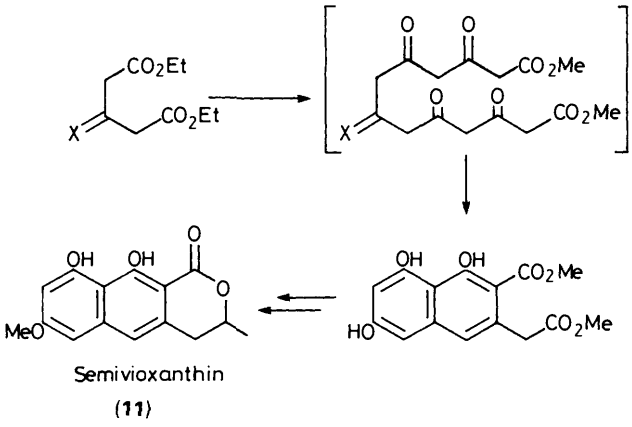
Synthesis of Semivioxanthin *via* a Polyketide

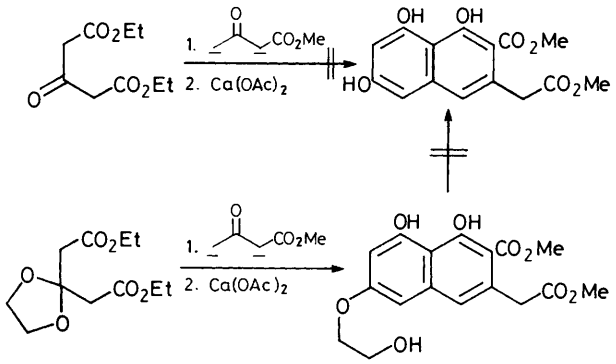
Masahiko Yamaguchi,* Tadashi Okuma, Shigeo Nakamura, and Toru Minami
Department of Applied Chemistry, Kyushu Institute of Technology, Sensui-cho, Tobata, Kitakyushu 804, Japan

The first synthesis of semivioxanthin has been achieved *via* the intermediate 3,5,7,9,11-pentaoxotridecanedioate one of whose ketone groups was protected as a ketal of *o*-phenylenedimethanol.

A number of antifungal naphtho[2,3-*c*]pyran-1(1*H*)-ones possessing a 7-methoxy group and 9- and 10-phenolic hydroxy groups, *e.g.* semivioxanthin (**11**), vioxanthin,[1] and SC-28762,[2] *etc.*, have been isolated from natural sources. Biosynthetically, they are considered to be produced from acetic acid *via* polyketides (β-polyoxoalkanoates). From our synthetic studies of polycyclic aromatic compounds utilizing the intramolecular condensation of polyketides,[3] the first synthesis of semivioxanthin (**11**) has been achieved. The synthesis is characterized by the following features (i) the 7,9,10-trihydroxynaphthalene nucleus of (**11**) was constructed by the $Ca(OAc)_2$-induced intramolecular condensation[3] of 3,5,7,9,11-pentaoxotridencanedioate. The polyketide intermediate, formed by the Claisen condensation of the β-oxoglutarate derivative and acetoacetate dianion (Scheme 1),[3,4] has ester groups which are useful for further functional modifications at later states. (ii) The present synthesis involves the use of a novel protecting group for a ketone (the ketal of *o*-phenylenedimethanol removable by



Scheme 1.

