Selective Oxygenation and Plant-Growth Regulatory Activity of Sesquiterpene Lactones

Sabir Hussain* and Mukta Sharma

Department of Chemistry, Rawal Institute of Engineering and Technology,
Faridabad-121002, India
Maharishi Dayanand University, Rohtak, Haryana, India

*Corresponding author: sabir_zhirka@rediffmail.com

Abstract: *Presence of a hydroxyl group at the C-3 position in guaianolides and at the C-5 position in alantolides has been established in biologically active compounds that act as plant-growth regulators. Sesquiterpene lactones like dehydrocostus lactone and isoalantolactone were subjected to allylic oxidations with selenium dioxide (SeO_2) in combination with urea hydrogen peroxide (UHP) replacing the common reagent tert-butyl hydroperoxide (TBHP) to form allylic alcohols. The reactions of dehydrocostus lactone and isoalantolactone with SeO_2/UHP/polyethylene glycol-400(PEG-400) were more selective, and the yields were higher than reactions with SeO_2/TBHP/ dichloromethane (CH_2Cl_2). The structures of all of the compounds were elucidated by spectroscopic techniques like infrared (IR) spectroscopy, proton nuclear magnetic resonance (^{1}H NMR) and Carbon 13 nuclear magnetic resonance (^{13}C NMR). All of the obtained compounds were subjected to biological evaluation as plant-growth regulators. The results were fairly good compared to the parent compounds.*

Keywords: sesquiterpene lactones, allylic oxidation, urea hydrogen peroxide, plant growth regulatory activity

1.   INTRODUCTION

Selective oxidation of alkenes to allylic alcohols, known as allylic oxidation, is an important transformation in organic chemistry. Several reagents are known[1] to carry out this reaction, but selenium dioxide (SeO_2) has been found to be a promising reagent. Some difficulties, such as the removal of colloidal selenium and the formation of organo-selenium by-products, have been circumvented by the Sharpless method,[2] which uses catalytic SeO_2 in combination with tert-butyl hydroperoxide (THBP). The allylic oxidation of terpenoids[3–5] with the well-known reagent SeO_2/TBHP/dichloromethane (CH_2Cl_2) has been published in reputable journals, but in our research, we have attempted to replace the use of TBHP by another oxidising agent: a urea hydrogen peroxide (UHP) complex. TBHP has several drawbacks; it is not safe to handle at higher concentrations, it is quite expensive, and it is not easily obtained. We have successfully achieved the allylic oxidation of sesquiterpene

lactones with UHP, and our results are quite comparable with those obtained using TBHP. The hydrogen-bonded urea adduct UHP[6] is a white crystalline solid formed when urea is recrystallised from aqueous hydrogen peroxide. Several oxidations using UHP have been reported.[7–12] So far, the available literature does not address its use as an oxidising agent in combination with SeO_2.

This paper reports our study of the allylic oxidations of terpenoids using SeO_2 as the solid catalyst and UHP as the oxidising agent.

2. EXPERIMENTAL

The reported melting points are uncorrected. The infrared (IR) spectra were recorded on a Perkin Elmer model 1430 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuterated chloroform ($CDCl_3$) on a Varian EM-360 (300 MHz) NMR spectrometer. Chemical shifts (δ) are reported in ppm with trimethyl silane (TMS) as the internal standard. All of the chromatographic separations were carried out on silica gel.
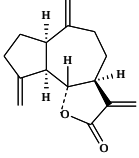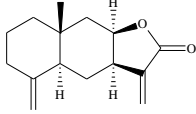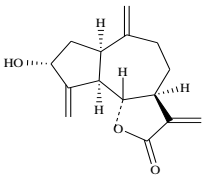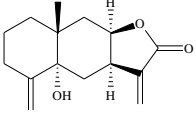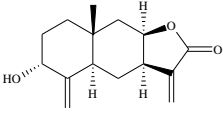
2.1 Reaction of Dehydrocostus Lactone (compound 1) with SeO_2/UHP in Polyethylene Glycol-400 (PEG-400)

UHP (3.0 g) was dissolved in 5 ml of polyethylene glycol-400 (PEG-400) and slightly heated to 25°C–30°C; SeO_2 (5 mg) was then added and the solution was stirred for 30 min. A solution of dehydrocostus lactone (compound 1), 1.5 g in CH_2Cl_2 (25 ml) was added, and the reaction was completed after stirring for 5 h at room temperature. The reaction mixture was diluted with cold water and extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried over sodium sulphate (Na_2SO_4). Evaporation of the solvent afforded a purified compound 3 (1.0 g) that showed satisfactory plant-growth regulatory activity as shown in Table 1. The purity of the compound was checked by thin layer chromatography (TLC) in toluene ethyl acetate formic acid (TEF).

