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Conversion of Sclareol into (+)-Galanolactone and (+)-Labdienedial

Mankil Jung,* Seokjoon Lee, and Byunghee Yoon

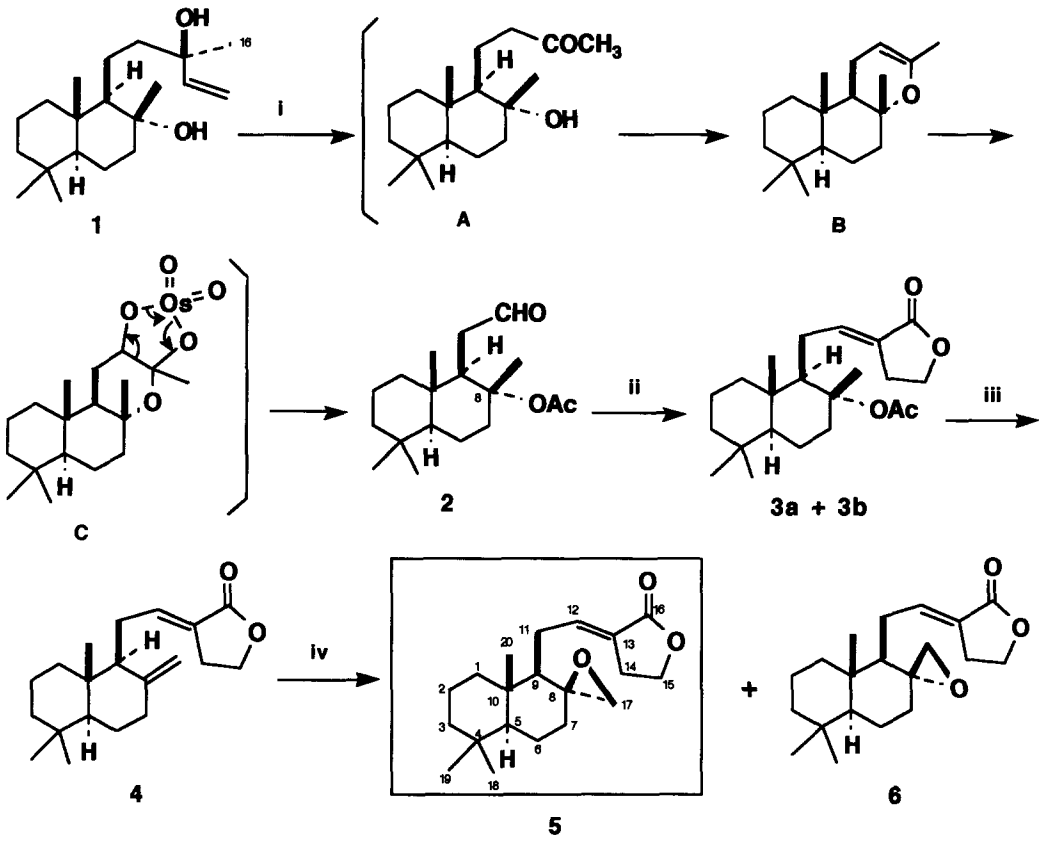
Department of Chemistry, Yonsei University, Seoul, Korea

Abstract: A short, regiospecific and first synthesis of (+)-galanolactone **5** and (+)-labdienedial **11** was achieved from sclareol, respectively. © 1997 Elsevier Science Ltd.

