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Ozonolysis of Phenolic Dehydroabietane Derivatives.[1]—Syntheses of optically Active (+)-Confertifolin, (+)-Valdiviolide, (+)-Winterin, (+)-Isodrimenin, and (+)-Pallescensin A—

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Ozonolysis of phenolic dehydroabietane derivatives was investigated and the products obtained by cleavage of the aromatic ring were found to be determined by the hydroxyl substitution pattern of the aromatic C-ring. Ozonolysis of the 12-hydroxy compound (ferruginol (**12**)) gave pentanorlabdane-type compounds (**14**, **15**, and **16**).

Ozonolysis of the 11-hydroxy derivative (**18**) and/or the 14-hydroxy derivatives (**19** and **20**) afforded optically active drimanic sesquiterpenes ((+)-isodrimenin (**8**), (+)-confertifolin (**7**), (+)-valdiviolide (**9**), and (+)-winterin (**10**)) in one step. In this case, the mode of cleavage was different from that of **12**. On the other hand, ozonolysis of the 13-hydroxy compound (**3**) caused cleavage in yet another manner to give the butenolide (**23**), which was easily converted into optically active pallescensin A (**11**). The mechanisms of the cleavage reactions are discussed.

Keywords——aromatic ring cleavage; ozonolysis; drimanic sesquiterpenes; phenolic diterpenes; catechol

In the course of our studies on the chemical conversion of *l*-abietic acid, a major component of pine rosin, to biologically active compounds, we were interested in a short synthesis of optically active drimanic sesquiterpenes (B) such as confertifolin and isodrimenin and a pallescensin A type sesquiterpene (C) by selective cleavage of the phenolic C-ring of compounds (**2** and **3**) derived from dehydroabietietic acid (**1**) by ozonolysis.

Ring opening of a substituted benzene ring by the use of ozone[2] or molecular oxygen[3] has been reported. For example, the low temperature ozonolysis of methyl podocarpate (**4**)[2b] bearing a hydroxyl group at the 12-position in MeOH–CH_2Cl_2 (1: 1) is known to afford the unsaturated lactone (**5**), which was produced by cleavage at the dotted line a (Chart 1). We thought that if cleavage could be induced at the dotted line b or c, the desired B or C would be produced in one step. Since we have succeeded in the synthesis of phenolic dehydroabietane derivatives bearing hydroxyl groups at all possible positions (11-, 12-, 13-, and 14-positions) on the aromatic C-ring (**2** or **3**),[4] ozonolysis of these phenols was carried out.

Meanwhile, warburganal (**6**)[5] was isolated by Kubo, Nakanishi, and co-workers from the bark of the East African medicinal tree *Warburgia ugandensis* and *W. stuhlmannii* (Canellaceae) and was found to exhibit remarkable bioactivity: antifeedant activity against the African army worm, molluscicidal activity against the schistosome-transmitting snail, *etc.* Total synthesis of (±)-warburganal (**6**) was, therefore, extensively studied and has been achieved by us[6] and several other groups.[7] One of the features of our synthesis of (±)-**6** was the use of readily obtainable (±)-confertifolin (**7**) and (±)-isodrimenin (**8**) as starting materials. Therefore, if (+)-confertifolin (**7**) and (+)-isodrimenin (**8**) can be synthesized by the ozonolysis of the above phenols (**2**), the synthesis of (+)-warburganal (**6**) from *l*-abietic acid would become possible.

1) Ozonolysis of the 12-Hydroxy Compound (12)

Ferruginol (**12**)[4] having a hydroxyl group at the 12-position and an extra isopropyl group at the 13-position was subjected to ozonolysis as a model experiment. Treatment of **12** with

