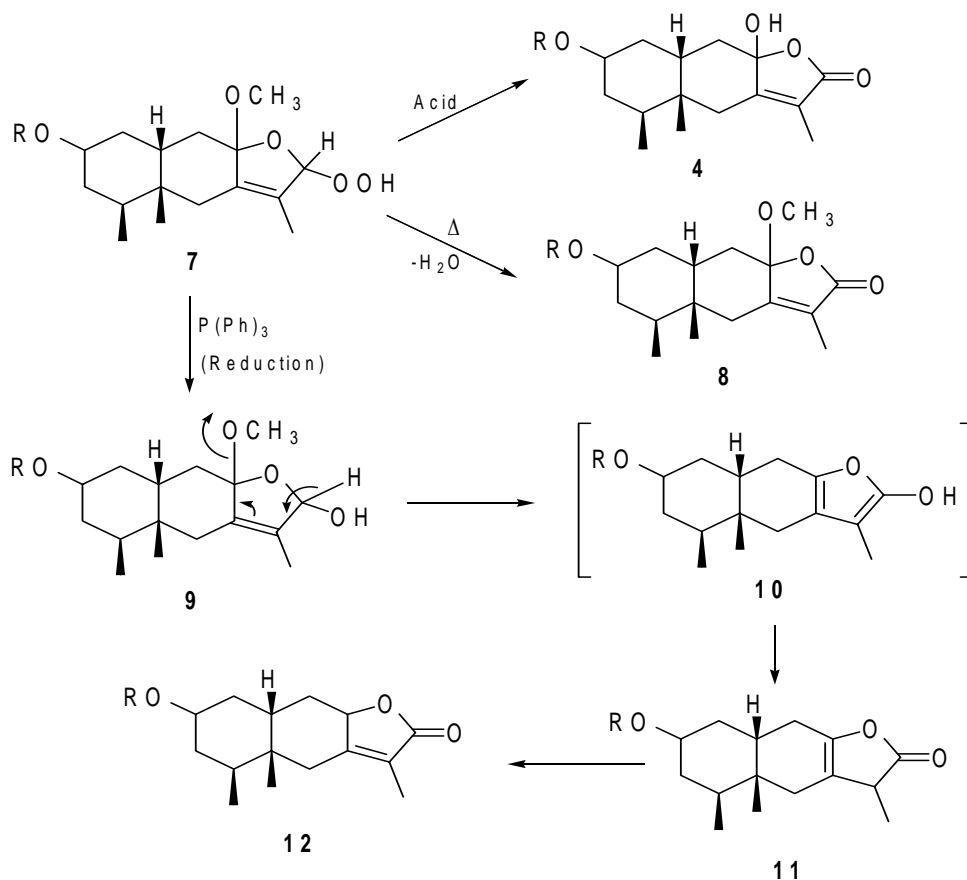
Scheme 3

Experimental Section

General Procedures. All chemicals used were of analytical grade. 2β-Angeloyloxy-10-β-H-furanoeremophilane **(1)** was extracted from the roots of *Senecio alatus* as described in the literature.[22] UV spectra were recorded on a Shimadzu 160 A instrument. IR spectra were recorded as KBr discs on a Perkin Elmer model spectrum RXI. ^{1}H-NMR and ^{13}C-NMRspectra were recorded on a Bruker Avance DRX-300 spectrometer using TMS as internal standard and CDCl$_3$ as solvent. EIMS were obtained on a VG-ZAB-HS mass spectrometer. HR-ESI-MS were recorded on a Bruker APEX II mass spectrometer. Gas chromatography was carried out with a Perkin Elmer model 154 (thermal chromatograph conductivity detector). Precoated silica gel plates (E-Merck, Germany, Art.5554 Keiselgel 60 F$_{254}$ 0.2mm thickness) were used for analytical TLC; column chromatography was performed on Merck silica gel 60 (70-230mesh).

Irradiation procedure. Irradiation of 2β-angeloyloxy-10β-*H*-furanoeremophilane (1) in benzene. Compound **1** (100 mg , 0.316 mmol) was dissolved in benzene (250ml) and the

solution was irradiated under continuous bubbling of air with a light from a 400W medium pressure mercury lamp housed in a water cooled immersion well quartz photo-reactor. The Progress of reaction was monitored by thin layer chromatography (TLC), which indicated gradual disappearance of starting material. When the rate of product formation became negligible, solvent was removed and the residue was purified by TLC on silica gel eluting with 50% ether-hexane, it yielded hydroxybutenolide **(4)** and epoxylactone **(6)** as the products (Scheme 1).

