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SIMPLE SYNTHESIS OF DIPLODIALIDES FROM A BUTADIENE TELOMER

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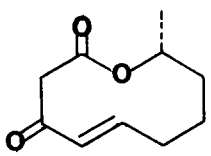
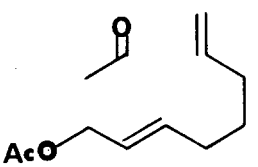
In this communication we wish to report simple syntheses of diplodialides A (1) and B (2), naturally occurring ten-membered lactones which were isolated from the culture filtrate of *Diplodia pinea* by Ishida and Wada[1] and show unique biological activity. A butadiene telomer 3 easily available by palladium catalyzed reaction is a starting material and the method is based on the two carbon elongation and lactone formation using modified intramolecular Reformatsky reaction. In our continuous effort to apply palladium catalyzed reactions to simple syntheses of natural products, we have synthesized a number of natural products such as civetone[2] and recifeiolide.[3] In the present synthesis of diplodialides, two important palladium catalyzed reactions, namely oxidation of terminal olefins to methyl ketones and telomerization of butadiene, were utilized. 8-Acetoxy-1,6-octadiene (3), which is easily prepared by the palladium catalyzed telomerization of butadiene with acetic acid,[4] is the starting material. As shown in scheme I, comparison of the structures of 1 and 2 with that of 3 clearly indicates that the functionality of 3 is very suitable for the construction of the unsaturated lactone skeleton. The double bond at C_6 in 3 has the required trans configuration and is located at the right position. Also there exists the appropriate oxygen function.

Scheme I



1



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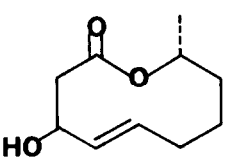

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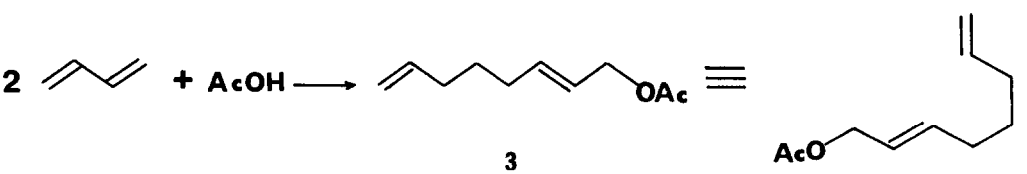
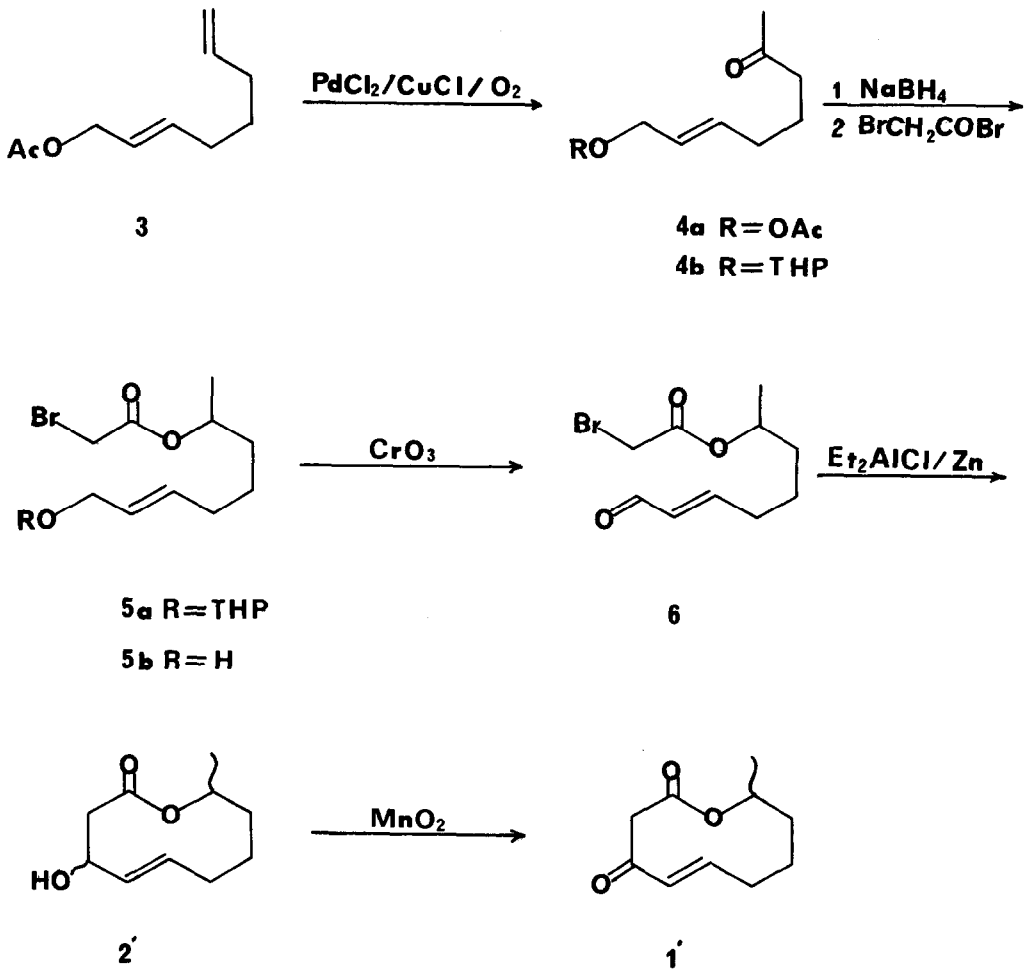