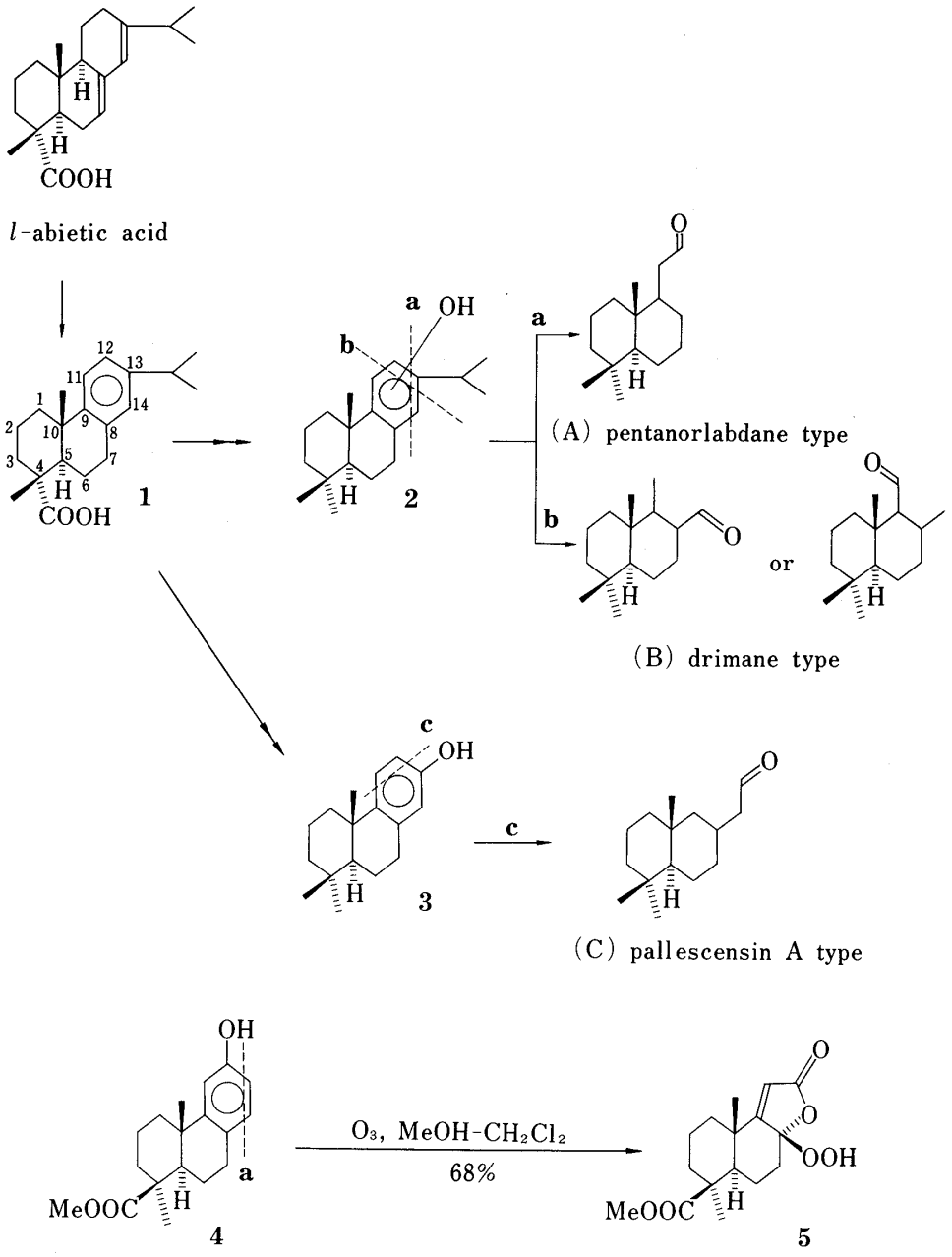
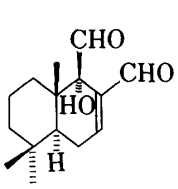


Chart 1

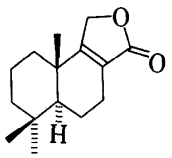
ozone in MeOH–CH_2Cl_2 (1: 1) under dry ice-acetone cooling and subsequent reduction with Na_2SO_3, $NaBH_4$, and Zn–AcOH gave pentanorlabdane type compounds (**14**, 20% yield; **15**, 36% yield; **16**, 63% yield). The cleavage took place at the dotted line a (Chart 3), as was expected. The physical data (infrared (IR), nuclear magnetic resonance (NMR), and mp) of these products (**14**, **15**, and **16**) were identical with those of the corresponding standard samples reported by Cambie.[8] It was found from the above experiments that when the reducing reagents were properly selected, compounds of different oxidation stage could be produced. Among them, the oxo-carboxylic acid (**16**) and its ester (**17**) are expected to be important intermediates in the synthesis of natural labdane type compounds.

2) Ozonolysis of the 11,12-Dihydroxy Compound (18)

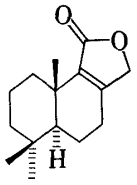
The 11,12-dihydroxy compound (**18**)[4] was subjected to ozonolysis and subsequent reduction with $NaBH_4$ to give (+)-isodrimenin (**8**; 26% yield). Physical data (NMR, IR, mp, and