2β-Angeloyloxy-8-hydroxy–10β-H-eremophilanolide (4). Yield: 38.48 mg; mp 210 °C; IR ν_{max}^{cm-1}: 3620 (-OH), 1765 (Lactone), 1715, 1650 (C=C-COOR); ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 1.06 (d, J=6.8 Hz , 3H, 15-H), 1.16 (s, 3H, 14-H), 1.41 (s, 1H, 10-H), 1.51 (m, 2H, 1-H & 3-H), 1.55 (dd, J=17& 9 Hz, 1H, 9-H), 1.59 (m, 1H, 4-H), 1.71 (d, J=1.5 Hz, 3H, 4'-H), 1.75 (s, 1H, 6-H), 1.76 (m, 2H, 1-H & 3-H), 1.80 (d, J=17& 9 Hz, 1H, 9-H), 1.93 (s, 6H, 5'-H & 13-H), 2.00 (s, 1H, 6-H), 3.91 (m, 1H, 2-H), 6.03 (m, 1H, 3'-H); ^{13}C-NMR (CDCl$_3$,100 MHz) δ 11.6 (C-13), 12.1 (C -4'), 16.4 (C-15), 17.5 (C -5'), 20.5 (C-14), 25.4 (C-10), 26.5 (C-6), 31.1 (C-4), 35.1 (C-1), 37.3 (C-3), 40.6 (C-9), 50.8 (C-5), 71.8 (C-2), 110.9 (C-8), 125 (C-11), 128.3 (C-2'), 138.6 (C-3'), 156.3 (C-7), 167.2 (C-1') 176.0 (C-12); EI-MS m/z (rel. int.%): 349 (M+1, 25), 245 (M+1-RCOOH, 42), 218 (100).HR-MS: m/z 348.199 (calcd.348.198).

2β-Angeloyloxy–7,8-epoxy-10β-H-eremophilanolide (6). Yield: 19.75 mg; mp 206 °C; IR ν_{max}^{cm-1} : 1765 (Lactone), 1715, 1650 (C=C-COOR) 1420, 1380, 1330, 1293, 1171, 964, 816, 733, 562; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 1.06 (d, J=6.8 Hz, 3H, 15-H), 1.16 (s, 3H, 14-H), 1.24 (d, J=7 Hz, 3H, 13-H), 1.33 (dd, J= 15 & 7 Hz, 1H, 6-H), 1.41 (s, 1H, 10-H), 1.51 (m, 2H, 1-H & 3-H), 1.58 (dd, J= 15 & 7 Hz, 1H, 6-H), 1.59 (m, 1H, 4-H), 1.64 (dd, J=15 & 7 Hz, 1H, 9-H), 1.71 (d, J=1.5 Hz, 3H, 4'-H), 1.76 (m, 2H, 1-H & 3-H), 1.89 (dd, J=15 & 7, 1H, 9-H) 1.93 (s, 3H, 5'-H), 2.78 (q, J=7 Hz, 1H, 11-H), 3.91 (m, 1H, 2-H), 6.03 (m, 1H, 3'-H); ^{13}C-NMR (CDCl$_3$) δ 10.3 (C-13), 12.1 (C-4'), 16.3 (C-15), 17.5 (C -5'), 20.1 (C-5), 27.4(C-10), 30.5 (C-9), 30.7(C-4), 34.4 (C-1), 36.7 (C-6), 37.2 (C-3), 71.8 (C-2), 93.3 (C-8), 128.3 (C-2'), 138.6 (C-3'), 167.2 (C-1'), 177.4 (C-12); EI-MS m/z (rel. int.%): 347 (M$^+$, 1), 329 (M$^+$-H$_2$O, 2), 247 (M$^+$-C$_4$H$_7$COOH, 12), 83 (C$_4$H$_7$CO$^+$, 100) , 55   (83-CO, 44). HR-MS: m/z 348.197 (cacld.: 348.198).

