Synthesis of Demethoxycapillarisin, a Naturally Occurring 2-Phenoxychromone, and Related Compounds

By HIDEKAZU TAKENO and MASASHI HASHIMOTO*

(*Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6, Kashima, Yodogawa, Osaka* 532, *Japan*)

and YOSHIYASU KOMA, HARUO HORIAI, and HIROYUKI KIKUCHI

(*Tokyo Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 3-8-3, Nukuikitamachi, Koganei, Tokyo* 184, *Japan*)

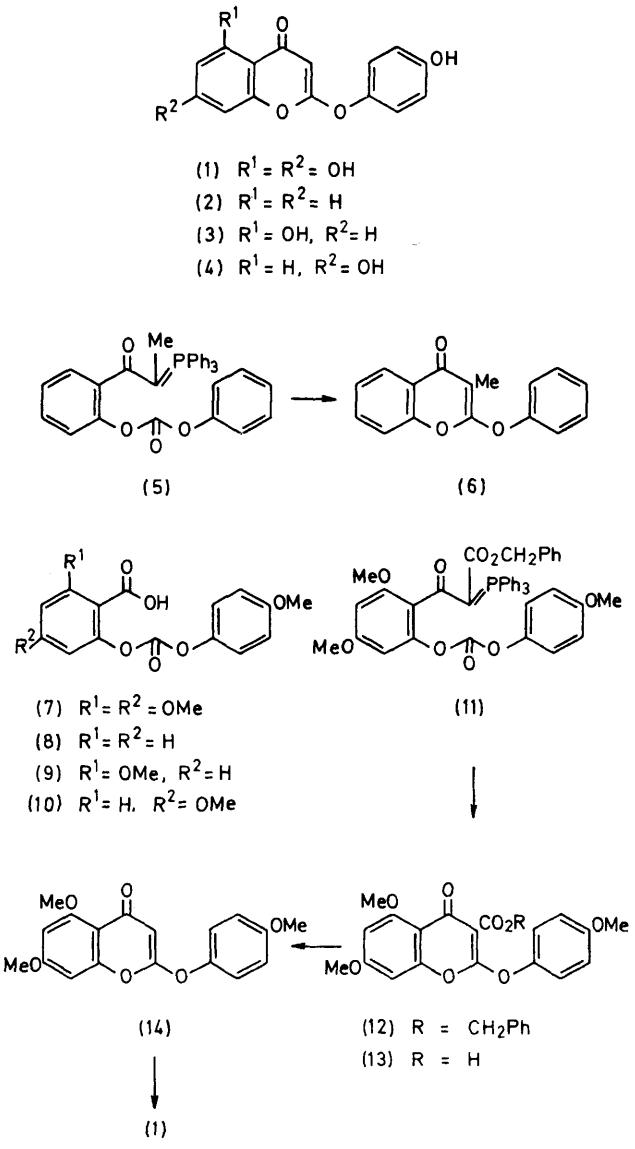
Summary Demethoxycapillarisin (**1**), a naturally occurring 2-phenoxychromone, and the related compounds (**2**)—(**4**) have been synthesized *via* a route involving, as a key step, an intramolecular Wittig reaction between a phosphorus ylide and a carbonate.

THE 2-phenoxychromones comprise a structurally new class of naturally occurring chromones,[1,2] of which a representative is demethoxycapillarisin (**1**) isolated as a biologically active principle from *Artemisia capillaris* Herba.† We report herein an expeditious synthesis of (**1**)‡ as well as the related compounds (**2**)—(**4**) which employs, as a key step, an intramolecular Wittig reaction to produce the keten–acetal function of compounds of this type. This approach was based on our previous finding that the intramolecular cyclization of the phosphorane–carbonate (**5**) provides the 2-phenoxychromone (**6**).[4] We also examined the cyclization of the related system (**11**) in which the methyl group of (**5**) is replaced by a carboxylate moiety. This latter function could be eliminated afterwards *via* thermal decarboxylation to the natural 2-phenoxychromone framework (**14**).

The requisite intermediate, the phosphorane (**11**), was prepared from the benzoic acid (**7**) which was readily derived from benzyl 4,6-dimethoxysalicylate by acylation with 4-methoxyphenyl chloroformate (pyridine–CH_2Cl_2, 0 °C to room temp., 30 min), followed by debenzylation ($AlCl_3$–anisole–nitromethane, 10 °C, 1 h). The acid (**7**) was then chlorinated ($SOCl_2$, benzene, reflux, 3 h) and subsequently alkylated with benzyl triphenylphosphonoacetate (benzene, room temp., 17 h) to give, after work-up with aq. $NaHCO_3$ and purification by silica gel chromatography, (**11**) (57%) [viscous oil; ν_{max} (CH_2Cl_2) 1770, 1730, and 1660 cm^{-1}].

The key cyclization was conducted, according to our previous work,[4] by heating (**11**) in toluene for 28 h. Under these conditions, the desired product (**12**) was obtained as a viscous oil in 59% yield after purification by silica gel chromatography. The structure of (**12**) was characterized on the basis of its physical data [M^+ *m/e* 462; ν_{max} (CH_2Cl_2) 1725 and 1640 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 5·33 (s, 2H), 6·18 (d, *J* 2 Hz, 1H), 6·37 (d, *J* 2 Hz, 1H), 7·00 (A_2B_2, *J* 9 Hz, 4H), and 7·1—7·5 (m, 5H)] and further confirmed by conversion into (**1**) (*vide infra*).

The conversion of (**12**) into compound (**14**) with the natural chromone framework required the elimination of the benzyloxycarbonyl group, which was accomplished as follows. The benzyl protecting group was first removed by hydrogenolysis (10% Pd–C–AcOEt) and the resulting carboxylic acid (**13**) [m.p. 208—210 °C (decomp.); 65%] was then pyrolysed under nitrogen at atmospheric pressure



† Komiya *et al.*[1] have isolated (**1**) as one of the choleretic substances in this plant. Three of us (Y. K., H. H., and H. K.) have also isolated (**1**) as a vasodilative principle (unpublished result).

‡ The synthesis of (**1**) by a different route has recently appeared.[3]

(240 °C, 45 min), affording the desired decarboxylation product (**14**) (79%) [m.p. 184—185 °C (lit.[3] 185·5—188 °C); M^+ *m/e* 328; ν_{max} (CH_2Cl_2) 1635 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 5·27 (s, 1H); λ_{max} (EtOH) 278 nm (ϵ 15,300)].

Finally, treatment of (**14**) with BBr_3 according to the known procedure[3] gave (**1**), identical in all respects with natural demethoxycapillarisin.

A similar sequence of reactions from the acyl salicylic acids (**8**)—(**10**) gave compounds (**2**)—(**4**) respectively.§

The process described here is an attractive method for the preparation of the keten–acetal function related to the natural 2-phenoxychromone system.

(*Received*, 26*th January* 1981; *Com.* 091.)

§ Details will be reported in a forthcoming full paper.

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[3] T. Okutani, K. Kawakita, O. Aki, and K. Morita, *Heterocycles*, 1977, **6**, 1581.
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