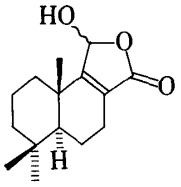
(±)−**6**
(+)−**6**
warburganal



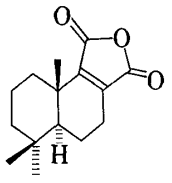
(±)−**7**
(+)−**7**
confertifolin



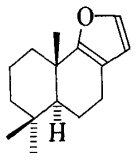
(±)−**8**
(+)−**8**
isodrimenin



(+)−**9**
validiviolide



(+)−**10**
winterin



(+)−**11**
pallescensin A

Chart 2

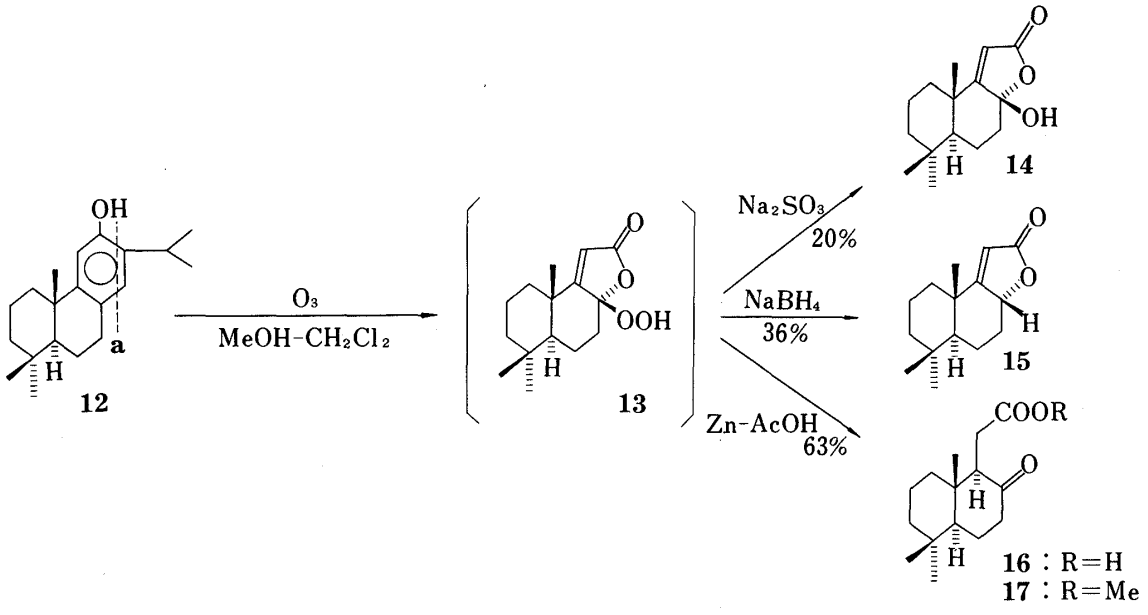
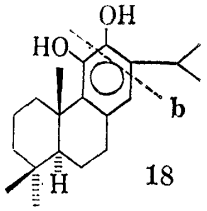


Chart 3



1) O_3, MeOH-CH_2Cl_2
2) $NaBH_4$
26%

8

Chart 4

$[\alpha]_D$) for **8** were identical with those of natural (+)-isodrimenin.[9] In this case, cleavage took place at the desired dotted line b (Chart 4). The mechanism will be discussed later.

3) Ozonolysis of the 13,14-Dihydroxy Compound (19) and the 14-Hydroxy Compound (20)

The 13,14-dihydroxy compound (**19**)[4] was ozonolyzed in the same manner as **18**, and subsequent reduction with $NaBH_4$ afforded (+)-confertifolin (**7**; 11% yield). Physical data (NMR, IR, mp, $[\alpha]_D$) for **7** were identical with those for natural (+)-confertifolin.[9] In this case, cleavage again took place at the dotted line b (Chart 5).