Galanolactone **5** and (+)-(E)-8(17), 12-labdiene-15, 16-dial **11**, new labdane-type diterpenes were isolated from *Alpinia galanga* by Morita *et. al*[1] and show cytotoxic, antifungal activities. Recently **5** also shows anti-5-HT (serotonin) effect.[2] No information is available on the synthesis of optically active galanolactone **5** and labdienedial **11**. Only total synthesis of galanolactone **5** as racemic form in multiple steps from geraniol was reported by Khuong-Huu *et. al.*[3] Its typical structure of epoxide and α, β unsaturated lactone of galanolactone **5** is commonly found in insect antifeedant natural products such as azadirachtin[4] isolated from the seeds of the neem, and ajugarin,[5] etc. Interesting biological activities, natural scarcity (0.002 % for **5** and 0.01 % for **11**, respectively) and labdane-type structure of **5** as a model for new agrochemicals prompted us to synthesize optically active galanolactone **5** and its related compounds. We report in this letter a short, regiospecific and first synthesis of (+)-galanolactone **5**, (-)-8-epi-galanolactone **6** and (+)-labdienedial **11** in optically active forms from commercially availble sclareol **1** (Schemes 1 and 3).

(-)-Sclareol **1**[6] is readily available natural product whose structure is suited as a chiral synthon in the semi-synthesis of galanolactone **5** and labdienedial **11**. Thus, oxidative degradation of (-)-sclareol **1** with osmium tetroxide and sodium periodate in aqueous t-butanol cleanly afforded the acetoxyaldehyde **2**[6a,7,10] in one step[8] (65%) (Scheme 1). This reaction may be processed *via* the proposed intermediates,[6b] A, B, and C and origin of the acetoxy group at C-8 of **2** could be derived from the original CH_3 at C-16 of sclareol **1** and one oxygen of the osmate ester of the intermediate C. The compound **2** could serve as a versatile intermediate for synthesis of variety of biologically active natural products including galanal A[1] and warburganal.[9] In our synthesis, the acetoxy group at C-8 of compound **2** serves as a protecting group for the later-generating exomethylene group at C-8 of compound **4**. Coupling of the aldehyde **2** with the anion of diethylphosphono-2-butyrolactone provided the isomeric lactones **3a** (E-form) and **3b** (Z-form), respectively, in the ratio of 3:1 (yield 67 %). Separation of the isomers by column chromatography gave desired **3a**.[10] While the NOESY spectrum of **3b** showed interaction between 12-H (δ 6.75) and one of the 14-H (δ 2.61) protons, no nOe enhancement was observed between 12-H (δ 6.86) and 14-H (δ 2.85) of **3a**, establishing that **3a** has E-form. Subsequent elimination of acetic acid at C-8 position of compound **3a** with quinoline (reflux, 2 h) provided the desired exomethylene compound **4**[10](71 %). The other regio isomers ($\Delta^{8,9}$ and $\Delta^{7,8}$) were not detected. Final epoxidation of exomethylene at C-8 of compound **4** with mCPBA (1 eq.) at 0 °C exclusively afforded (-)-8-epi-galanolactone **6**[10] (45 %). As expected, no epoxidation occurred at the electron deficient α, β-unsaturated double bond of the lactone **4**. Natural galanolactone **5** was not detected. Steric hindrance by

butanolide ring in β-face may force mCPBA approach in the direction of less hindered α-face, resulting in the epimer **6**. However, with excess (2 eq.) mCPBA or peracetic acid and prolonged reaction time, the lactone **4** successfully provided natural (+)-galanolactone **5**[1,11] and (-)-8-epi-galanolactone **6** in the ratio of 1 to 3.4.