2.2 Reaction of Isoalantolactone (compound 2) with SeO_2/UHP in Polyethylene Glycol-400 (PEG-400)

UHP (7.0 g) was dissolved in 10 ml of PEG-400 with slight heating at 25°C–30°C, and SeO_2 (10 mg) and a solution of isoalantolactone (compound 2), 3.5 g in CH_2CI_2 (25 ml) was added to the mixture. The reaction was completed by the procedure as discussed above to furnish 2 products, compounds 5 (1.4 g) and 6 (1.5 g), which were obtained after column chromatography. Compound 5

Table 1: Plant-growth regulatory activity of isozaluzanin-C, telekin and isotelekin in terms of adventitious root formation in hypocotyl cuttings of *Vigna radiata* after 7 days.

Chemical structure (compound no.)	No. of roots produced (mean±SD) in different concentration (mg/l)			
	2.5	5.0	7.5	10
(1)	5.0±1.18	6.0±1.22	6.9±1.56	9.0±1.12
(2)	5.8±0.6	6.8±1.2	7.2±0.9	10.1±1.3
(3)	6.0±1.22	7.9±2.11	9.5±2.32	10.5±1.56
(5)	7.5±0.9	7.9±1.1	8.4±2.1	9.2±2.4
(6)	7.0±1.4	8.0±2.1	8.5±2.1	11.5±2.8
IAA	8.1±0.72			

Note: *Control (distilled water), 4.6±0.5

showed IR bands (CHCl$_3$) at 3500, 1760, 1669, 1455, 920, and 862 cm^{-1} and ^{1}H NMR signals (CDCl$_3$, 300 MHz) at δ 1.05 (s, 3H, C$_{10}$-CH$_3$), 4.59 (m, 1H, C$_8$-H). 4.73 and 4.90 (bs, 1H each, C$_4$=CH$_2$) as well as 5.70 and 6.15 (bs, 1H each, C$_{11}$=CH$_2$),. Compound 6 showed IR bands (CHCl$_3$) at 3600, 1760, 1669, 1650 and 892 cm^{-1} and ^{1}H NMR signals (CDCl$_3$, 300 MHz) at δ 0.90 (s, 3H, C$_{10}$-CH$_3$), 4.40 (m, 1H, C$_8$-H), 4.50 (t, 1H, J = 8Hz, > CHOH), 4.73 and 4.90 (bs, 1H each, C$_4$=CH$_2$) as well as 5.70 and 6.15 (bs, 1H each, C$_{11}$=CH$_2$).

2.3   Biological Testing

For the root initiation study using hypocotyl cuttings of *Vigna radiata*, seedlings were grown under continuous illumination. When the hypocotyls were 5–6 cm long, cuttings were made by excision 4 cm below the cotyledonary node, leaving the cotyledonary leaves and apex intact. In all experiments, four concentrations (2.5, 5, 7.5 and 10 mg/l) were tested along with distilled water as control. For all treatments, 10 replicates were cultured in vials with each containing 30 ml of the test solution. The final observations were recorded on day 8. The experiment was repeated 3 times at 27 ± 2°C.

3.   RESULTS AND DISCUSSION

Sesquiterpene lactones having an α-methylene-γ-lactone moiety, like dehydrocostus lactone and isoalantolactone, were treated with SeO$_2$ in combination with TBHP for 5 h, after which allylic oxidation products (compounds 3, 4, 5, 6, and 7) were obtained (Fig. 1–7).
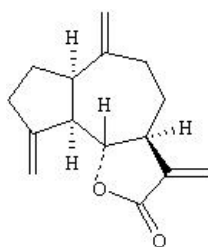

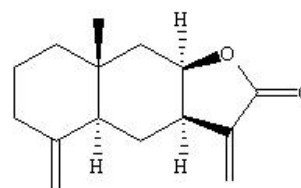Figure 1: Chemical structure of compound 1 (dehydrocostus lactone).