3

Diplodialide A was synthesized by Ishida and Wada.[5] Their method involved the γ-selenenylation of a saturated keto lactone, followed by selenoxide elimination. Also diplodialide C (dihydrodiplodialide B) was prepared by Wakamatsu, Akasaka, and Ban by ring expansion.[6] In comparison, our method is simple because it utilizes the unique starting material with very suitable functionality. The synthesis was carried out by the sequence of reactions outlined in scheme II.

Scheme II



The telomerization of butadiene with acetic acid catalyzed by $Pd(OAc)_2$ and PPh_3 produced 8-acetoxy-1,6-octadiene (3) as a main product, accompanied by 3-acetoxy-1,7-octadiene. The former was isolated by fractional distillation at 106°/24 Torr. The selective oxidation of the terminal double bond of 3 (16.8 g, 0.1 mol) was carried out in aqueous DMF at 25° with $PdCl_2$ (1.77 g, 10 mmol) and CuCl (9.9 g, 0.1 mol) by shaking under oxygen atmosphere. The keto acetate 4a was isolated in 77% yield (14.2 g), bp 87°/3 Torr; IR (film), 1740, 1715, 1670, and 975 cm^{-1}, ^1H NMR (CCl_4) δ 1.30-1.90 (m, 2H, CH_2), 1.95 (s, 3H, $OCOCH_3$), 2.04 (s, 3H, $COCH_3$), 1.90-2.20 (m, 2H, $CH_2C=C$), 2.35 (t, 2H, CH_2CO), 4.40 (d, 2H, CH_2O), and 5.20-5.80 (m, 2H, CH=CH). The acetoxy group was hydrolyzed and the alcohol was reprotected as THP ether to give 4b. The methyl ketone was reduced to secondary alcohol with $NaBH_4$. The reaction of this alcohol with bromoacetyl bromide produced bromo ester 5a and the protecting group was removed with 50% aqueous acetic acid to give 5b in 76% yield from 4b; IR (film), 3375, 1738, and 975 cm^{-1}; ^1H NMR (CCl_4) δ 1.25 (d, 3H, J = 6 Hz, CH_3), 1.30-1.80 (m, 4H, CH_2), 1.80-2.30 (m, 2H, $CH_2C=C$), 3.00 (broad s, 1H, OH), 3.70 (s, 2H, CH_2CO), 3.92 (d, 2H, CH_2O), 4.60-5.00 (m, 1H, CH-O), and 5.20-5.90 (m, 2H, CH=CH). The oxidation of the alcohol 5b with pyridinium chlorochromate in dichloromethane[7] at 20° for 1 hr gave the desired α,β-unsaturated aldehyde 6 in 60% yield; IR (film), 2750, 1755, 1695, and 1640 cm^{-1}; ^1H NMR (CCl_4) δ 1.20 (d, 3H, J = 6 Hz, CH_3), 1.40-1.80 (m, 4H, CH_2), 2.00-2.60 (m, 2H, $CH_2C=C$), 3.70 (s, 2H, CH_2CO), 4.60-5.20 (m, 1H, CH-O), 5.90 (dd, 1H, J = 7 Hz and 15 Hz, C=CHCO), 6.64 (dt, 1H, J = 6Hz and 15 Hz, CH=CCO), and 9.27 (d, 1H, J = 7Hz, CHO).