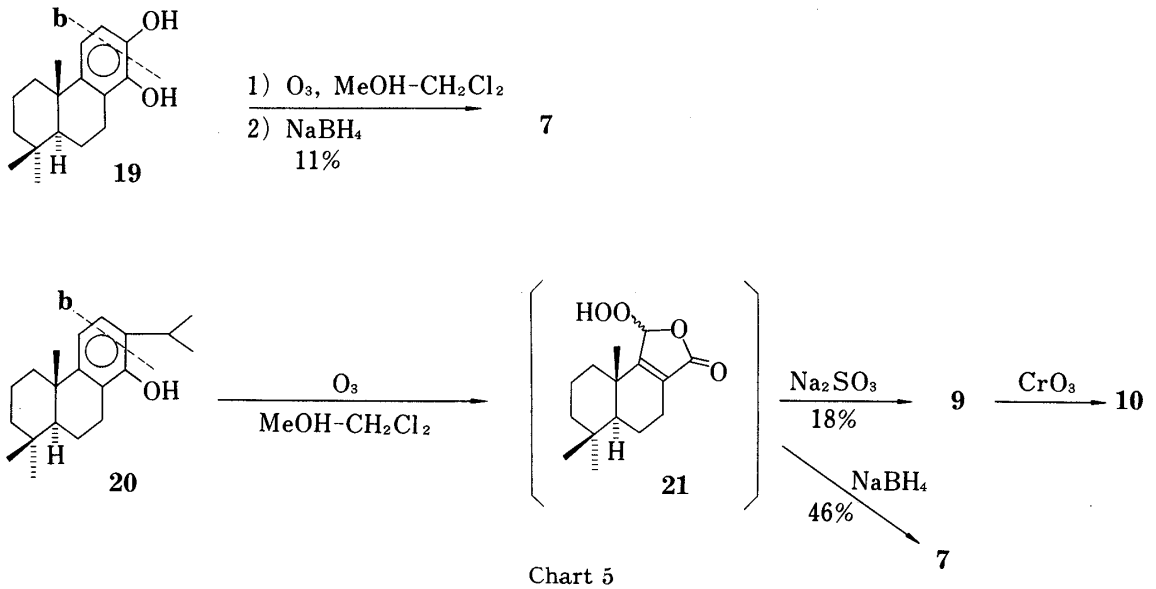


Chart 5

Ozonolysis of the 14-hydroxy compound (**20**)[4] and subsequent reduction of the crude product with $NaBH_4$ also gave (+)-confertifolin (**7**; 46% yield), while reduction with Na_2SO_3 afforded (+)-valdiviolide (**9**; 18% yield). The latter (**9**) was oxidized with Jones reagent to give (+)-winterin (**10**). Physical data (NMR, IR, mp, and $[\alpha]_D$) for the above three compounds (**7**, **9**, and **10**) were identical with those for natural (+)-confertifolin,[9] (+)-valdiviolide,[10] and (+)-winterin,[10] respectively. In both cases, the newly generated lactone carbonyl group is located at the 14-position, which corresponds to the position of the hydroxyl group in the aromatic ring of the starting material.

4) Ozonolysis of the 13-Hydroxy Compound (3)

Ozonolysis of the 13-hydroxy compound (**3**)[4] and subsequent $NaBH_4$ reduction afforded the butenolide (**23**; 22% yield), which was reduced with diisobutylaluminumhydride (DIBAL) in tetrahydrofuran (THF) and then acidified with 10% H_2SO_4 to give the furano compound (**11**). The spectral data[11] (NMR) were identical with those for natural (+)-pallescensin A (**11**)[12] or synthetic (+)-**11**.[13] In this case, although cleavage may occur at both dotted lines b and c, only the product due to cleavage at the dotted line c was obtained (Chart 6).

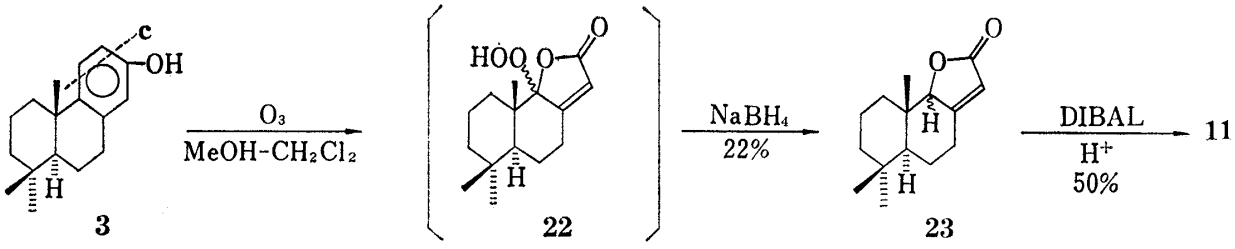


Chart 6

The mechanism of the present reaction is considered to be as follows: ozone should attack the most reactive site of the phenols, as shown in Chart 8, and the following stages can be reasonably explained by taking into account the mechanism presented by Bell and Gravestock[2b] for the formation of **5** from **4**. The pathway for (+)-confertifolin formation, for example, may be visualized as shown in Chart 7. The attack of a second molecule of ozone should take place predominantly on the more reactive δ-double bond of the diene carboxylic acid (*cf.* **25**). Carboxylate anion-assisted cleavage of the ozonide (*cf.* **26**) is expected to produce the hydroperoxide, an important intermediate in the present ozonolysis.

