

## SYNTHESIS OF DEHYDROXY-*trans*-RESORCYLIDE BY INTRAMOLECULAR ALKYLATION OF THE PROTECTED CYANOHYDRIN USING A BUTADIENE TELOMER AS A BUILDING BLOCK

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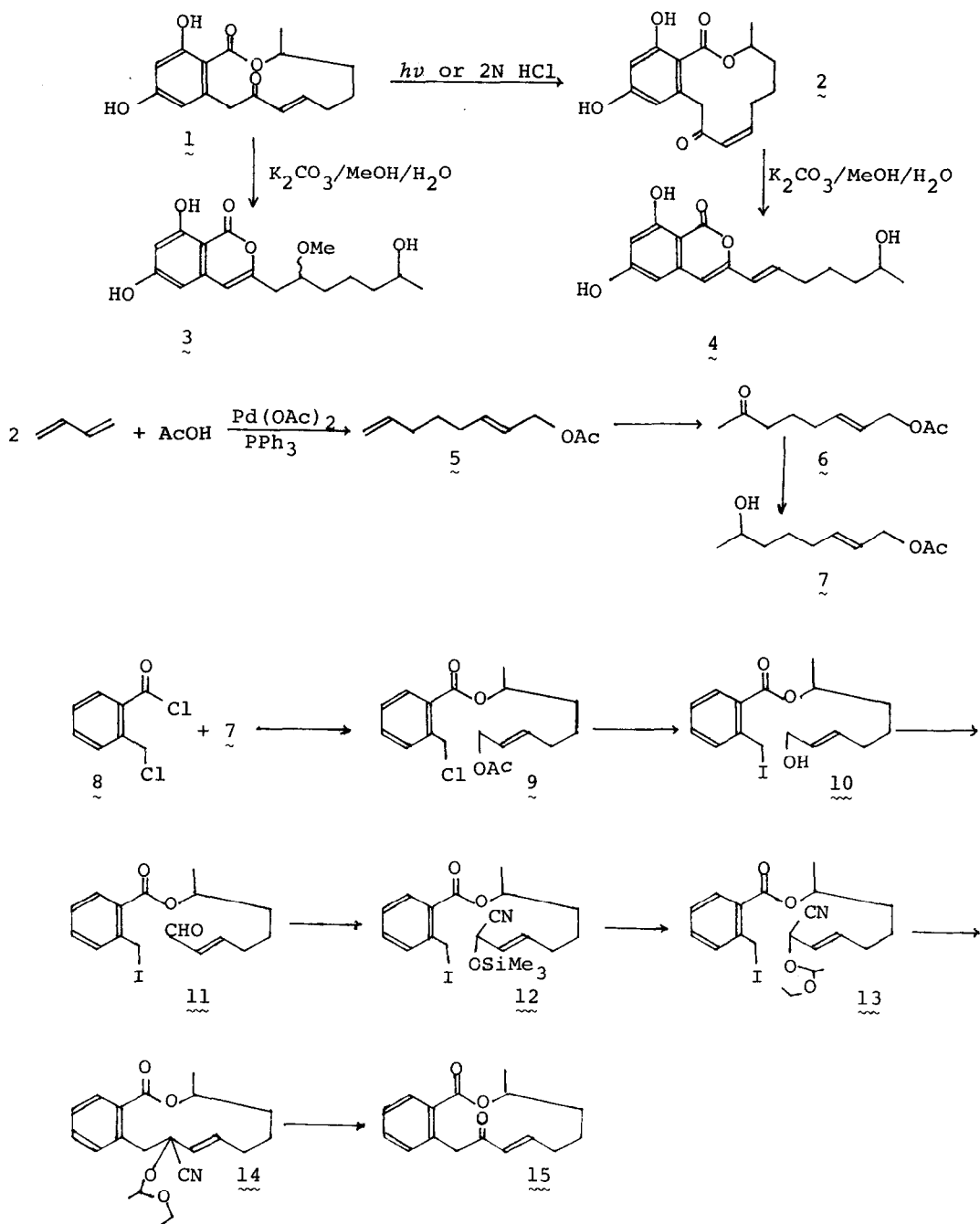
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Summary: Dehydroxy-*trans*-resorcyllide (15) was synthesized by efficient intramolecular alkylation of the protected cyanohydrin. The butadiene telomer obtained by the palladium catalyzed reaction of butadiene with acetic acid was used as a suitable building block of the carbocycle.

