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NEW SYNTHETIC METHOD FOR ORSELLIC ACID TYPE MACROLIDES BY INTRAMOLECULAR ALKYLATION OF PROTECTED CYANOHYDRIN. THE SYNTHESIS OF (±)-ZEARALENONE.

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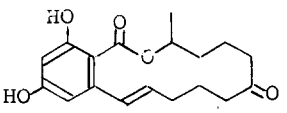
Summary: Zearalenone was synthesized by a general cyclization method of orsellic acid type macrolides having ketone moiety using the intramolecular alkylation of the protected cyanohydrin. This alkylation tolerates the presence of ester group and requires short reaction time.

A number of naturally occurring orsellinic acid (2,4-dihydroxy-6-methylbenzoic acid) type macrolides such as zearalenone (1),[1] monorden (2),[2] and hypothemycin (3)[3] are known. They have both ketone and lactone moieties. The most widely used cyclization method for these macrolides is intramolecular esterification of ω-hydroxy acids.[4] Recently developed another approach to the cyclization by intramolecular carbon-carbon bond formation has been attracting attention.[5] We have introduced three types of macrocarbocycle formation based on carbon-carbon bond formation. The first one is the intramolecular alkylation of ω-haloalkyl 2-phenylthiomethyl-4,6-dimethoxybenzoate, and the method was successfully applied to the syntheses of zearalenone[6] and lasiodiplodin.[7] The second one is the intramolecular alkylation of ω-haloalkyl phenylthioacetates as a general construction method for α,β-unsaturated lactones.[8] The third one is the intramolecular alkylation of protected cyanohydrins for macrocyclic ketones.[9]



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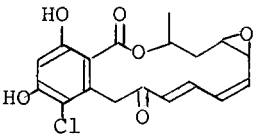

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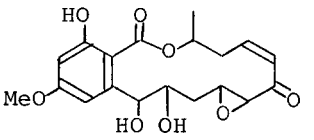

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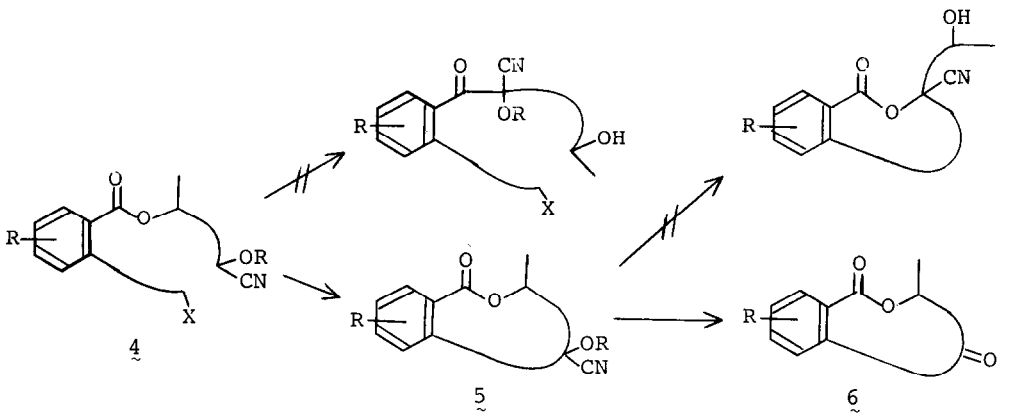
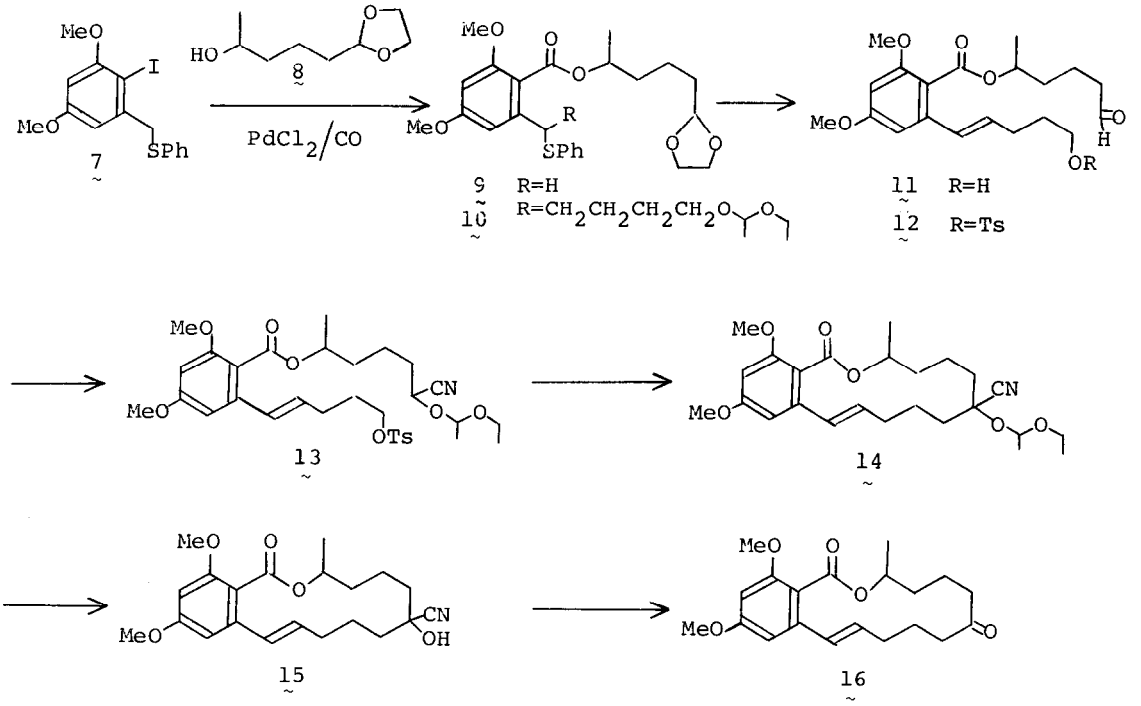
In this paper we wish to report the general cyclization method for orsellic acid type keto lactones based on the intramolecular alkylation of the protected cyanohydrin 4 as shown by Scheme 1. The cyclized product 5 can be converted to the ketone 6 by mild treatments with an acid and a base. This cyclization method has several characteristic features. In this reaction, the acyl carbanion of the

