Biomimetic Synthesis of (±)-Chrysomelidial, (±)-Dehydroiridodial, and (±)-Iridodial

Shinichi Uesato, Yasuko Ogawa, Masaharu Doi, and Hiroyuki Inouye

Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606, Japan

Treatment of 10-oxocitral (**3**), a key intermediate for iridoid biosynthesis, with 50% aqueous formic acid yielded (±)-chrysomelidial (**5**) and (±)-dehydroiridodial (**6**), while reduction of (**3**) or (**5**) and (**6**) in 70% aqueous formic acid with the coenzyme model (**8**) gave rise to (±)-iridodial (**4**).

Recently, it has been demonstrated that crude enzyme extracts from *Rauwolfia serpentina* cell suspension cultures convert 10-hydroxygeraniol (**1**)–10-hydroxynerol (**2**) into 10-oxocitral (**3**) and cyclize (**3**) to iridodial (**4**), a pivotal intermediate in iridoid biosynthesis,[1] in the presence of oxidized and reduced pyridine nucleotides (Figure 1). This communication reports a synthesis of iridodial (**4**) from 10-oxocitral (**3**) which mimics the biological cyclization process.

Formic acid would be expected to catalyse cyclization of 10-oxocitral (**3**) to iridodial (**4**) by initial protonation of the 1- and 10-aldehyde oxygen atoms. This induces nucleophillic attack of a hydride ion at the C-3 position and formation of the C-2–C-7 bond. Thus, the following reaction was attempted: 10-oxocitral (**3**) prepared from citral by SeO_2 oxidation[2] was dissolved in 50% aquous HCO_2H, and the solution was heated at reflux for 1 h under an Ar atmosphere. The usual work-up and fractionation by preparative t.l.c. (n-hexane–diethyl ether, 1:1) gave the oils (±)-(**5**) (less polar) and (±)-(**6**) (more polar) each in 15% yield.

The spectroscopic data† of these substances, together with their high-resolution mass spectra, are consistent with the structures of natural chrysomelidial (−)-(**5**) (the defensive secretion of *Plagiodera versicolora*)[3] and dehydroiridodial, (−)-(**6**) (the pungent principle of *Actinidia polygama*),[4] respectively. Compounds (±)-(**5**) and (±)-(**6**) are assumed to be formed from (**3**) *via* (±)-7,8-dehydroiridodial (**7**) as shown in Figure 2. Interestingly, formic acid functioned as a cyclase mimic, which catalysed formation of the iridane skeleton from (**3**) without donation of a hydride ion. This finding prompted us to synthesize (**4**) from (**3**) by adding a coenzyme model as a hydride ion source. Attempted treatment of (**3**) with 70% aqueous HCO_2H (5 ml) containing Hantzsch ester[5] under various conditions resulted in the formation of only (±)-(**5**) and (±)-(**6**). However, reaction of (**3**) (0.3 mmol) with 70% aqueous HCO_2H (5 ml) containing the coenzyme model (**8**)[6] (1.2 mmol) (heating at reflux for 2.5 h) followed by immediate treatment of the reaction mixture with a 2,4-dinitrophenyl-

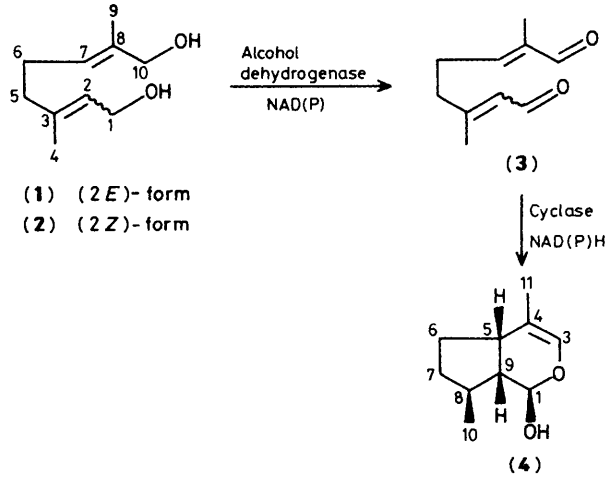

Figure 1. Enzymatic synthesis of iridodial (**4**).

† *Spectroscopic data:* (±)-(**5**): $\lambda_{max.}$ (EtOH) 252 nm (ε 11 471); $\nu_{max.}$ (neat) 1720, 1660, 1625 cm^{-1}; δ_H ($CDCl_3$) 0.89 (3H, d, *J* 6.9 Hz, 11-Me), 1.42—2.10 (2H, m, 6-H), 2.17 (3H, s, 10-Me), 9.71 (1H, d, *J* 0.7 Hz, 3-H), 10.01 (1H, s, 1-H). (±)-(**6**): $\lambda_{max.}$ (EtOH) 252 nm (ε 11 680); $\nu_{max.}$ (neat) 1720, 1660, 1625 cm^{-1}; δ_H ($CDCl_3$) 1.01 (3H, d, *J* 7.3 Hz, 11-Me), 1.60—2.20 (2H, m, 6-H), 2.17 (3H, s, 10-Me), 9.67 (1H d, *J* 1.1 Hz, 3-H), 10.01 (1H, s, 1-H).

