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A CONVENIENT SYNTHESIS OF THE ANTIBIOTIC BOTRYODIPLODIN

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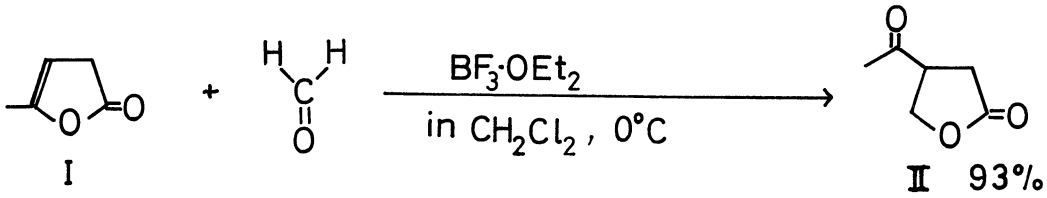
It was established that the antibiotic and anti-leukemic agent botryodiplodin (VIIIa) is synthesized in good yield from cis-α-methyl β-acetyl-γ-butyrolactone, produced by the reaction of α-methyl-α-angelicalactone with formaldehyde.

In the preceding paper, it was shown that γ-substituted-β-acetyl-γ-butyrolactones were obtained in good yields by the reaction of α-angelicalactone with various aldehydes activated by $BF_3 \cdot O(C_2H_5)_2$[1]. In the present experiment, it was established that β-acetyl-γ-butyrolactone (II) was obtained in 93% yield by the reaction of α-angelicalactone (I) with formaldehyde in CH_2Cl_2 at 0°C in the presence of $BF_3 \cdot O(C_2H_5)_2$. (Figure 1)



I II 93%

Figure 1

In a similar fashion, the reaction of α-methyl-α-angelicalactone (III) with formaldehyde in CH_2Cl_2 at 0°C in the presence of $BF_3 \cdot O(C_2H_5)_2$, followed by quenching with $NaHCO_3$-saturated aqueous solution, resulted in the formation of corresponding α-methyl-β-acetyl-γ-butyrolactone (V) in 92% yield by column chromatography. [cis-product Va : trans-product Vb=85 : 15, Va: mp: 68°~69°C, IR(KBr), 1705cm^{-1} (CH_3-C=O), 1770cm^{-1}(lactone C=O), NMR($CDCl_3$, 60 MHz), δ1.16(3H, d, -CH_3), δ2.20(3H, s, CH_3-C=O), δ2.93(1H, qiun, H^D), δ3.67(1H, qiun, H^C), δ4.60~4.13(2H, m, H^A, H^B), Vb: bp: 92°~93°C/2 mmHg, IR(NaCl): 1715cm^{-1}(CH_3C=O), 1780cm^{-1}(lactone C=O), NMR($CDCl_3$, 60 MHz), δ1.35(3H, d, -CH_3), δ2.25(3H, s, CH_3-C=O), δ3.50~2.65(2H, m,

H^C, H^D), δ4.67~4.03(2H, quin, H^A, H^B)].

The present lactone synthesis was successfully applied to the synthesis of the antibiotic and anti-leukemic agent botryodiplodin (VIIIa), recently synthesized by McCurry and Abe according to two routes starting from the enol ether of acetoacetic ester and 3,5-dimethyl-4-carbethoxycyclohex-2-en-1-one respectively[2), 3)].

The synthetic conversions of the present method are outlined in Figure 2.

