Tetrahedron Letters No. 40, pp 3871 - 3872. 0040-4039/79/1001-3871$02.00/0

STEREOSELECTIVE SYNTHESIS OF (±)-PHOMENONE, A PHYTOTOXIC METABOLITE OF *PHOMA EXIGUA*, AND (±)-3-EPIPHOMENONE[1]

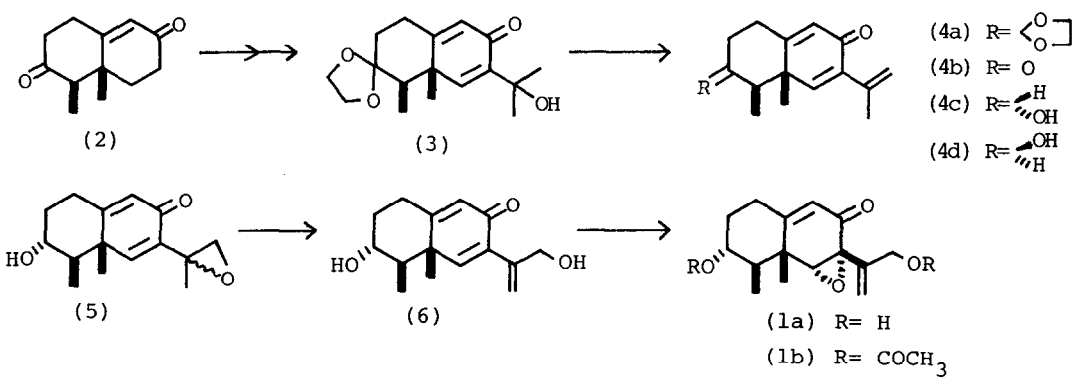
Koji Yamakawa,* Masato Kobayashi, Shotaro Hinata, and Tsuyoshi Satoh

Faculty of Pharmaceutical Sciences, Science University of Tokyo
Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

Summary Stereoselective synthesis of (±)-phomenone, a phytotoxic metabolite from the fungus *Phoma exigua*, and (±)-3-epiphomenone is described.

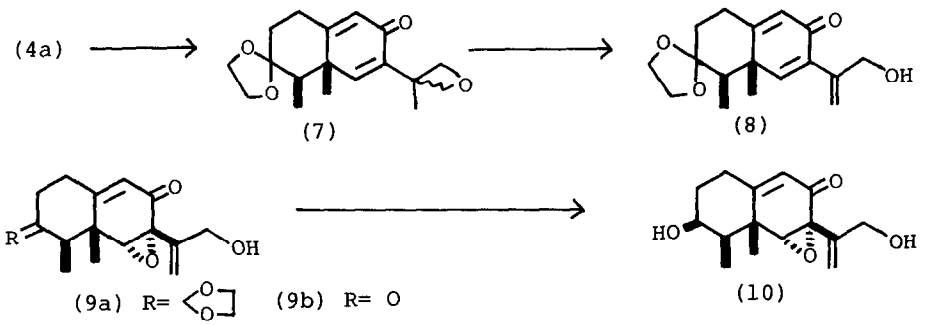
Phomenone, a phytotoxic metabolite from the fungus *Phoma exigua* was found by Bousquet *et al.*[2] The structure of phomenone was established as an eremophilane-type sesquiterpenoid (1a) by physicochemical data and single crystal X-ray analysis.[2] Some mycotoxins, PR-toxin[3] and eremofortins,[4] have been isolated from *Penicillium roqueforti* and their structure has been elucidated as eremophilane-type sesquiterpenoids.

We wish to report the first total synthesis of (±)-phomenone (1a), a biologically active sesquiterpenoid metabolite, and (±)-3-epiphomenone (10) from the bicyclic enone (2).[5a,b] Treatment of (±)-3[5b] derived from 2 with methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt gave a trienone (4a), mp 55-58° (87% yield), which was treated with 70% AcOH solution at 100° for 1 hr to give a diketone (4b), mp 64.5-66° and 82-83°, as dimorphic forms (90% yield). Reduction of 4b with $NaBH_4$ afforded 3α-ol (4c), oil, and 3β-ol (4d), mp 88-90°, in 15% and 75% yield, respectively. Oxidation of 4d with CrO_3-pyridine-H_2O gave 4b in 82% yield. Epoxidation of 4c with *m*-chloroperbenzoic acid in methylene chloride in the presence of $NaHCO_3$ solution gave a mixture of α- and β-epoxides (5) in 86% yield. Treatment of 5 with lithium diethylamide in refluxing ether for 2 hr afforded a dihydro-trienone (6) in 26% yield. Epoxidation of 6 with 30% H_2O_2 in refluxing ethanol in the presence of catalytic amount of $NaHCO_3$ solution for 3 hr afforded an α-epoxide (±)-1a, oil (40% yield), stereoselectively.



