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OZONOLYSIS OF PHENOLIC DEHYDROABIETIC ACID DERIVATIVES[1)]

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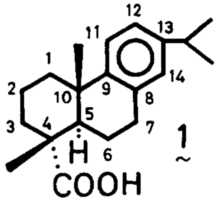
In the course of our study of chemical conversion of *l*-abietic acid, a major component of pine rosin, to biologically active compounds, we intended the short path syntheses of optically active drimanic sesquiterpenoids (3) based on the cleavage of phenolic C-rings of the compounds (2) derived from dehydroabietic acid (1) by means of ozonolysis.



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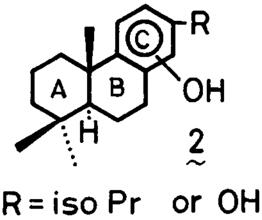

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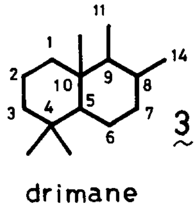

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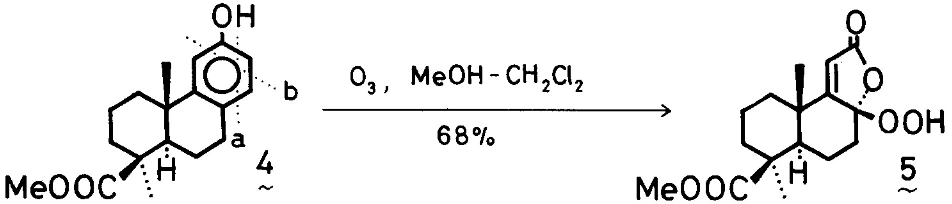
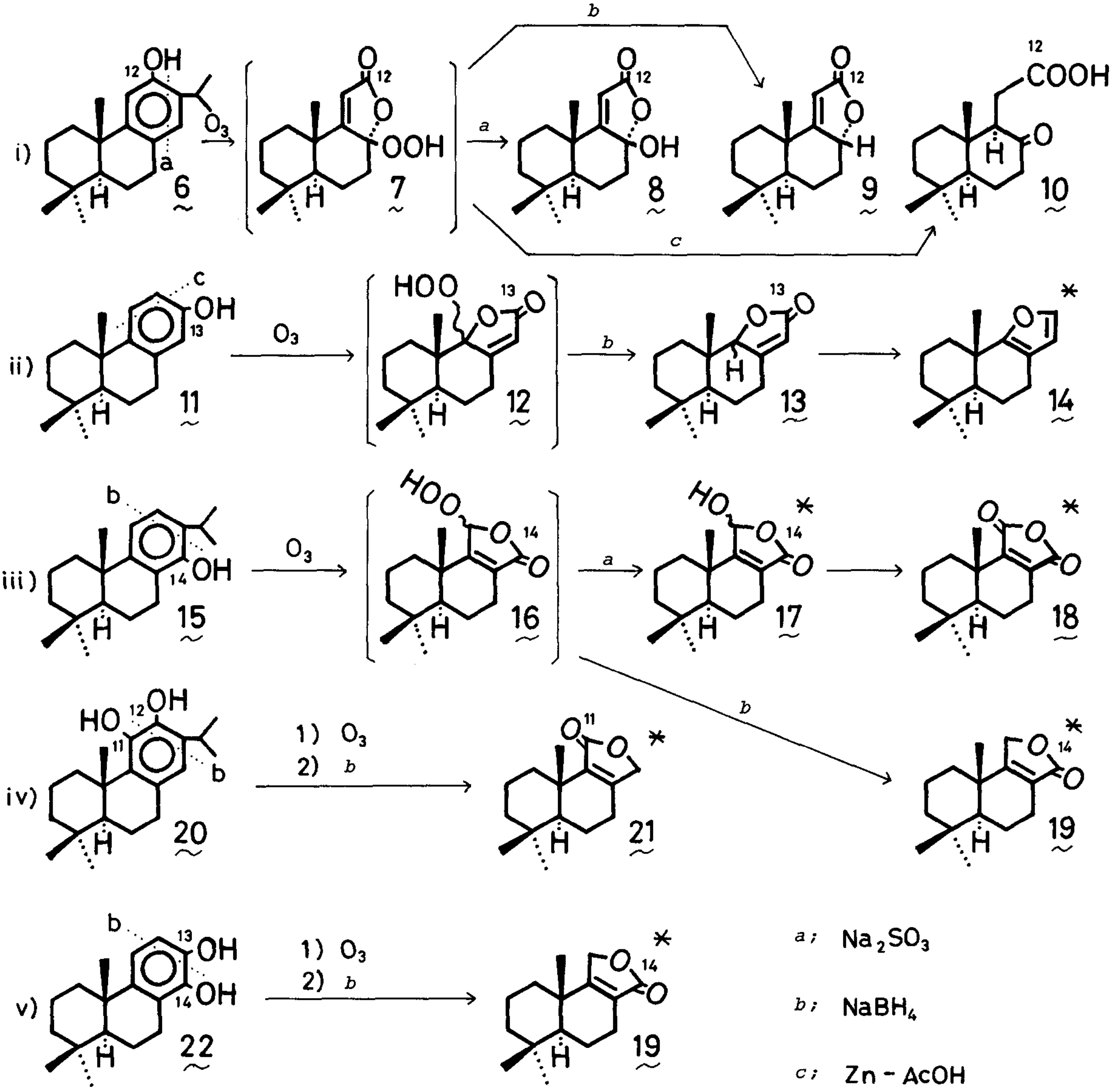
It has been reported that ozonolysis of methyl podocarpate (4) bearing hydroxyl group at 12-position in MeOH-CH_2Cl_2 (1:1) affords the hydroperoxylactone (5)[2)]. In this case, cleavage took place preferentially at the dotted line *a*. If cleavage occurs at the dotted line *b*, the desired 3 would be produced in one-step. Therefore, we intended the ozonolysis of 2 bearing hydroxyl group at every possible position of aromatic ring to find out the relation between substitution pattern and the products.