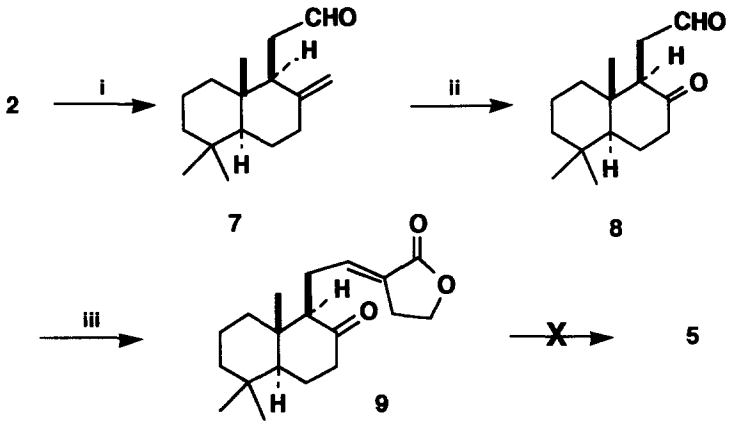


Scheme 1 *Reagents and conditions:* i OsO_4(cat.)/$NaIO_4$(1.8 eq.), t-butanol, THF, 25 °C, 5.5 h (65 %); ii diethylphosphono-2-butyrolactone (1.0 eq.) , NaH(1.2 eq.), dry toluene, 0 °C, 4 h. then 80 °C, 1 h. (67 %, E/Z=3/1); iii quinoline, reflux, 2 h (71 %); iv mCPBA (2.0 eq.), $CHCl_3$, 0 °C, overnight (52 %).

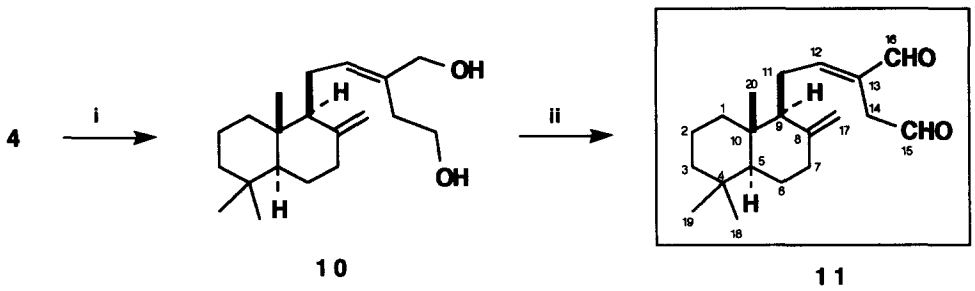
In another attempt, compound **2** was converted into compound **9**[3,11] in three steps (overall yield 29 %) via **7** and **8**[1,11] (Scheme 2). We failed again in our attempts to introduce the exomethylene function on **9** to give (+)-galanolactone **5** by treatment with dimethyl sulfonium methylide.[3] Compound **4** is a versatile intermediate for useful synthesis of galanolactone-related compounds. Reductive ring cleavage of **4** with excess LAH (5 eq.) in anhydrous diethylether (room temperature, 2 h.) afforded dienediol **10**[10] (yield 85 %). Subsequent oxidation of the diols of **10** with PCC (2.5 eq.) in methylene chloride cleanly provided the target compound, (+)-labdienedial **11**[1,11] (81 % yield) (Scheme 3). During this reduction-oxidation procedure, two olefin groups of **4** and **10** were left intact.

In conclusion, our approach is highlighted by its simplicity and efficiency. We have outlined a first

synthesis of optically active (+)-galanolactone **5**, (-)-8-epi-galanolactone **6** and (+)-(E)-8 (17), 12-labdiene-15, 16-dial **11** from readily available sclareol. These syntheses make it possible to resolve the natural scarcity, to test further biological activities of galanolactone and its related compounds, and to provide labdane-type structure as a model for new agrochemicals.



Scheme 2 *Reagents and conditions:* i Collidine, reflux, 8 h, 68 %; ii ozone, -78 °C, 30 min.,60 %; iii diethylphosphono-2-butyrolactone (1.5 eq.), NaH (7 eq.), 0 °C, 2 h, 71 %.



Scheme 3 *Reagents and conditions:* i LAH (5 eq.), ether, r. t., 2 h, [85 %]; ii PCC (2.5 eq.), CH_2Cl_2, r. t., 50 min., [81 %].