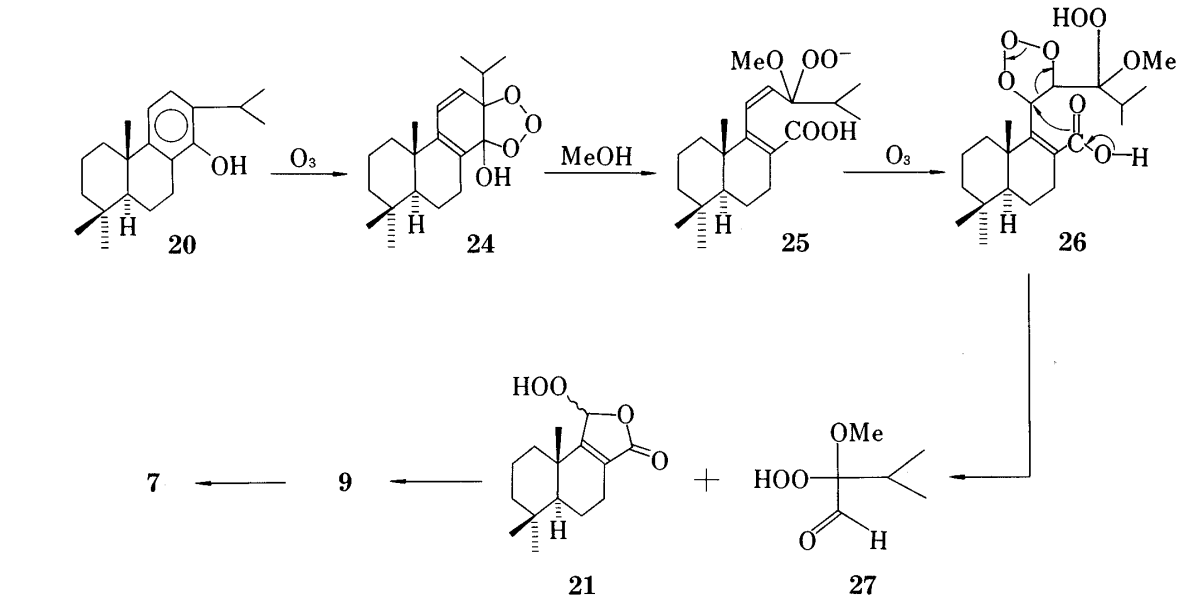


Chart 7

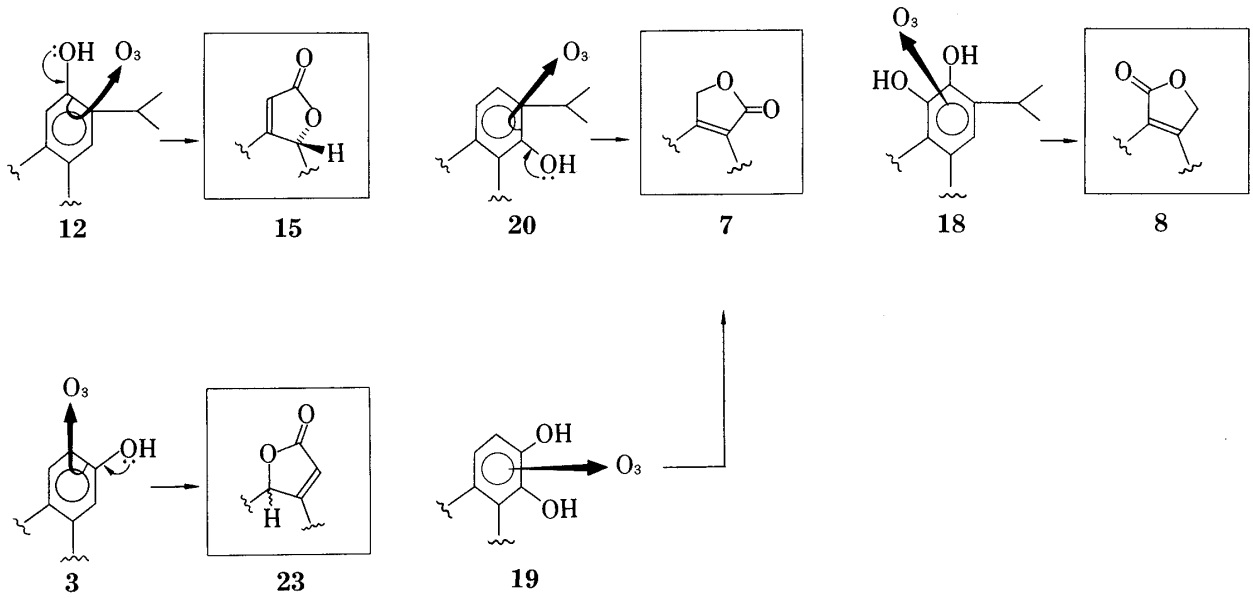


Chart 8

The relationship between phenolic derivatives and ozonolysis products is illustrated in Chart 8.