Photosensitized oxygenation of 2β-angeloyloxy-10β-H-furanoeremophilane (1) in methanol. Compound **1** (100 mg, 0.316 mmol), was dissolved in 250 ml MeOH containing 100mg of rose bengal. The solution was irradiated with a 400W medium pressure mercury lamp in a water-cooled immersion well type quartz photo reactor with continuous supply of O$_2$. The progress of the reaction was monitored by TLC (silica gel, ether-hexane). When the rate of product formation became negligible solvent was evaporated in a rotatory evaporator, and the residue taken up in ether, the ether was washed with water, treated with activated charcoal, dried and evaporated to yield **7** as colorless oil (Scheme 2).

2β-Angeloyloxy-10β-H-8-methoxy-12-hydroperoxy-dihydro-furanoeremophilane (7). Yield: 37.20 mg; mp 198 °C; IR ν_{max}^{cm-1}: 3514, 2130, 1830, 1715, 1650, 1250; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 1.06 (d, J=6.8 Hz, 3H, 15-H), 1.16 (s, 3H, 14-H), 1.41 (m, 1H, 10-H), 1.42 (dd, J= 15 & 7 Hz, 1H, 9-H), 1.57 (m, 2H, 1-H), 1.51 (m, 2H, 3-H), 1.59 (m, 1H, 4-H), 1.67 (dd, J= 15 & 7

Hz, 3H, 9-H), 1.71 (d, J=1.5 Hz, 3H, 4'-H), 1.75 (dd, J=15 & 7 Hz, 1H, 6-H), 1.76 (m, 2H, 3-H), 1.81 (d, J=1.5 Hz, 3H, 13-H), 1.93 (s, 3H, 5'-H), 3.24 (s, -0CH$_3$), 3.91 (m, 1H, 2-H), 6.03 (m, 1H, 3'-H), 8.16 (s, 1H, 12-H); ^{13}C-NMR (CDCl$_3$, 100MHz) δ 7.6 (C-13), 12.1 (C-4'), 16.3 (C-15), 17.5 (C-5'), 20.5 (C-14), 21.2 (C-6), 25.8 (C-10), 35.4 (C-1), 37.3 (C-3), 39.5 (C-9), 51.4 (C-5), 51.6 (-OCH$_3$), 71.8 (C-2), 110.3 (C-12), 112.0 (C-8), 128.3 (C-2'), 130.8 (C-11), 138.6 (C-3'), 141.7 (C-7), 167.2 (C-1'); EI-MS m/z (rel. int.%): 381 (M$^+$, 7), 363 (M-H$_2$O, 13), 209 (15), 180.15 (3), 83 (100). HR-MS: m/z 380.220 (cacld.: 380.219).

Rearrangement of 7 under acidic conditions. A small amount of **7** (0.2 mM) was taken in MeOH to which 5% HCl was added until the solution became cloudy. The mixture was refluxed for 2 hr, cooled, diluted with water, and extracted with ether to yield a compound identified as **4** (27.84 mg). All the spectral values in IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectra were found to correspond to that of **4** (Scheme 2).

Pyrolysis of photoproduct 7. A sample of **7** (0.2 mM) was taken in benzene and injected into the gas chromatograph (column, 200°, injection block 250°). A single product as **8** was formed. The product was collected from the gas chromatograph (Scheme 3).