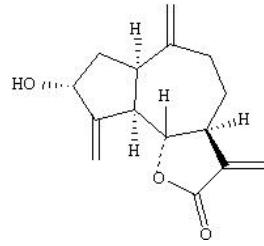Figure 2: Chemical structure of compound 2 (isoalantolactone).

Figure 3: Chemical structure of
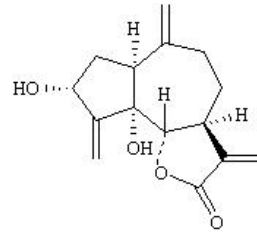compound 3 (isozaluzanin-c).

Figure 4: Chemical structure of
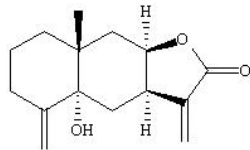compound 4.

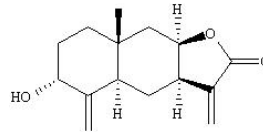Figure 5: Chemical structure of
compound 5 (telekin).

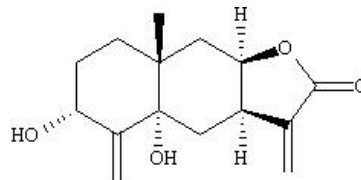Figure 6: Chemical structure of
compound 6 (isotelekin).

Figure 7: Chemical structure of
compound 7.

With the drawbacks of TBHP in mind, attempts were made to bring about allylic oxidations of dehydrocostus lactone and isoalantolactone by using UHP in combination with SeO_2. First, the solubility of UHP was investigated in different solvents, as UHP is insoluble in the usual solvent to carry out reactions in TBHP, CH_2Cl_2. After this trial, it was found that UHP is soluble in solvents like methanol (CH_3OH) and PEG-400 and is partially soluble in acetone, dioxane and tetrahydrofuran. When dehydrocostus lactone was treated with SeO_2/UHP in CH_3OH, it yielded a mixture of two compounds. Column chromatography of the mixture yielded compound 8 (36%) in addition to the expected product, compound 3 (42%), which had a melting point of 143°C identical in all respects to naturally occurring isozaluzanin-C. The IR spectrum of compound 8 showed a band at 1780 cm^{-1} due to the presence of γ-lactone as well as bands at 3090, 1640, and 890 cm^{-1} corresponding to exomethylenic double bonds. The ^{1}H NMR (300 MHz) spectrum included peaks at δ 3.46 (s, 3H) for the –OCH$_3$ group and 3.73 (d, 2H, J = 4 Hz) for the –CH$_2$ OCH$_3$ protons.^{1}H NMR signals at δ 4.76 and 4.85 (bs, 1H each) as well as δ 5.36 and 5.43 (bs, 1H each) were attributed to exomethylenic double bonds. The presence of the intact lactone moiety was confirmed by a triplet at δ 4.15, J = 9.0 Hz due to C$_6$-H. A peak at δ 4.6 (t, 1H, J = 18 Hz) for > CHOH proton indicates a hydroxyl group at the C-3 position. All of these structural features suggested that methoxylation at C-11 had taken place, and compound 8 was identified to be methoxy-isozaluzanin-C.
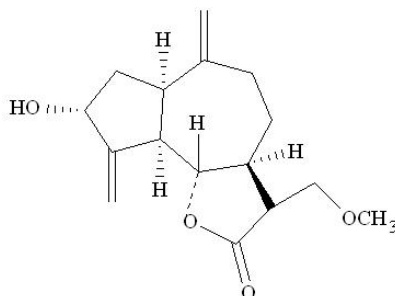

Figure 8: Chemical structure of compound 8 (methoxy-isozaluzanin-C).