In the present experiment, it was found that the products obtained by cleavage of the aromatic ring by means of ozonolysis were determined by the substitution pattern of the hydroxyl group in the aromatic ring. Thus, it become clear that the desired optically active sesquiterpenes could be obtained by suitable selection of the starting phenols. Further synthetic studies along this line will be described in an accompanying paper.

Experimental

Melting points were measured with a Kofler micro melting point apparatus and are uncorrected. IR spectra (CCl_4) were measured on a JASCO A-3 spectrophotometer. NMR spectra were measured either on a Varian HA-100 spectrometer or a JEOL MH-60 instrument. Spectra were taken as 5—10% w/v solutions

in $CDCl_3$ with Me_4Si as an internal reference. Gas chromatography–mass spectroscopy (GC–MS) spectra were measured on a Hitachi RMU-6M mass spectrometer. Gas–liquid chromatography (GLC) was carried out on a column (2 m×4 mm) of 1.5% OV-17 on Shimalite W (80—100 mesh). $[\alpha]_D$ was measured on a Perkin-Elmer model 241 MC polarimeter. Ultraviolet (UV) spectra were measured on a Shimadzu UV-200 spectrometer.

Ozonolysis of 12-Hydroxy Dehydroabietane (Ferruginol (12) to 8,8-Dihydroxy-(13→17)-pentanorlabd-9(11)-en-12-oic Acid 8α→12-Lactone (14), 8α-Hydroxy-(13→17)-pentanorlabd-9(11)-en-12-oic Acid 8α→12-Lactone (15), 8-Oxo-(13→17)-pentanorlabdan-12-oic Acid (16), and 8-Oxo-(13→17)-pentanorlabdan-12-oic Acid Methyl Ester (17)——i) Ozone was passed through a solution of **12** (1.998 g) in 40 ml of 1: 1 MeOH–CH_2Cl_2 under dry ice–acetone cooling for 30 min. A solution of Na_2SO_3 (4 g) in H_2O (80 ml) was added to the above ozonolyzed product and the reaction mixture was stirred for 19 hr at room temperature. The reaction mixture was then extracted with $CHCl_3$ after acidification with 10% HCl and the extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave an oily product (1.63 g), which was chromatographed on silica gel (50 g) to give colorless needles (**14**) (348 mg, 20% yield) from the petr. ether–ether (1: 1) eluate. This product was recrystallized from *n*-hexane–ethyl acetate to give colorless needles (**14**), mp 174—176°. The physical data (mp and NMR) were identical with those of an authentic sample (**14**).[8] *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.03; H, 8.86. IR ν_{max}^{KBr} cm^{-1}: 3410, 1730, 1635. NMR δ: 0.92, 0.95 (each 3H, s, 4-*gem* Me), 1.31 (3H, s, 10-Me), 4.57 (1H, br s, $W_{h/2}$=9.6 Hz, 8β-OH), 5.52 (1H, s, 11-H).

ii) Ozone was passed through a solution of **12** (5.144 g) in 100 ml of 1: 1 MeOH–CH_2Cl_2 under dry ice–acetone cooling for 75 min. A solution of $NaBH_4$ (2.5 g) in 50% (v/v) EtOH–H_2O (30 ml) was added to the above ozonolyzed product and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was treated as in case i) to afford an oily product (5.045 g), which was chromatographed on silica gel (120 g) to give crystal (**15**) (1.536 g, 36% yield) from the *n*-hexane–ethyl acetate (9: 1—4: 1) eluate. The product was recrystallized from *n*-hexane to give colorless plates (**15**), mp 107—107.5°. The physical data (mp and NMR) were identical with those of an authentic sample (**15**).[8] *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.08; H, 9.39. IR ν_{max} cm^{-1}: 1788, 1758, 1635. NMR δ: 0.95 (6H, s, 4-*gem* Me), 1.17 (3H, s, 10-Me), 4.87 (1H, octet, J=1.5, 6.6, 9.6 Hz, 8β-H), 5.48 (1H, d, J=1.5 Hz, 11-H).

iii) Ozone was passed through a solution of **12** (5 g) in 100 ml of 1: 1 MeOH–CH_2Cl_2 under dry ice–acetone cooling for 1.5 hr. A mixture of Zn-dust (50 g) in AcOH (100 ml) was added to the ozonolyzed product and the reaction mixture was stirred for 2.5 hr at room temperature. The filtrate was concentrated under reduced pressure, H_2O was added, and the solution was extracted with ether. The ether extract was washed with 10% KOH aq. then dried over Na_2SO_4. Removal of the solvent gave an oily product (1.904 g), which was inseparable by thin-layer chromatography (TLC) and GLC. On the other hand, the alkaline layer was extracted with $CHCl_3$ after acidification with 10% HCl. The extract (acidic part) was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave a homogeneous oil (**16**) (2.766 g, 63% yield). The methyl ester (**17**) obtained from **16** by treatment with CH_2N_2 was found to be a single product by GLC analysis. Physical data of the above carboxylic acid (**16**) were identical with those of an authentic sample (**16**).[8] IR ν_{max} cm^{-1}: 1720, 1709. NMR δ: 0.72, 0.87, 0.99 (each 3H, s, 4-gem Me, 10-Me), 8.91 (1H, br s, 11-COOH).