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10. All new compounds gave satisfactory analytical and spectral data. *Selected spectral data for* **2**: solid; IR (CCl_4)/cm^{-1}: 1724 (C=O), 1252. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 9.61 (1H, dd, J=2.6, 1.9 Hz, CHO), 1.83 (3H, s, OAc), 1.46 (3H, s, CH_3-17), 0.85 (3H, s, CH_3-20), 0.81 (3H, s, CH_3-19), 0.76 (3H, s, CH_3-18). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 202.3, 169.5, 86.0, 55.5, 53.5, 41.5, 40.2, 39.8, 38.9, 38.4, 33.2, 22.5, 21.3, 20.5, 20.0, 19.7, 18.2, 15.8; for **3a** (E-form): white solid; m.p. 96 °C; IR (KBr)/cm^{-1}: 2927, 2369, 1735 (C=O), 1660 (C=C), 1259, 1039; ^{1}H-NMR (250 MHz, $CDCl_3$): δ 6.86 (1H, m, H-12), 4.29 (2H, t, J=7.5 Hz, CH_2-15), 2.85 (2H, t, J=7.35 Hz, CH_2-14), 1.89 (3H, s, OAc), 1.48 (3H, s, CH_3-17), 0.87 (3H, s, CH_3-20), 0.82 (3H, s, CH_3-19), 0.79 (3H, s, CH_3-18); for **4**: colorless oil; IR(neat)/cm^{-1}: 2934, 2853, 1767 (C=O), 1686 (C=C). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 6.71 (1H, m, H-12), 4.81 and 4.37 (2H, 2d, J=1.0 Hz, H-17), 4.34 (2H, t, J=6.4 Hz, CH_2-15), 2.85 (2H, m, CH_2-14), 0.88 (3H, s, CH_3-20), 0.81 (3H, s, CH_3-19), 0.71 (3H, s, CH_3-18); m/z (70 eV); 303 (M+1, 100); for **6**: colorless oil ; $[\alpha]_D^{25}$ + 5.38 ° (c 0.26, $CHCl_3$); IR(neat)/cm^{-1}: 2933, 1768 (C=O), 1686 (C=C), 1216 (epoxide); ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.75 (1H, m, H-12), 4.37 (2H, t, J= 6.43 Hz, CH_2-15), 2.84 (2H, m, CH_2-14), 2.64 and 2.55 (2H, 2d, J= 4.1 Hz, CH_2-17), 1.78 and 1.98 (2H, m, CH_2-11), 1.67 (1H, m, H-9), 0.90 (3H, s, CH_3-20) , 0.85 (3H, s, CH_3-19), 0.84 (3H, s, CH_3-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5 (C-16), 142.6 (C-12), 123.9 (C-13), 65.3 (C-15), 58.4 (C-8), 54.9 (C-9), 54.1 (C-5), 50.5 (C-17), 41.7 (C-3), 40.1 (C-10), 39.5 (C-1), 35.9 (C-7), 33.4 (C-4), 33.3 (C-18), 25.1 (C-14), 22.8 (C-11), 21.7 (C-19), 21.6 (C-6), 18.6 (C-2), 14.5 (C-20). m/z (70 eV); 318 (M^+, 100). for **10**: colorless oil; $[\alpha]_D^{25}$ + 29.2 ° (c 0.36, $CHCl_3$); IR(neat)/cm^{-1}: 3329 (OH), 1651 (C=C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.46 (2H, t, J= 6.3 Hz, CH_2-11), 4.80 and 4.42 (2H, s, H-17), 3.96 (2H, s, H-16), 3.69 (2H, dt, J= 5.5, 6.2 Hz, H-14), 3.50 (2H, m, H-15), 3.34 (2H, s, diols), 2.41 (2H, m, H-11), 0.86 (3H, s, CH_3-20), 0.77 (3H, s, CH_3-19), 0.65 (3H, s, CH_3-18); m/z (70 eV): 306 (M^+, 100).
11. for **5**, **8**, **9**, **11**: Synthetic intermediates, **8**, **9** and galanolactone **5**, labdienedial **11** are identical by comparison of mmp, specific rotation ($[\alpha]_D^{25}$ + 28.0 ° (c 0.26, $CHCl_3$) for **5** and $[\alpha]_D^{25}$ + 18.0 ° (c 0.48, $CHCl_3$) for **11**) and spectral properties with known compounds,[1, 3] and natural galanolactone[1] and labdienedial,[1] respectively.

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