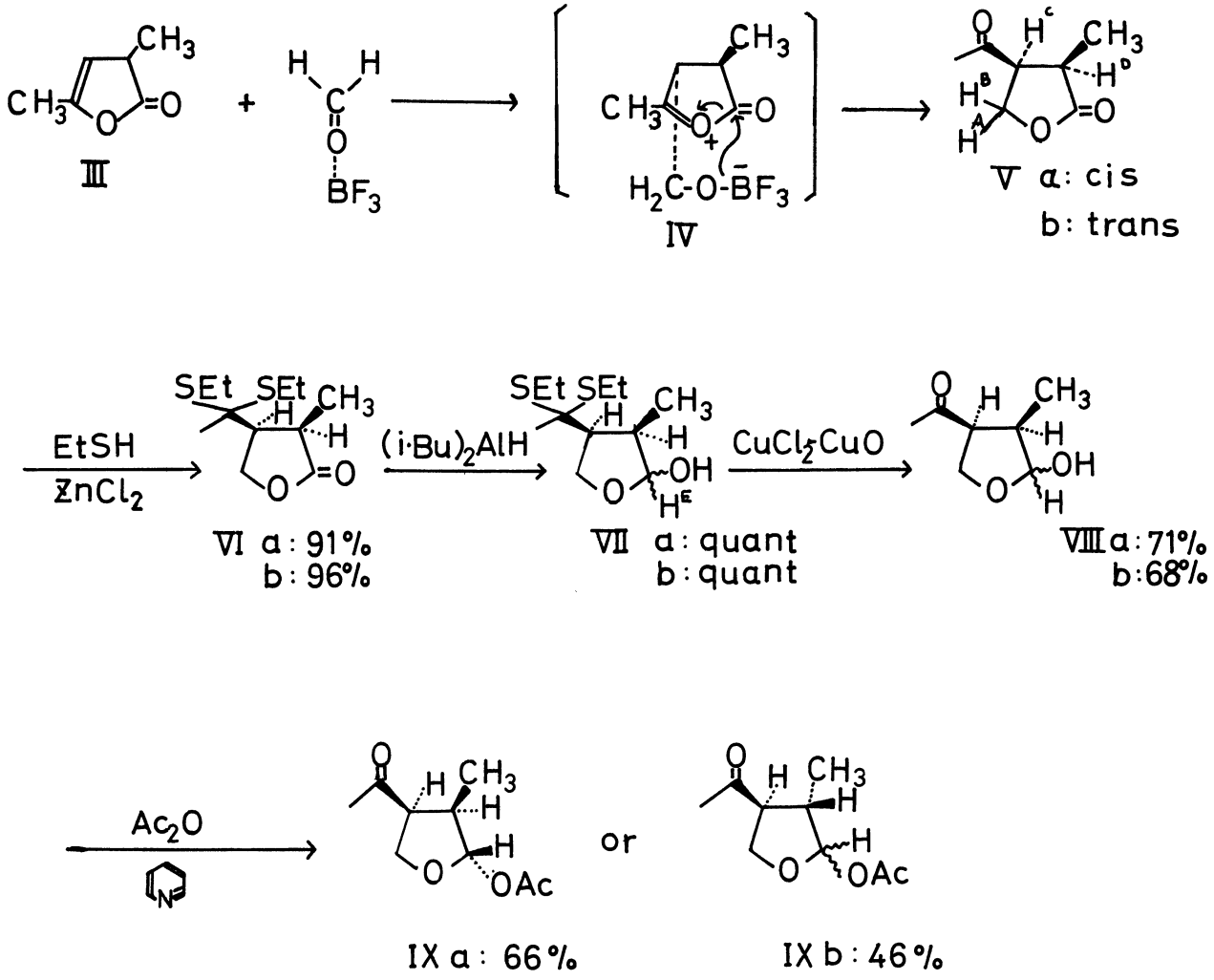


Figure 2

The preferential formation of cis isomer may be explained by assuming an initial formation of aldehyde-$BF_3 \cdot O(C_2H_5)_2$ complex, which in turn is attacked by III from the opposite side of methyl group of the lactone III to give an additional intermediate (IV). This intermediate IV immediately cyclizes to give cis-product i.e., Va.

Thus, the stereoselectivity was observed in the present reaction.

The reduction of the carbonyl group of the lactone Va was tried by the following procedure; when Va was allowed to react with EtSH (used as solvent) in the presence of $ZnCl_2$ at 0°C, the corresponding VIa was obtained 91% yield. Similarly, the trans isomer Vb was converted to the compound VIb in 96% yield.

Reduction of VIa and VIb with equimolar amount of $(i\text{-}Bu)_2AlH$ in toluene at -78°C affored VIIa and VIIb in almost quantitative yields.

The treatment of VIIa with 2 equiv of $CuCl_2$ and 4 equiv of CuO in aqueous acetone at room temperature gave VIIIa in 71% yield based on VIa by preparative thin layer chromatography[4]. [VIIIa: anomeric mixture, IR(NaCl), 1715cm^{-1}(C=O), 3400cm^{-1}(-OH), NMR(CCl_4, 60 MHz), δ 0.80, 1.00(3H, Ca, 2.6H : 0.4H, d, $-CH_3$), δ 2.17, 2.27(3H, Ca, 2.6H : 0.4H, s, CH_3-C=O), δ 2.50(1H, q, H^D), δ 4.20~3.50(3H, m, H^A, H^B, H^C), δ 4.60(1H, s, -OH), δ 5.07(1H, s, H^E)].

The corresponding trans isomer VIIIb was obtained in 68% yield based on VIb. [VIIIb: anomeric mixture, IR(NaCl), 1715cm^{-1}(C=O), 3400cm^{-1}(-OH), NMR(CCl_4, 60 MHz), δ 1.05(3H, m, $-CH_3$), δ 2.10, 2.17(3H, Ca, 2.6H : 0.4H, s, CH_3-C=O), δ 3.20~2.30(2H, m, H^C, H^D), δ 4.30~3.60(3H, m, H^A, H^B, -OH), δ 5.10(1H, m, H^E)].

Acetylation of VIIIa and VIIIb (Ac_2O/pyridine) produced the acetate IXa and IXb in 66% and 46% yields, respectively. Satisfactory IR and NMR data were obtained for IXa and IXb. [IXa : IR(NaCl), 1715cm^{-1}(CH_3-C=O), 1740cm^{-1}(CH_3-COO-), NMR(CCl_4, 60 MHz), δ 0.90(3H, d, $-CH_3$), δ 2.00(3H, s, CH_3COO-), δ 2.20(3H, s, CH_3-C=O), δ 2.67(1H, q, H^D), δ 4.37~3.45(3H, m, H^A, H^B, H^C), δ 5.90(1H, s, H^E). IXb : anomeric mixture, IR(NaCl), 1715cm^{-1}(CH_3-C=O), 1740cm^{-1}(CH_3-COO-), NMR(CCl_4, 60 MHz), δ 1.03, 1.17(3H, d, $-CH_3$), δ 1.97, 2.00(3H, s, CH_3-COO-), δ 2.13(3H, s, CH_3-C=O), δ 3.10~2.50(2H, m, H^C, H^D), δ 4.20~3.90(2H, m, H^A, H^B), δ 5.78, 6.17(1H, d, H^E), Chemical Shifts of IXa and IXb were in agreement with those of the literature[2)3)]].

We have therefore shown a convenient method for the synthesis of the antibiotic and anti-leukemic agent botryodiplodin. The synthesis of analogues of the antibiotic botryodiplodin is now in progress.

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