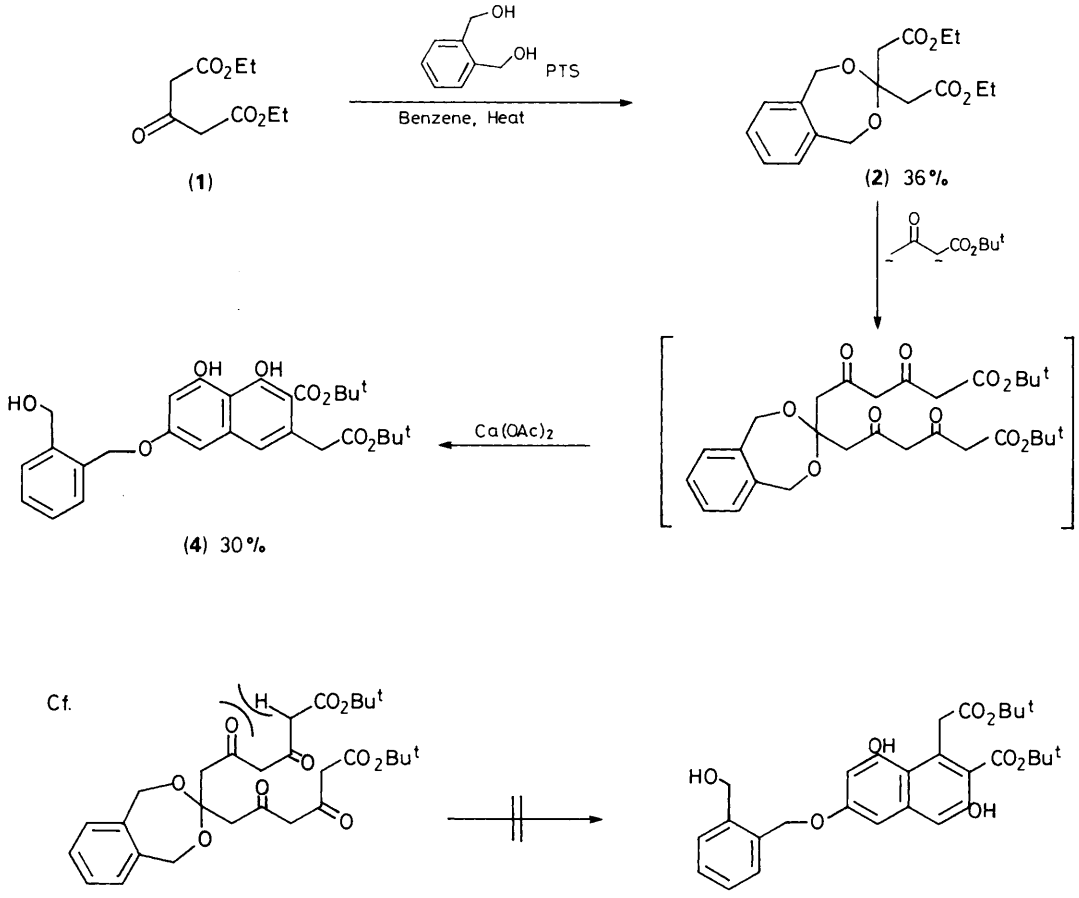


Scheme 2.

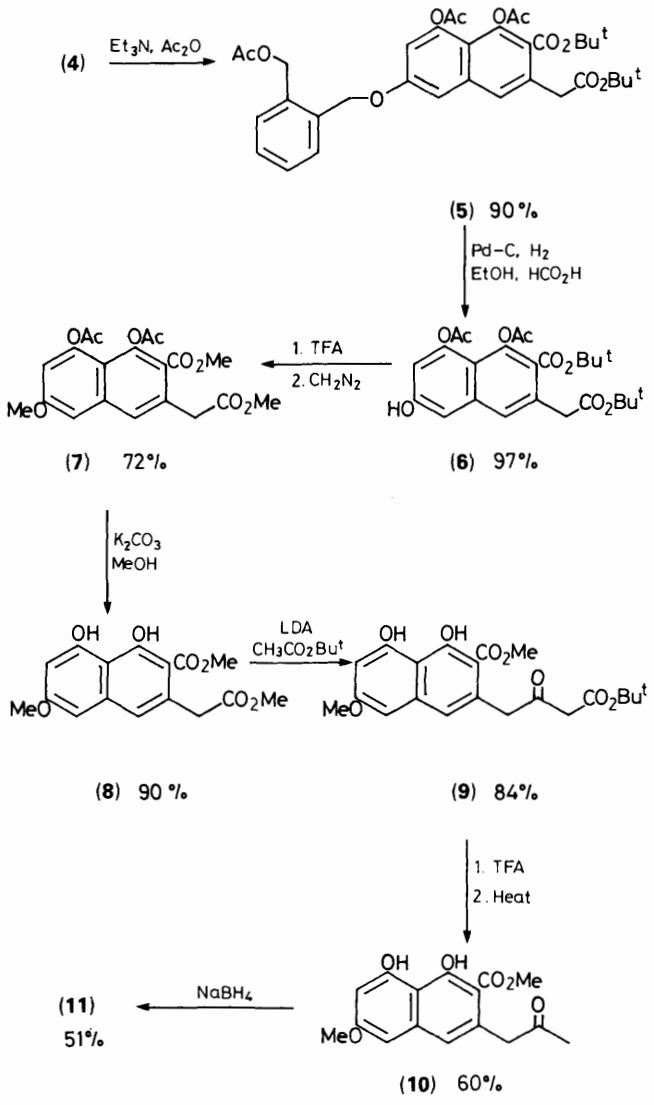
hydrogenation) which allows selective methylation at a 7-hydroxy group.