A part of the above acid was treated with a solution of CH_2N_2 in ether to give an oily product, which was purified on a short column of silica gel to afford a homogeneous oil (**17**) from the petr. ether–ether (9: 1) eluate. The product was crystallized from petr. ether under dry ice–acetone cooling to give colorless prisms (**17**), mp 73—74°. *Anal.* Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.22; H, 9.77. IR ν_{max}^{KBr} cm^{-1}: 1740, 1715. NMR δ: 0.72, 0.86, 0.98 (each 3H, s, 4-*gem* Me, 10-Me), 3.64 (3H, s, 11-COOMe).

Ozonolysis of 11,12-Dihydroxy Dehydroabietane (18) to (+)-Isodrimenin (8)——A solution of **18** (2.019 g) in 40 ml of 1: 1 MeOH–CH_2Cl_2 was subjected to ozonolysis under dry ice–acetone cooling for 45 min. A solution of $NaBH_4$ (2 g) in 50% (v/v) EtOH–H_2O (20 ml) was added to the above ozonolyzed product and the reaction mixture was stirred for 45 min at room temperature. The reaction mixture was treated as in the case of the preparation of **15** to give an oily product, which was chromatographed on silica gel (60 g) to afford a homogeneous oil (**8**) (411 mg, 26% yield). This was crystallized from *n*-hexane to give colorless prisms (**8**) (238 mg), mp 131—132°. The physical data (mp, $[\alpha]_D$, IR, and NMR) were identical with those of natural isodrimenin (**8**)[9] and synthetic (±)-isodrimenin (**8**).[9] *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.93; H, 9.50. $[\alpha]_D$ +86° ($CHCl_3$, c=2.00). IR ν_{max} cm^{-1}: 1766, 1671. NMR (100 MHz) δ: 0.89, 0.92 (each 3H, s, 4-gem Me), 1.14 (3H, s, 10-Me), 4.55 (2H, s, 14-H_2).

Ozonolysis of 13,14-Dihydroxy-13-Deisopropyldehydroabietane (19) to (+)-Confertifolin (7)——A solution of **19** (258 mg) in 10 ml of 1: 1 MeOH–CH_2Cl_2 was subjected to ozonolysis under dry ice–acetone cooling for 50 min. A solution of $NaBH_4$ (200 mg) in 50% (v/v) EtOH–H_2O (2 ml) was added to the above ozonolyzed product and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was treated as in the case of the preparation of isodrimenin (**8**) to give an oily product, which was chromatographed on silica gel (40 g) to afford colorless crystal (**7**) (25 mg, 10% yield) from the *n*-hexane–ethyl acetate (4: 1) eluate. This product was recrystallized from *n*-hexane to give colorless plates (**7**). The physical data (IR, NMR, GLC, and GC–MS) were identical with those of natural confertifolin (**7**).[9]

Ozonolysis of 14-Hydroxy Dehydroabietane (20) to (+)-Confertifolin (7) and (+)-Valdiviolide (9)——i) A solution of **20** (953 mg) in 20 ml of 1: 1 MeOH–CH_2Cl_2 was subjected to ozonolysis under dry ice–acetone cooling for 50 min. A solution of $NaBH_4$ (800 mg) in 50% (v/v) EtOH–H_2O (10 ml) was added to the above ozonolyzed product and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was treated as in the case of the preparation of isodrimenin (**8**) to give an oily product (974 mg), which was crystallized from *n*-hexane to give colorless prisms (**7**) (339 mg, 46% yield), mp 153—153.5°. The physical data (mp, $[\alpha]_D$, IR, and NMR) were identical with those of natural confertifolin (**7**).[9] *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.69; H, 9.39. $[\alpha]_D$ +68.1° ($CHCl_3$, c=1.13). IR ν_{max} cm^{-1}: 1769, 1680. NMR (100 MHz) δ: 0.92, 0.95 (each 3H, s, 4-*gem* Me), 1.17 (3H, s, 10-Me), 4.66—4.76 (2H, m, 11-H_2).

