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SYNTHESIS OF (±)-DIMETHYL CURVULARIN BASED ON THE PALLADIUM-CATALYZED CARBONYLATION OF 3,5-DIMETHOXYBENZYL CHLORIDE USING A BUTADIENE TELOMER AS A BUILDING BLOCK

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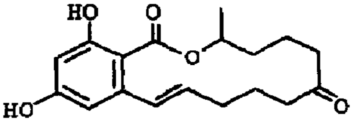
Summary: Palladium-catalyzed carbonylation of 3,5-dimethoxybenzyl chloride (13) with benzyl 7-hydroxyoctanoate (12) afforded benzyl 7-(3,5-dimethoxyphenylacetoxy)octanoate (6) in 70% yield, which is the precursor of Curvularin (4). The ester (12) was easily prepared from the butadiene telomer obtained by the palladium-catalyzed reaction of butadiene with acetic acid.

A number of naturally occurring orsellinic acid (2,4-dihydroxy-6-methylbenzoic acid) type macrolides such as Zearalenone (1),1) Lasiodiplodin (2),2) and Monorden (3)3) are known. Curvularin (4),4) a metabolite of various curvularia species, has the structure related to the above macrolides. In an earlier synthesis of Curvularin,5,6) two cyclization methods for the 12-membered lactone have been attempted.5) One was the common method of intramolecular esterification and the other was the intramolecular acylation (Scheme - 1). However, several attempts to cyclize the seco acid or seco ester 5 by various methods were unsuccessful. So far the intramolecular acylation of the ester 6 to Curvularin (4) was the only acceptable method.6) In this paper we wish to report the improved synthesis of the valuable ester 6 by applying palladium-catalyzed carbonylation.



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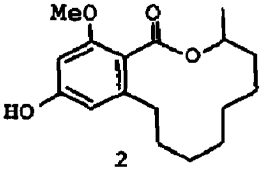

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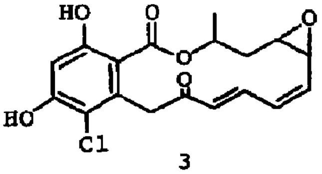

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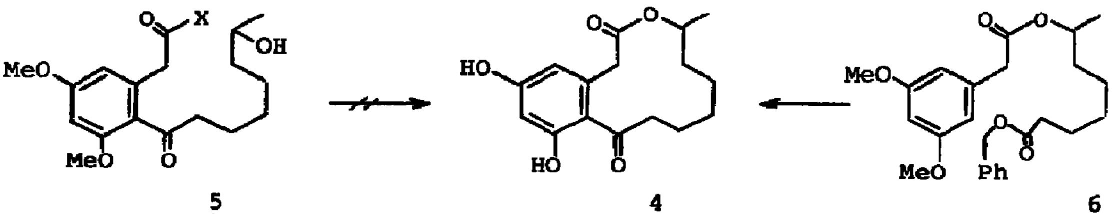
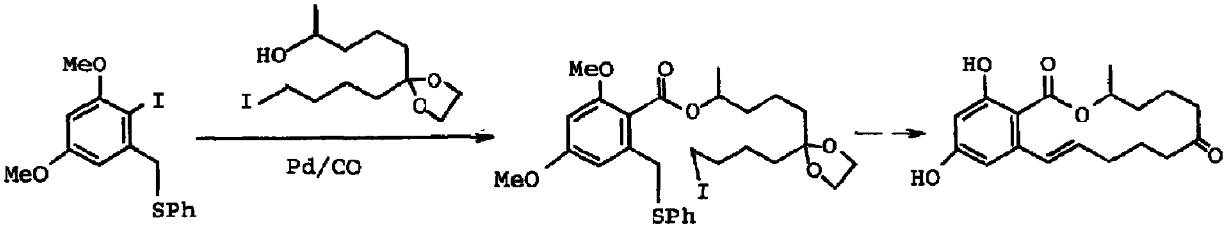


Scheme - 1

The palladium-catalyzed carbonylation of aryl and alkenyl iodides and bromides in alcohol or amine gives esters or amides.[7)] As an application of this reaction to the synthesis of Zearalenone (1), we have recently introduced a simple preparative method of the ester **7**,[8)] which was smoothly cyclized by intramolecular alkylation.[9)] The subsequent oxidative removal of phenylthio group from the cyclized product afforded Zearalenone (**1**) (Scheme - 2).