The starting phenols were prepared by the methods developed in this laboratory [3)]. The main difficulty associated with these syntheses was the preparation of the 11-hydroxy compound, so the 11,12-dihydroxy compound (20) was prepared instead . The 13,14-dihydroxy compound (22) was prepared in connection with the compound (20). The results were shown in scheme 1.

Scheme 1. Ozonolysis of phenols in MeOH-CH_2Cl_2
(Compounds marked with asterisks are all natural sesquiterpenoids)[4]



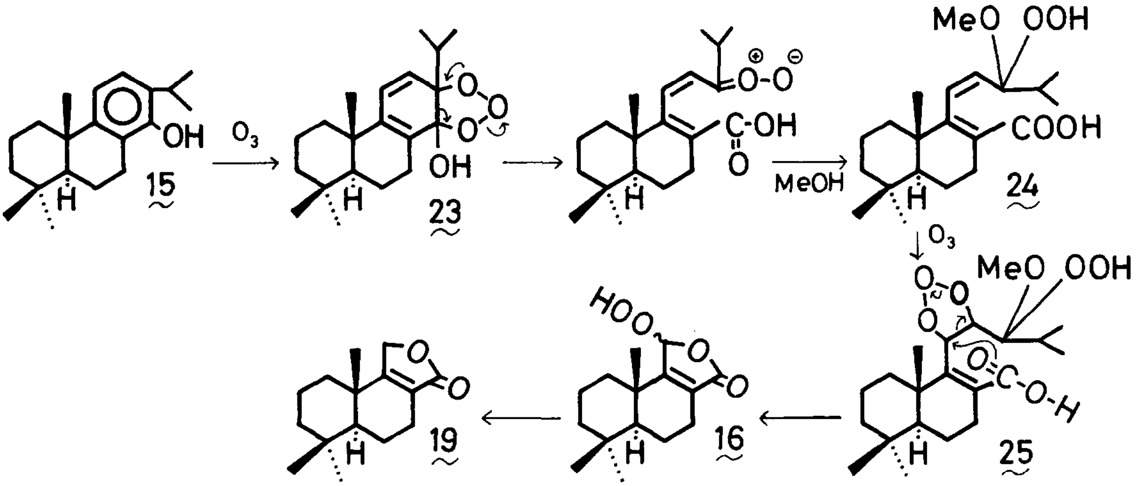
Ozonolysis of ferruginol (6) having hydroxyl group at 12-position proceeded in the same way as that of 4 as expected. Reduction of the hydroperoxylactone (7) by Na_2SO_3, $NaBH_4$ and Zn-AcOH afforded 8 [mp 173-175°, 20%], 9 [mp 107-107.5°, 36%], and 10 [63%], respectively. In the case of the 13-hydroxy compound (11), cleavage occurred at the dotted line *c* and the butenolide (13) was obtained after $NaBH_4$ reduction. Subsequent treatment of 13 with DIBAH followed by acidification with 10% H_2SO_4 afforded pallescensin A (14)[5] [MS : $M^+=218(C_{15}H_{22}O)$,

$[\alpha]_D$ +60.4° ($CHCl_3$, C=0.9)]. The desired cleavage (dotted line *b*) took place when hydroxyl group was present at 14-position. Thus, 15 was converted to (+)-valdiviolide (17)[6] [mp 177-178°, $[\alpha]_D$ +109° ($CHCl_3$, C=1.18), 18%] and (+)-confertifolin (19)[7] [mp 153-153.5°, $[\alpha]_D$ +68.1° ($CHCl_3$, C=1.13), 46%], the lactone carbonyl being located at 14-position in both cases. Jones oxidation of 17 afforded (+)-winterin (18)[6] [mp 157.5-158.5°, $[\alpha]_D$ +105.6° ($CHCl_3$, C=2.2)].