Since the Claisen condensation of diethyl β-oxoglutarate (**1**) with methyl acetoaceate dianion failed to give the expected naphthalene derivative after $Ca(OAc)_2$-treatment, the ketone moiety was protected as a ketal (Scheme 2). When subjected to the same sequences of reactions, one of the C–O bonds of this ketal was cleaved to give the naphthalenediol. However, difficulties in the removal of β-hydroxyethyl group by several reductive or oxidative methods including HI treatment[4a] led us to use a new protecting group, the ketal of *o*-phenylenedimethanol.[5] Reaction of (**1**) with the diol in the presence of toluene-*p*-sulphonic acid in refluxing benzene gave the ketal (**2**) in 36% yield. Ester exchange proceeded gradually, and a 3 molar excess of (**1**) was employed in the ketalization. The *o*-hydroxymethylbenzyloxynaphthalene (**3**) was synthesized by the above aromatic ring formation sequences using t-butyl acetoacetate dianion (Scheme 3). Although the polyketide intermediate can adopt another conformation which leads to an isomeric naphthalene, the present structure (**3**) was confirmed by conversion into the natural product.

Three hydroxy groups of (**4**) were acetylated (Ac_2O, Et_3N; CH_2Cl_2, 0 °C, 2 h), and the 7-phenolic protecting group was removed by hydrogenation (Pd–C, HCO_2H–methanol; room temp., overnight) to give the naphthol (**6**) (mp 164.5–5.0 °C). The di-t-butyl ester (**6**) was converted into the dimethyl ester (**7**) (mp 132.5–3.5 °C) by ester exchange [(a) TFA; CH_2Cl_2, room temp., overnight. (b) CH_2N_2; ether–CH_2Cl_2, 0 °C, 1 h] which was accompanied by methylation at the 7-phenolic hydroxy group. Here, the differentiation of the 7-hydroxy group from the 9- and 10-hydroxy groups was accomplished, after which one-carbon homologation at the aliphatic carboxylate was achieved. After the removal of two acetyl groups (K_2CO_3; MeOH, room temp., 30 min) the naphthalenediol (**8**) (mp 162.0–2.5 °C) was treated with lithiated t-butyl acetate in THF at −78 °C to 0 °C, and the keto ester (**9**) (mp 155.5–156.0 °C) was obtained in high yield. The Claisen condensation took place selectively at the aliphatic ester.[6] Removal of the t-butyl ester (TFA; CH_2Cl_2, room temp., overnight) and decarboxylation (THF, reflux, 30 min) gave the methyl ketone (**10**) (mp 165.0–5.5 °C). Finally, reduction ($NaBH_4$; ethanol, −78 °C, 1 h) gave semivioxanthin



Scheme 3.



Scheme 4.

(**11**), whose ^{1}H NMR, IR, and UV spectra, agreed with reported values[1] (Scheme 4).*

* Detailed experimental procedures for the preparation of compounds (**2**), (**4**), (**5**), (**6**), (**7**), (**8**), (**9**), (**10**), and (**11**) together with their spectral data are available as a Supplementary publication [SUP No. 56774 (5 pp.)]. Details of the Supplementary publications scheme are given in 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1.

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4 The methodology was originally developed by Harris employing acetylactone dianion: (*a*) T. M. Harris, A. D. Webb, C. M. Harris, P. J. Wittek, and T. P. Murray, *J. Am. Chem. Soc.*, 1976, **98**, 6065; (*b*) A. D. Webb and T. M. Harris, *Tetrahedron Lett.*, 1977, 2069. The use of acetoacetate dianion was reported recently: (*c*) S. Mahalingam, P. C. Kuzuma, J. Y.-C. Lee, and T. M. Harris, *J. Am. Chem. Soc.*, 1985, **107**, 7760; (*d*) S. G. Gilbreath, C. M. Harris, and T. M. Harris, *J. Am. Chem. Soc.*, 1988, **110**, 6172; (*e*) T. M. Harris, C. M. Harris, T. A. Oster, L. E. Brown, Jr., J. Y.-C. Lee, *J. Am. Chem. Soc.*, 1988, **110**, 6180; (*f*) T. M. Harris, C. M. Harris, P. C. Kuzuma, J. Y.-C. Lee, S. Mahalingam, and S. G. Gilbreath, *J. Am. Chem. Soc.*, 1988, **110**, 6186.
5 The protecting group was recently employed in the synthesis of glycinoeclepin A: H. Watanabe and K. Mori, *Tennenyukikagoubutsu Toronkai*, 1988, **30**, 447. The ketalization reaction of *o*-phenylenedimethanol is known. For example, J. G. Smith and G. Kruger, *J. Org. Chem.*, 1985, **50**, 5759.
6 This selective Claisen condensation was found in our laboratory during the synthesis of aromatic antibiotics, and further details will be reported in due course. Also see ref. 4*d*.

Paper 9/03955D
Received 29*th June* 1989
Accepted 18*th September* 1989