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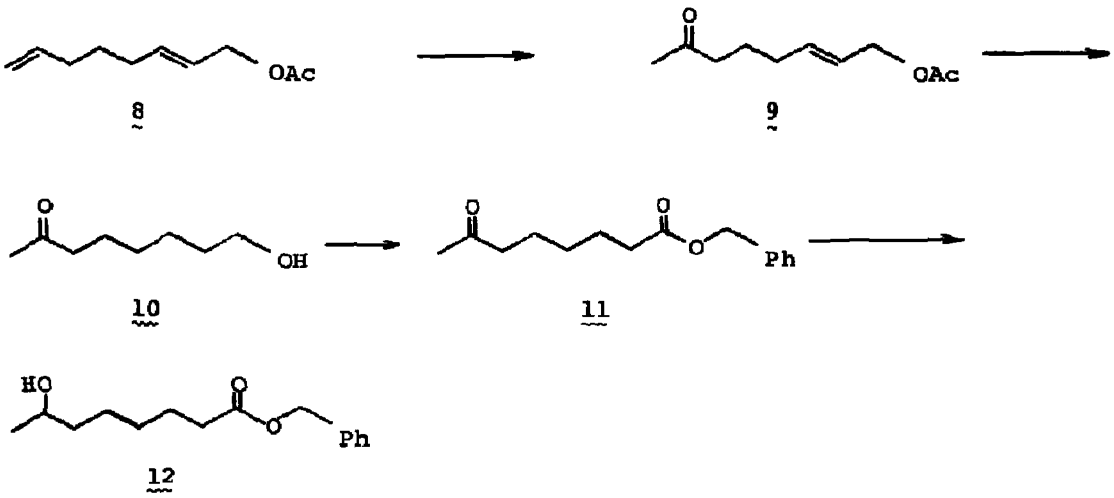
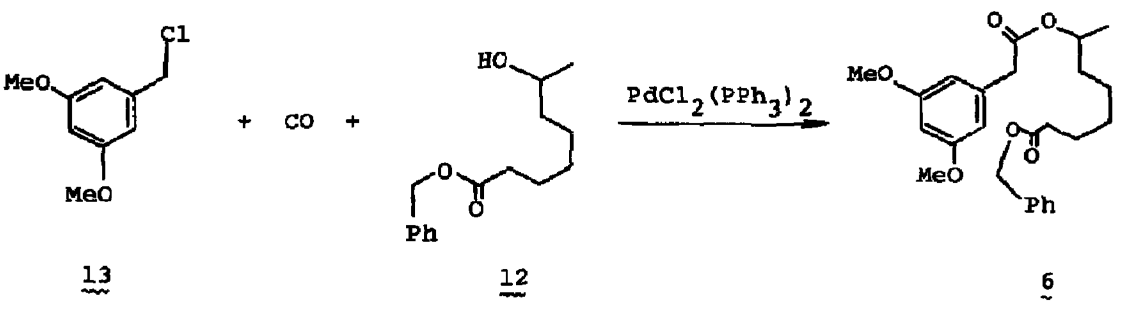
Scheme - 2

We now wish to report the application of this efficient palladium-catalyzed carbonylation to prepare benzyl 7-(3,5-dimethoxyphenylacetoxy)octanoate (**6**) as a precursor of Curvularin. In addition, we found that the telomer **8**,[10)] easily prepared by the palladium catalyzed telomerization of butadiene with acetic acid, is an extremely useful building block of carbon chain of **4**. The synthesis of benzyl 7-hydroxyoctanoate (**12**) was carried out by the following sequence of reactions. The terminal olefin of the telomer **8** was oxidized with $PdCl_2/CuCl/O_2$[11)] in aqueous DMF to give methyl ketone **9** in 90% yield: NMR (CCl_4) δ 1.93 (s, 3H, CH_3CO_2), 2.01 (s, 3H, CH_3CO), 2.32 (t, J = 7.2 Hz, 2H, CH_2CO), 4.18-4.28 (d, J = 6.0 Hz, 2H, CH_2OAc), 5.29-5.70 (m, 2H, olefinic); IR (film) 1740 and 1720 cm^{-1}. The hydrolysis of acetate in aqueous KOH, followed by hydrogenation (Pd/C, H_2 in EtOH) of olefin gave the alcohol **10** in 85% yield; NMR (CCl_4) δ 2.07 (s, 3H, CH_3CO), 2.38 (t, J = 6 Hz, 2H, CH_2CO), 3.23 (bs, 1H, OH), 3.50 (t, J = 6 Hz, 2H, CH_2-O); IR (film) 3400 and 1710 cm^{-1}. Jones oxidation of the primary alcohol and subsequent esterification of the resulting carboxylic acid with benzyl bromide in the presence of NaH in HMPA at 0°C gave the ester **11** in 80% overall yield: NMR (CCl_4) δ 2.00 (s, 3H, CH_3CO), 2.00-2.48 (m, 4H, CH_2CO), 4.99 (s, 2H, CH_2Ph), 7.24 (s, 5H, Ph); IR (film) 1710 and 1735 cm^{-1}. The ketone was reduced with $NaBH_4$ in ethanol to give the alcohol **12** in 90% yield: NMR (CCl_4) δ 1.12 (d, J = 7.0 Hz, 3H, $C\underline{H}_3$-CH), 1.20-1.83 (m, 8H, CH_2), 2.09-2.54 (m, 2H, CH_2CO), 3.62-3.80 (m, 1H, $C\underline{H}COH$), 5.07 (s, 2H, CH_2Ph), 7.32 (s, 5H, Ph); IR (film) 3550 and 1735 cm^{-1}.



3,5-Dimethoxybenzyl chloride (13) was prepared from 3,5-dihydroxybenzoic acid in four steps (esterification of acid with CH_2N_2, methylation of phenol with CH_3I/K_2CO_3, reduction of ester with LAH and chlorination of benzyl alcohol with CCl_4/PPh_3). Carbonylation of the benzyl chloride 13 was carried out in the following way. A mixture of the benzyl chloride 13 (0.40 mmol), the alcohol 12 (1.34 mmol), NaOAc (0.50 mmol) and $PdCl_2(PPh_3)_2$ (0.04 mmol) in dry benzene (5 ml) was stirred at 100°C in an autoclave under carbon monoxide (10 atm) for 36 h. The reaction mixture was filtered and the ester 6 was isolated in 70% yield: NMR (CCl_4) δ 1.19 (d, J = 7 Hz, 3H, $\underline{CH_3}$-CH), 1.05-1.80 (m, 8H, CH_2), 1.93-2.39 (m, 2H, CH_2CO), 3.37 (s, 2H, $PhCH_2CO$), 3.69 (s, 6H, OMe), 4.5-5.0 (m, 1H, -$\underline{C}$HOCO-), 5.00 (s, 2H, OCH_2Ph), 6.12-6.41 (m, 3H, aromatic), 7.22 (s, 5H, Ph); IR (film) 1730 cm^{-1}. The conversion of the ester 6 to Curvularin (4) is a known process.[5)]



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