(±)-Phomenone (1a): High-resolution MS: M^+, 264.1329 for $C_{15}H_{20}O_4$; NMR δ: 1.19 (3H, d, J=6 Hz; 4-CH_3), 1.26 (3H, s; 5-CH_3), 3.40 (1H, s; 6-H), 4.22 (2H, d, J=4 Hz; 13-H), 5.21 and 5.24 (each 1H, m, W/2=3 Hz; =CH$_H$), 5.71 (1H, d, J=2 Hz; 9-H); UV λ_{max}^{MeOH} 243 nm; IR cm^{-1}: 3400 (OH), 1670 (CO); MS: 264 $(M)^+$, 249 $(M-15)^+$, 246 $(M-18)^+$, 235 $(M-29)^+$, 231 $(M-18-15)^+$, 123, 91.
Diacetate (±)-1b (prepared with Ac_2O-pyridine): NMR δ: 1.12 (3H, d, J=7 Hz; 4-CH_3), 1.29 (3H, s; 5-CH_3), 2.03 and 2.09 (each 3H, s; 3- and 13-OAc), 3.31 (1H, s; 6-H), 4.76 (2H, m, W/2=3 Hz; 13-H), 5.38 (2H, m, W/2=4 Hz; 12-H), 5.75 (1H, d, J=1.5 Hz; 9-H); UV λ_{max}^{EtOH} 241 nm; IR cm^{-1}: 1740, 1680 (CO), 1245, 1030 (OAc); MS: 288 $(M-60)^+$.

NMR, UV, and IR spectral data of (±)-1a and (±)-1b were in good agreement with those of phomenone and phomenone diacetate, respectively, reported by Bousquet *et al.*[2]



A stereoselective synthesis of (±)-3-epiphomenone (10) was examined by a route similar to that for (±)-1a. Trienone (4a) was treated with *m*-chloroperbenzoic acid to afford a mixture of epoxides (7). Treatment of 7 with lithium diethylamide under the same condition as for 5 afforded a trienone alcohol (8), oil, in 70% yield. Epoxidation of 8 with 30% H_2O_2-Na_2CO_3 gave α-epoxide (9a), mp 135-136° (56% yield). Deketalization of 9a with 70% AcOH solution at room temperature for 3 days afforded a ketone (9b)(75% yield). Reduction of 9b with $NaBH_4$ gave (±)-3-epiphomenone (10), mp 130-132°, (70% yield) together with a small amount of the minor product.
(±)-10: High-resolution MS: M^+, 264.1338 for $C_{15}H_{20}O_4$; NMR δ: 1.28 (3H, d, J=7 Hz; 4-CH_3), 1.44 (3H, s; 5-CH_3), 3.37 (1H, s; 6β-H), 4.00 (1H, m, W/2=9 Hz; 3α-H), 4.26 (2H, m, 13-H), 5.32 and 5.41 (each 1H, m; =CH$_H$), 5.83 (1H, d, J=1.5 Hz; 9-H); UV λ_{max}^{EtOH} 247 nm (ε 11200); IR cm^{-1}: 3445 (OH), 1650 (CO), 1615 (C=C), 1055. The minor product, (±)-1a, was not obtained completely pure, but crude (±)-1a and its diacetate (±)-1b were indicated by NMR spectral comparison with those of the authentic specimens.

References

1. Studies on Terpenoids and Related Alicyclic Compounds. XX. Part XIX. K. Yamakawa, T. Satoh, N. Ohba, and R. Sakaguchi, *Chem. Lett.*, 755 (1979).
2. C. Riche, C.P. Billy, M. Devys, A. Gaudemer, M. Barbier, and J.F. Bousquet, *Tetrahedron Lett.*, 2765 (1974).
3. R.D. Wei, H.K. Schnoes, P.A. Hart, and F.M. Strong, *Tetrahedron*, 31, 109 (1975).
4. S. Moreau, M. Cacan, and A.L. Combier, *J. Org. Chem.*, 42, 2632 (1977).
5. a) K. Yamakawa, I. Izuta, H. Oka, and R. Sakaguchi, *Tetrahedron Lett.*, 2187 (1974);
   b) K. Yamakawa, I. Izuta, H. Oka, R. Sakaguchi, M. Kobayashi, and T. Satoh, *Chem. Pharm. Bull. (Tokyo)*, 27, 331 (1979).

(Received in Japan 30 June 1979)