The final step of the synthesis is the cyclization. For this step, modified intramolecular Reformatsky reaction was used. A novel method of cross aldol condensation of α-halo ketones with a variety of carbonyl compounds promoted by Et_2AlCl and zinc has recently been reported,[8] and we found that this method is very suitable for our cyclization. Activated zinc powder (7.61 g) and Et_2AlCl (4.66 mmol) were mixed in THF (10 ml) and the mixture was stirred at 55° (oil bath) for 30 min. The aldehyde 6 (610 mg, 2.33 mmol) dissolved in THF (80 ml) was added over a period of 20 hr by using a mechanically driven syringe at 55° (oil bath). After the usual work-up, (±)diplodialide B (2') was isolated as a mixture of diastereomers in 45% yield after column chromatographic purification. In this Reformatsky type cyclization reaction, no product of 1,4-addition to the α,β-unsaturated carbonyl system was obtained and the reaction was selective 1,2-addition. The structure of 2' thus obtained was confirmed by mass spectrum m/e 184 (M^+) and 166 (M^+-18), elemental analysis, NMR and IR spectra. Anal. Found: C, 64.91; H, 8.82. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75; mol wt 184. IR (film), 3410, 1725, 1710 (shoulder), 1440, 1360, 1320, 1290, 1240, 1195, 1161, 1140, 1120, 1070, 1040, 1020, and 970 cm^{-1}; ^1H NMR (CCl_4) δ 1.15 (d, 3H, J = 5.6 Hz, CH_3), 1.30-2.05 (m, 4H, CH_2), 2.05-2.40 (m, 2H, $CH_2C=C$), 2.30 (dd, 1H, J = 8.7 Hz and 8.7 Hz, CH_2CO), 2.65 (dd, 1H, J = 5 Hz and

8.7 Hz, CH_2CO), 3.68 (broad s, 1H, OH), 4.20-4.55 (m, 1H, CHOH), 4.55-5.00 (m, 1H, CH-O), and 5.15-5.75 (m, 2H, CH=CH).

Conversion of diplodialide B to A has been carried out by Wada.[1] Similarly, we oxidized 2' with MnO_2 in dichloromethane to give (±)diplodialide A (1'). Its structure was fully confirmed by spectral data. IR (film), 1740, 1260, 1190, 1065, and 962 cm^{-1}; ^1H NMR (CCl_4) δ 1.23 (d, 3H, J = 6.5 Hz, CH_3), 1.30-2.50 (m, 6H, CH_2), 3.35 (dd, 2H, J = 15 Hz, $COCH_2CO$), 4.90-5.20 (m, 1H, CH-O), 5.68 (d, 1H, J = 16 Hz, C=CHCO), and 6.30-6.80 (m, 1H, CH=CCO), ms (m/e) 182 (M^+). Calcd. mol wt 182.

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