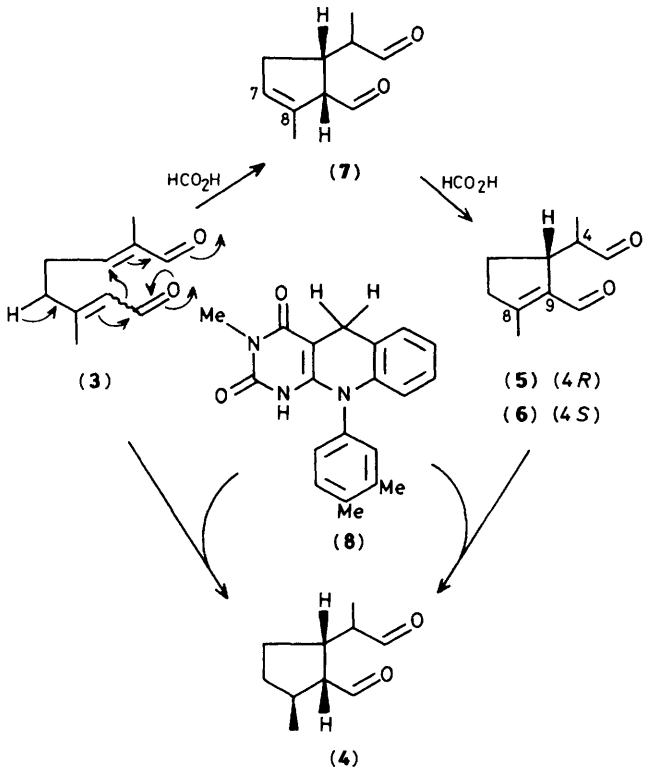

Figure 2. Proposed mechanism for chemical synthesis of iridodial (**4**).

hydrazine reagent gave rise to a hydrazone as orange needles, m.p. 227 °C, in 5% yield. Its physical data‡ corresponded with those of the bis-2,4-dinitrophenylhydrazone derived from synthetic iridodial (**4**)[7] except that the weak i.r. band observed around 920 cm^{-1} in the hydrazone of authentic material, was slightly split in the above hydrazone. Therefore, the reduction product was considered to be (±)-iridodial (**4**) contaminated by its stereoisomer(s). Cyclization to (±)-iridodial (**4**) was probably caused by hydride ion attack at the C-3 position of (**3**). Since treatment of (±)-(**5**) and (±)-(**6**) in a similar manner to (**3**) also yielded (±)-iridodial (**4**), another route to (**4**) *via* (±)-(**5**) and (±)-(**6**) should also be feasible.

We thank Professor F. Yoneda of this Faculty for a gift of deazaflavin and dicussions and Professor T. Fujita of this Faculty for suggestions.

Received, 10th February 1987; Com. 176

‡ Mass: found, *M* (electron impact) 528.1699; calc. for $C_{22}H_{24}N_8O_8$: *M*, 528.1719; *m/z* 528 (3%, M^+), 511 (1, *M* − OH), 498 (1, *M* − NO), 331 (100, *M* − PhN_4O_4), 148 (9, $C_{10}H_{14}N$), 81 (24, C_6H_9); $\nu_{max.}$ (KBr) 1680, 1590, 1510, 1330, 1260, 1220, 920, 830 cm^{-1}.

References

1 S. Uesato, S. Matsuda, and H. Inouye, *Chem. Pharm. Bull.*, 1984, **32**, 1671; *Yakugaku Zasshi*, 1984, **104**, 1232; S. Uesato, S. Matsuda, A. Iida, H. Inouye, and M. H. Zenk, *Chem. Pharm. Bull.*, 1984, **32**, 3764; S. Uesato, S. Kanomi, A. Iida, H. Inouye, and M. H. Zenk, *Phytochemistry*, 1986, **25**, 839; S. Uesato, Y. Ogawa, H. Inouye, K. Saiki, and M. H. Zenk, *Tetrahedron Lett.*, 1986, **27**, 2893.

2 A. R. Battersby, M. Thompson, K. H. Glüsenkamp, and L. H. Tietze, *Chem. Ber.*, 1981, **114**, 3430.

3 J. Meinwald, T. H. Jones, T. Eisner, and K. Hicks, *Proc. Natl. Acad. Sci. USA*, 1977, **74**, 2189; J. Meinwald and T. H. Jones, *J. Am. Chem. Soc.*, 1978, **100**, 1883; K. Kon and S. Isoe, *Tetrahedron Lett.*, 1980, **21**, 3399.

4 K. Yoshihara, T. Sakai, and T. Sakan, *Chem. Lett.*, 1978, 433; H. Takeshita, T. Hatsui, N. Kato, T. Masuda, and H. Tagoshi, *ibid.*, **1982**, 1153.

5 U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1.

6 F. Yoneda, K. Tsukuda, K. Shinozuka, F. Hirayama, K. Uekama, and A. Koshiro, *Chem. Pharm. Bull.*, 1980, **28**, 3049; F. Yoneda, *Yakugaku Zasshi*, 1984, **104**, 97.

7 H. Inouye, S. Ueda, S. Uesato, and K. Kobayashi, *Chem. Pharm. Bull.*, 1978, **26**, 3384.