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A Facile Synthesis of Mellein

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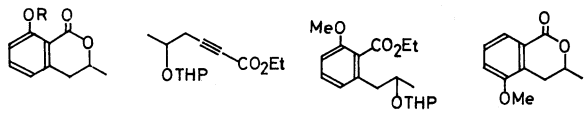
The application of the Diels-Alder reaction to the preparation of 2,3-disubstituted phenols[1] from 1-methoxycyclohexa-1,4-diene and suitable dienophiles has now been extended to the synthesis of mellein (**1a**),[2] which had been isolated from the culture broth of *Aspergillus mellus*. In this paper we report a four-step synthesis of **1a**.

4-(2-Tetrahydropyranyloxy)pent-1-yne[3] was treated with *n*-butyllithium and ethyl chloroformate to give an ethyl ester (**2**). Heating the mixture of **2** and 1-methoxycyclohexa-1,4-diene in a sealed tube at 180 °C for 22 hr gave an aromatic ester (**3**; 73%), which, on base hydrolysis and acid treatment, gave (±)-mellein methyl ether (**1b**), [mp 67—68 °C], in 87% yield. Treatment of **1b** with boron tribromide gave (±)-mellein **1a**, [mp 38—38.5 °C], in 85% yield, which was identical in all respects (IR and NMR) with the authentic sample.[2]



(1a) R=H (1b) R=Me (2) (3) (4)

The minor product of the Diels-Alder reaction, after hydrolysis and acid treatment, was proved to be **4** from physical data.

Birch and Dastur found that dichloromaleic anhydride catalyzes the conversion of 1-methoxycyclohexa-1,4-diene into 1-methoxycyclohexa-1,3-diene.[4]

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4) A. J. Birch and K. P. Dastur, *Tetrahedron Lett.*, **1972**, 4195.

Hoping the improvement of the yield, we have applied this reagent to the Diels-Alder reaction. Heating the mixture of 1-methoxycyclohexa-1,4-diene, **2** and dichloromaleic anhydride gave **1b** in one step in 48% yield.

Experimental

Ethyl 5-(2-Tetrahydropyranyloxy)-2-hexynoate (2). To a solution of 4-(2-tetrahydropyranyloxy)pent-1-yne (16.8 g) in 50 ml of abs. ether was added an ethereal solution of *n*-butyllithium (prepared from 17.13 g of *n*-butyl bromide and 2.15 g of lithium in 100 ml of abs. ether) at −70 °C in 15 min under argon atmosphere and the mixture was stirred for 15 min at this temperature. The mixture was gradually allowed to warm to −10 °C during 5 hr, then poured into ice-water and extracted with ether. The solvent was removed and the residue was distilled under reduced pressure to give **2** (14.5 g, 60%), bp. 112—112.5 °C/0.15 mmHg. ν_{max} (liquid film) 2240, 1715, and 1250 cm^{-1}.

The Ester (3). (a) A mixture of 2.4 g of 1-methoxycyclohexadienes (1,3- and 1,4- 1:3), 2.4 g of **2** and 30 mg of *N*-phenyl-2-naphthylamine was heated at 180 °C for 22 hr in a sealed tube. The crude product was distilled under reduced pressure to give 0.54 g of the recovered ester (**2**) and 2.26 g (73%) of the ester (**3**), bp 125—127 °C/0.07 mmHg. ν_{max} (liquid film) 1730, 1600, 1585, and 1470 cm^{-1}. (b) A mixture of 10 g of 1-methoxycyclohexadienes, 13.8 g of **2**, 10 mg of dichloromaleic anhydride, and 100 mg of *N*-phenyl-2-naphthylamine was heated at 180 °C for 20 hr in a sealed ube. Fractional distillation under reduced pressure gave (±)-mellein methyl ether (**1b**) bp 112—113 °C/0.03 mmHg (5.2 g, 48%), which was recrystallized from ether–light petroleum to give colorless prisms, mp 67—68 °C (lit,[2] mp 66—67 °C).

(±)-Mellein Methyl Ether (1b). The ester (**3**; 3.27 g) was dissolved in 10 ml of 0.5 M methanolic sodium hydroxide solution and the solution was allowed to stand at room temperature for 48 hr. The mixture was acidified with 40 ml of 2 M hydrochloric acid and refluxed for 30 min. After removal of the organic solvent, the aqueous phase was extracted with chloroform. Evaporation of the extract gave an oil (2.64 g) which was chromatographed on silica gel. Elution with benzene–AcOEt (9:1) gave **4** as colorless prisms, mp 85—86 °C (from $CHCl_3$–ether), (0.27 g, 13%). ν_{max} ($CHCl_3$) 1715, 1600, and 1590 cm^{-1}, δ ($CDCl_3$) 1.50 (d, 3H, *J* 5 Hz), 2.62 (dd, 1H, *J* 11, 17 Hz), 3.14 (dd, 1H, *J* 4, 17 Hz), 3.84 (s, 3H), 5.40 (m, 1H), 7.05 (dd, 1H, *J* 2, 8 Hz), 7.32 (t, 1H, *J* 8 Hz), and 7.70 (dd, 1H, *J* 1.5, 8 Hz). Found: C, 68.69; H, 6.31%. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29%.

Further elution with the same solvent mixture gave (±)-mellein methyl ether (**1b**), mp 67—68 °C, colorless prisms (from ether–light petroleum), (1.69 g; 87%).

(±)-Mellein (1a). To a cooled soln of BBr_3 (0.4 ml) in 10 ml of dry CH_2Cl_2 was added a soln of **1b** (192 mg) in 8 ml of dry CH_2Cl_2 (−70°) under atmosphere of argon. The mixture was gradually allowed to warm up to room temperature and kept overnight. The mixture was poured into ice-water and extracted with $CHCl_3$. Removal of the solvent gave (±)-mellein (**1a**) as crystals (151 mg, 85%), which was recrystallized from *n*-hexane to give colorless prisms, mp 38—38.5 °C (lit,[2] mp 37—38 °C). The IR and NMR spectra are identical with that of the published data.[2]