The 11,12-dihydroxy compound (20) afforded (+)-isodrimenin (21)[7] [mp 131-132°, $[\alpha]_D$ +86° ($CHCl_3$, C=2.00), 26%], a positional isomer of confertifolin (19). In this case, although the cleavage took place in the same manner as with 15, the lactone carbonyl is located at 11-position. The 13,14-dihydroxy compound (22) afforded the same compound, confertifolin (19) [11%], with the 14-hydroxy compound (15), which suggests that the 11-hydroxy compound also should give isodrimenin (21).

A variety of compounds were thus obtained when phenols having hydroxyl groups at different position were subjected to ozonolysis. However, their formation could reasonably be explained by taking into accounts of a mechanism presented by Bell and Gravestock[2] for the formation of 5 from 4. The pathway for (+)-confertifolin formation, for example, may be delineated as follows. (Scheme 2)

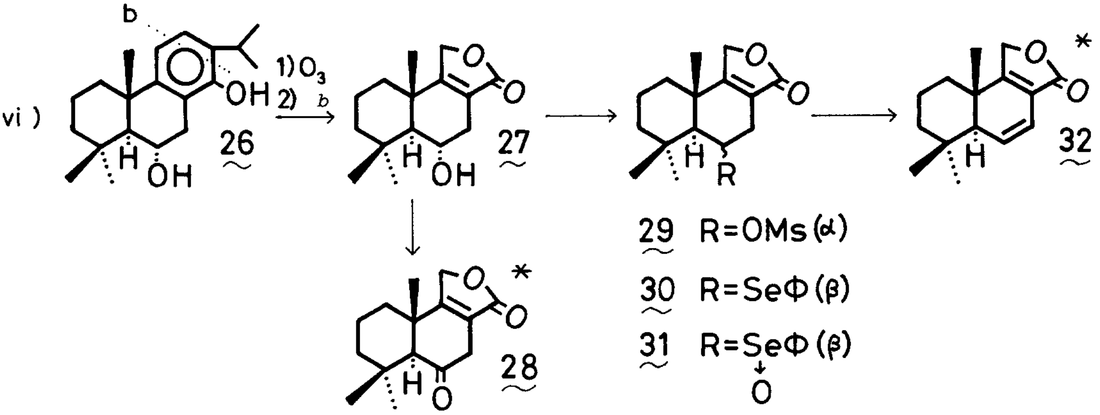
Scheme 2



The main features of the present reactions are as follows : 1) Ozone initially attacks at the most reactive site of the phenols (*cf.* 23). 2) Of the two double bonds newly formed (*cf.* 24), one is more deactivated by the direct conjugation with a carbonyl group. Therefore, a further molecule of ozone attacks the other double bond (*cf.* 25) and thus α,β-unsaturated acids survive in every case.

This method was successfully applied for the syntheses of other sesquiterpenoids of this class. Ozonolysis followed by $NaBH_4$ reduction of the 6,14-dihydroxy compound (26) afforded 27 [mp 190.5-191.5°, $[\alpha]_D$ +79° ($CHCl_3$, C=1.00), 48%], Jones oxidation of which gave (+)-fragrolide (28)[8] [mp 163-164°, $[\alpha]_D$

+145.1° ($CHCl_3$, C=1.00)]. Mesylation of 27 followed by S*N* 2-type substitution of α-OMs group with selenophenolate anion afforded 30. Oxidation of 30 with 30% H_2O_2 in the presence of AcOH in THF afforded (+)-bemadienolide (32)8) [mp 124 -124.5°, $[\alpha]_D$ +20.4° ($CHCl_3$, C=1.00)]. The selective elimination of 7β-hydrogen located *cis* to the intermediary β-selenoxide (31) must be involved in this transformation9). Further application of the present method for the syntheses of more complex natural products is being continued.



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References and notes

1) New compounds indicated by mp gave satisfactory analytical values.
2) R. A. Bell and M. B. Gravestock, Can. J. Chem., 48, 1105 (1970).
3) The structures of these phenols have been rigorously established by the physico-chemical methods.
4) The structures of the all synthetic natural products were confirmed by physico-chemical methods or direct comparison with the natural products. The details will be reported in the forthcoming paper.
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