ii) A solution of **20** (1.102 g) in 22 ml of 1: 1 MeOH–CH_2Cl_2 was subjected to ozonolysis under dry ice–acetone cooling for 70 min. A solution of Na_2SO_3 (4 g) in H_2O (80 ml) was added to the above ozonolyzed product and the reaction mixture was stirred for 2 hr at room temperature. The reaction mixture was treated as in the case of the preparation of **14** to give an oily product (1.170 g), which was chromatographed on silica gel (100 g) to afford a homogeneous oil from the petr. ether–ether (1: 1) eluate. This was recrystallized from petr. ether–ether to give colorless prisms (**9**) (174 mg, 18% yield). A part of this product was recrystallized again from benzene to give colorless prisms (**9**), mp 177—178°, whose physical data (mp, $[\alpha]_D$, IR, and NMR) were identical with those of natural valdiviolide (**9**).[10] *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.99; H, 8.83. $[\alpha]_D$ +109° ($CHCl_3$, c=1.18). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1678. ν_{max}^{KBr} cm^{-1}: 3360. NMR (100 MHz) δ: 0.94 (6H, s, 4-*gem* Me), 1.27 (3H, s, 10-Me), 5.02 (1H, br s, $W_{h/2}$=14 Hz, 11-OH), 6.14 (1H, br s, 11-H).

Oxidation of (+)-Valdiviolide (9) to (+)-Winterin (10)——A solution of **9** (55 mg) in acetone (5 ml) was oxidized with Jones reagent (0.3 ml) under stirring for 15 min at room temperature. The reaction mixture was extracted with ether after MeOH and H_2O had been added. The extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave colorless crystals, which were recrystallized from ether to give colorless plates (**10**) (27 mg), mp 157.5—158.5°. The physical data (mp, $[\alpha]_D$, IR, and NMR) were identical with those of natural winterin (**10**).[10] *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.37; H, 8.05. $[\alpha]_D$ +105.6° ($CHCl_3$, c=2.2). IR ν_{max} cm^{-1}: 1850, 1775, 1670. NMR (100 MHz) δ: 0.91, 0.95 (each 3H, s, 4-*gem* Me), 1.22 (3H, s, 10-Me), 2.30—2.58 (2H, m, 7-H_2).

Ozonolysis of 13-Hydroxy-13-Deisopropyldehydroabietane (3) to the Butenolide (23)——A solution of **3** (1.777 g) in 36 ml of 1: 1 MeOH–CH_2Cl_2 was subjected to ozonolysis under dry ice–acetone cooling for 1 hr. A solution of $NaBH_4$ (1 g) in 50% (v/v) EtOH–H_2O (10 ml) was added to the above ozonolyzed product and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was treated as in the case of the preparation of isodrimenin (**8**) to give an oily product, which was chromatographed on silica gel (160 g) to give colorless crystals (**23**) (371 mg, 22% yield) from the *n*-hexane–ethyl acetate (4: 1) eluate. This product was recrystallized from *n*-hexane to give colorless prisms (**23**), mp 101—102°. *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.07; H, 9.36. IR ν_{max} cm^{-1}: 1790, 1765. UV λ_{max}^{EtOH} nm (log ε) 213 (4.0367). NMR δ: 0.74 (3H, s, 10-Me), 0.89, 1.00 (each 3H, s, 4-*gem* Me), 4.35 (1H, br s, $W_{h/2}$=6 Hz, 9ξ-H), 5.68 (1H, t, 14-H).

Synthesis of (+)-Pallescensin A (11) from 23——A solution of **23** (82 mg) in THF (2 ml) was treated with DIBAL (20% in hexane, 95% liquid, 1.57 ml) under a nitrogen atmosphere at −25 to −20°. The reaction mixture was stirred for 3 hr then extracted with ether after 10% H_2SO_4 (2 ml) and H_2O had been added. The extract was washed with sat. Na_2CO_3 aq. and sat. NaCl aq., then dried over Na_2SO_4. Removal of the solvent gave an oily product, which was chromatographed on silica gel (15 g) to give a homogeneous oil (**11**) (38 mg, 50% yield) from the *n*-hexane eluate. The physical data (NMR and GC–MS) were identical with those of natural pallescensin A (**11**)[12] and a synthetic sample (**11**).[13] GC–MS *m/e*: 218 (M^+). $[\alpha]_D$ +60.4° ($CHCl_3$, c=0.9). UV λ_{max}^{MeOH} nm (log ε): 220 (3.7096). NMR (CCl_4): 0.93 (6H, s, 4-*gem* Me), 1.18 (3H, s, 10-Me), 5.97 (1H, d, J=2 Hz, 14-H), 7.05 (1H, d, J=2 Hz, 13-H).

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