Similarly, the reaction of isoalantolactone was carried out by using UHP/SeO_2 in CH_3OH, and it yielded compound 9 (24%) in addition to 2 known compounds 5 (24%) and 6 (29%) that were identified by comparison with the mp, IR and NMR of the authentic samples. Compound 9 showed IR bands at 1780 cm^{-1} due to the presence of δ-lactone, bands at 3540 cm^{-1} due to the hydroxyl group and bands at 1755 and 1640 cm^{-1} indicating the presence of exomethylenic double bonds. ^{1}H NMR (300 MHz) peaks at δ 3.40 (S, 3H) for –OCH$_3$, 3.60 (d, 2H, J = 4Hz) due to > CH$_2$OCH$_3$ protons, 4.95 and 5.00 (bs, 1H each)

corresponding to C_{15}-H's, a singlet at δ 0.9 due to $-CH_3$ at C_{10}, 4.50 (t, 1H, J = 8 Hz) for the > CHOH proton and broad multiplet centred at δ 4.66 due to the C-8 proton suggest structure 9 for the methoxy isotelekin.
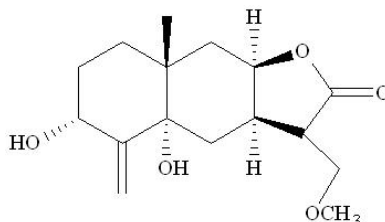

Figure 9: Chemical structure of compound 9 (methoxy isotelekin).

In order to get rid of side products of compounds 8 and 9 that are a result of Michael-type addition to the α-methylene of γ-lactone by OCH_3, we changed the solvent to PEG-400. Dehydrocostus lactone and isoalantolactone were treated with SeO_2/UHP using PEG-400 as a solvent, which yielded compound 3 with a 71% yield as well as compounds 5 and 6 with a 41% and 44% yield, respectively. The yields of the products were higher in the UHP/SeO_2/PEG-400 system, and no side products were found in the CH_3OH reaction. Compounds 3 (mp 143°C), 5 (mp 157°C) and 6 (mp 144°C) were identified as isozaluzanin-C, telekin, and isotelekin. The IR bands [in chloroform ($CHCl_3$)] of compound 3 were obtained at 3440, 1775, 1670, 1640 and 890 cm^{-1} and ^{1}H NMR signals ($CDCl_3$, 300 MHz) were observed at δ 3.9 (t, 1H, J = 10 Hz, C_6-H), 4.68 (t, 1H, J = 8 Hz, > CHOH), 4.78 and 4.90 (bs, 1H each, C_{10}=CH_2), 5.35 and 5.65 (bs, 1H each, C_4=CH_2) as well as 5.45 and 6.20 (d, 2H, J = 3Hz, C_{11}=CH_2). Compound 5 showed IR bands ($CHCl_3$) at 3500, 1760, 1669, 1455, 920, and 862 cm^{-1} and ^{1}H NMR signals ($CDCl_3$, 300 MHz) δ at 1.05 (s, 3H, C_{10}-CH_3), 4.59 (m, 1H, C_8-H), 4.73 and 4.90 (bs, 1H each, C_4=CH_2) as well as 5.70 and 6.15 (bs, 1H each, C_{11}=CH_2), and compound 6 showed IR bands ($CHCl_3$) at 3600, 1760, 1669, 1650 and 892 cm^{-1} and ^{1}H NMR signals ($CDCl_3$, 300 MHz) at δ 0.90 (s, 3H, C_{10}-CH_3), 4.40 (m, 1H, C_8-H), 4.50 (t, 1H, J = 8Hz, > CHOH), 4.73 and 4.90 (bs, 1H each, C_4=CH_2) as well as 5.70 and 6.15 (bs, 1H each, C_1=CH_2).

4.   CONCLUSION

The SeO_2/UHP/PEG-400 system is more reactive and selective, and when one considers the combined benefits of economics, selectivity and safety, UHP emerges as one of the best sources of oxygen atoms for a variety of organic oxygenation reactions. The compounds were monitored for their biological potential as plant growth regulators (PGRs) in terms of adventitious root initiation in hypocotyl cuttings of *V. radiata*. The compounds were tested at four

concentrations (2.5, 5, 7.5 and 10 mg/l) and results were compared with a control (distilled water). It was found that substituted pyrazolines, which have a methyl group at C-13 and C-16, cause an appreciable increase in rooting when compared to control and parent compounds.

5.   ACKNOWLEDGEMENT

6.   REFERENCES

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