2β-Angeloyloxy-10β-*H*-8-methoxy-eremophilenolide (8). Yield: 31.15 mg; UV λ$_{max}$ 216 nm; mp 200 °C; IR ν$_{max}$$^{cm-1}$: 1779, 1760, 1698, 1650, 1533; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 1.06 (d, J=6.8 Hz, 3H, 15-H), 1.16 (s, 3H, 14-H), 1.41 (m, 1H, 10-H), 1.51 (m, 2H, 1-H & 3-H), 1.53 (dd, J=15 & 7 Hz, 1H, 9-H), 1.59 (m, 1H, 4-H), 1.71 (d, J= 15 Hz, 3H, 4'-H), 1.75 (dd, J=15 & 7 Hz, 1H, 6-H), 1.76 (m, 2H, 1-H & 3-H), 1.78 (dd, J=15 & 7 Hz, 1H, 9-H), 2.00 (dd, J=15 & 7, 1H, 6-H), 3.24 (s, -OCH$_3$), 3.91 (m, 1H, 2-H), 6.03 (m, 1H, 3'-H); ^{13}C-NMR (CDCl$_3$, 300MHz) δ 7.6 (C-13), 12.1 (4'-C), 16.4 (C-15), 17.5 (C-5'), 20.5 (C-14), 21.2 (C-6), 25.8 (C-10), 31.1 (C-4), 35.4 (C-1), 39.5 (C-9), 51.4 (C-5), 51.6 (-OCH$_3$), 71.8 (C-2), 110.3 (C-12), 112.0 (C-8), 128.3 (C-2'), 130.8 (C-11), 138.6 (C-3'), 141.7 (C-7), 167.2 (C-1'); EI-MS m/z (rel. int.%): 363 (M+, 34), 332 (M$^+$-OCH$_3$, 13), 263 (M$^+$-C$_4$H$_7$COOH, 11), 83 (C$_4$H$_7$CO$^+$, 93), 55 (C$_4$H$_7$CO$^+$-CO, 40). HR-MS: m/z 362.209 (calcd.: 362.208).

Reduction of 7 with triphenylphosphine. A solution of **7** (0.2 mM) in ether was added drop wise to a refluxing solution of triphenylphosphine in 30 ml ether during 1.5 h. The solution was refluxed 1 h, chilled to -5 ^{0}C and filtered to remove the triphenylphosphine oxide. The ether was removed with a rotatory evaporator, and the residue was chromatographed on silica gel column to give **12** (Scheme 3).

2β-Angeloyloxy-10β-H-eremophilanolide (12). Yield: 31.85 mg; UV λ$_{max}$ 217 nm; mp 195 °C; IR ν$_{max}$$^{cm-1}$: 1808, 1800, 1765, 1715, 1650, 1000; ^{1}H-NMR (CDCl$_3$, 300 MHz): δ 1.06 (dd, J=15 & 7 Hz, 3H, 15-H), 1.16 (s, 3H, 14-H), 1.40 (dd, J=15 &7 Hz, 1H, 9-H), 1.41 (m, 1H, 10-H), 1.51 (m, 2H, 1-H & 3-H), 1.59 (m, 1H, 4-H), 1.65 (dd, J=15 & 7 Hz, 1H, 9-H), 1.75 (d, J=17 Hz, 1H, 6-H), 1.76 (m, 2H, 1H & 3-H), 1.93 (s, 3H, 5'-H), 1.93 (s, 3H, 13-H), 3.91 (m, 1H, 2-H), 4.91 (dd br, J=6.5 & 10 Hz, 1H, 8-H), 6.03 (m, 1H, 3'-H); ^{13}C-NMR (CDCl$_3$, 100 MHz): δ 11.3 (C-13), 12.1 (C-4'), 16.4 (C-15), 17.5 (C-5'), 20.5 (C-14), 31.1 (C-4), 31.6 (C-10), 32.7 (C-6), 34.0 (C-9), 34.8 (C-1), 37.3 (C-3), 50.5 (C-5), 71.8 (C-2), 81.2 (C-8), 125.9 (C-11), 128.3 (C-2'), 138.6 (C-3'), 164.6 (C-7), 167.2 (C-1'), 176.0 (C-12); EI-MS m/z (rel. int.%): 333 (M$^+$, 37), 277

(M^+-C_4H_7, 24), 233 (M^+-C_4H_7COOH, 31), 83 ($C_4H_7CO^+$, 91), 55 ($C_4H_7CO^+$-CO, 13). HR-MS:m/z 332.199(calcd.:332.198).

Irradiation of 1 in silica gel bound rose Bengal. Compound **1** (100 mg, 0.316 mmol), [P_{si}]–rose bengal[26] (200 mg, 6.5 mg/g) and 100ml of methanol were placed in the photochemical reactor and irradiated at 10 ^{0}C in the presence of bubbling oxygen. The progress of reaction was monitored by TLC. After 10 h of irradiation, the reaction mixture was removed, washed with methanol and chromatographed on silica gel to give two products, identified to be same as **4** and **6** by comparison of their spectral data. It was found that upon standing the reaction mixture and so also on addition of dil HCl in the reaction mixture, the product **6** (epoxy lactone) converted into hydroxy butenolide **4** (Scheme 2).

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