protected cyanohydrin[10] selectively attacks the halide and not the ester group. The cyclized product has no acidic protons and is quite stable in a base. Regeneration of the ketone from the protected cyanohydrin 5 can be carried out without the internal translactonization[11] or aldol condensation under either acidic or basic conditions. Thus the following overall transformation is very suitable for the construction of the keto macrolides.



This methodology was successfully applied to the synthesis of (±)-zearalenone (1) by the following sequence of reactions (Scheme 2). The introduction of two chains into the aromatic compound 7 to afford the key precursor 12 was carried out by applying the methods previously developed in this laboratory. Palladium-catalyzed carbonylation[12] [$PdCl_2$ (0.04 mmol), Et_3N (0.5 mL), and CO (14 atm) in benzene at 100°C for 13 h] of 1-iodo-2-phenylthiomethyl-4,6-dimethoxybenzene (7) (0.39 mmol) with 2 equiv. of the alcohol 8[13] gave the ester 9 in 70% yield: IR (film) 1710 cm^{-1}; NMR (CCl_4) δ 1.25 (d, J = 6.0 Hz, 3 H, CH_3), 3.58 (s, 3 H, OCH_3), 3.70 (bs, 7 H, OCH_3, $-OCH_2CH_2O-$), 4.00 (s, 2 H, CH_2SPh), 6.10 (d, J = 2 Hz, 1 H, aromatic), 6.20 (d, J = 2 Hz, 1 H, aromatic), 7.05 (bs, 5 H, aromatic). Alkylation[6,7] (3 equiv. of potassium hexamethyldisilazane in THF at -78°C) of the ester 9 (0.897 mmol) with 1.4 equiv. of 1-ethoxyethyl 4-iodobutyl ether gave 10 in 90% yield. Oxidation of 10 with sodium periodate, subsequent reflux in toluene, and hydrolysis of the acetal group gave the aldehyde 11 in 75% overall yield: IR (film) 1715 cm^{-1}; NMR (CCl_4) δ 3.53 (t, J = 6 Hz, 2 H, CH_2O), 3.72 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 6.04-6.35 (m, 3 H, olefinic and aromatic), 6.48 (d, J = 2 Hz, 1 H, aromatic), 9.70 (bt, J = 2 Hz, 1 H, CHO). After tosylation (p-TsCl/pyridine, 70%) of the primary alcohol, the aldehyde 12 was converted into its cyanohydrin by addition of aqueous sodium bisulfite, followed by aqueous sodium cyanide at 0°C. Protection of the secondary alcohol of the resulting cyanohydrin with ethyl vinyl ether gave the protected cyanohydrin 13 in 90% overall yield: NMR (CCl_4) δ 4.03 (t, J = 6.0 Hz, 2 H, CH_2OTs), 4.20-4.67 (m, 1 H, OCHCN). The cyclization of 13 was carried out by the following way. The ester

13 (0.081 mmol) in THF (3 mL) was added slowly over 1.0 h at 45°C under a nitrogen atmosphere to sodium hexamethyldisilazane (0.41 mmol) in THF (8 mL). The reaction mixture was stirred for 30 min at 60°C and quenched. The cyclized product 14 was isolated in 85% yield after chromatography. Acid treatment (3N-HCl/THF, 0°C, 1 h) of the cyclized product 14 gave the cyanohydrin 15, which was dissolved in ether and washed vigorously for 5 min with 5% KOH in a separatory funnel. The dimethyl ether of zearalenone 16 was isolated in 90% yield, which showed the identical NMR spectra with those of an authentic sample prepared in this laboratory.[6]



Further application of this method to the syntheses of more complex macrolides is in progress.

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