A number of naturally occurring orsellinic acid (2,4-dihydroxy-6-methylbenzoic acid) type macrolides such as lasiodiplodin,<sup>1)</sup> zearalenone,<sup>2)</sup> monorden,<sup>3)</sup> and hypothemycin,<sup>4)</sup> are known. Recently as new orsellinic acid type macrolides, *trans*- and *cis*-resorcyllides (1 and 2) have been isolated as plant growth inhibitors from an unidentified species of penicillium by Sassa and coworkers, who determined their structure.<sup>5)</sup> *trans*-Resorcyllide (1) is a 12-membered lactone and characterized by an  $\alpha,\beta$ -unsaturated ketone system at the homobenzyl position which is sensitive to both acid and base or fluorescent light.<sup>5)</sup> Acid treatment or irradiation by light causes facile isomerization of the *trans*-enone to the *cis*-enone. Also facile transformation of *trans*-resorcyllide to the isocoumarine 3 takes place by the Michael addition of various nucleophiles (MeOH, PhSH, imidazole) under weakly basic conditions. *cis*-Resorcyllide is converted to a similar isocoumarine 4 by the base treatment. These facile transformations are one of important problems to be solved in designing the synthesis of resorcyllides. Thus it seems to be essential to incorporate the *trans*- or *cis*-enone moiety at the late stage of the synthesis of these macrolides. So far no synthetic studies of resorcyllides has been reported.

In this paper, we wish to report the synthesis of dehydroxy-*trans*-resorcyllide (15). The isomerization of the *trans*-enone to the *cis*-enone and conversion to the isocoumarine did not take place in our synthesis. Recently we have introduced an efficient cyclization method based on intramolecular alkylation using various carbanions,<sup>6)</sup> and applied the method to total syntheses of a number of naturally occurring macrolides. The present total synthesis of dehydroxy-*trans*-resorcyllide has two characteristic features. One of them is the efficient intramolecular alkylation of a carbanion generated from the protected cyanohydrin 13.<sup>7)</sup> The cyclized product 14 was selectively converted to the *trans*-enone 15 in a high yield by mild treatments with acid and base without the internal translactonization to form the isocoumarine. This cyclization reaction proceeds rapidly and

the cyclized product **14** is stable in the base. Therefore, the cyclization need not be carried out under high dilution conditions. As another characteristic feature, we found that the butadiene telomer **5**<sup>8,9)</sup> has very suitable functionality for facile preparation of the carbon chain of the macrolide as shown below



The terminal double bond of 8-acetoxy-1,6-octadiene (5), obtained by the palladium-catalyzed telomerization, was selectively oxidized with  $\text{PdCl}_2/\text{CuCl}$  under oxygen in aq. DMF to give the methyl ketone 6,<sup>10)</sup> which was reduced to alcohol 7 with  $\text{NaBH}_4$  in ethanol in 80% overall yield. [NMR ( $\text{CCl}_4$ ):  $\delta$  1.05 (d,  $J = 6.0$  Hz, 3 H), 1.95 (s, 3 H), 2.0-2.2 (m, 2 H), 3.30-3.85 (m, 1 H), 4.84 (bd,  $J = 5.0$  Hz, 2 H), 5.30 (dt,  $J = 6.0$  and 15 Hz, 1 H), 5.68 (dt,  $J = 5.0$  and 16 Hz, 1 H); IR (neat): 3400 and 1750  $\text{cm}^{-1}$ ] 2-Chloromethylbenzoyl chloride (8) was prepared<sup>11)</sup> by the reaction of phthalide with triphenylphosphine dichloride at 180°C and converted to the ester 9 by treating with the alcohol 7 at 0°C in 90% yield. [NMR ( $\text{CCl}_4$ ):  $\delta$  1.30 (d,  $J = 6.6$  Hz, 3 H,  $\text{CH}_3$ ), 1.95 (s, 3 H,  $\text{COCH}_3$ ), 4.35 (d,  $J = 5.6$  Hz, 2 H,  $\text{CH}_2\text{OAc}$ ), 4.94 (s, 2 H,  $\text{ArCH}_2\text{Cl}$ ), 5.30-5.81 (m, 2 H, olefinic), 7.00-8.10 (m, 4 H, aromatic); IR (neat): 1715  $\text{cm}^{-1}$ ] The allylic acetate was selectively hydrolyzed in methanolic  $\text{K}_2\text{CO}_3$  at 0°C and the benzyl chloride was converted to the iodide 10 by the treatment with NaI in boiling acetone in 80% yield. The allylic alcohol was oxidized with pyridinium chlorochromate<sup>12)</sup> in dichloromethane at room temperature to the *trans*-enal 11 in 75% yield. [NMR ( $\text{CCl}_4$ ):  $\delta$  1.38 (d,  $J = 6.4$  Hz, 3 H,  $\text{CH}_3$ ), 4.88 (s, 2 H,  $\text{ArCH}_2\text{I}$ ), 6.00 (dd,  $J = 8.0$  and 15 Hz, 1 H, olefinic), 6.67 (dt,  $J = 7.0$  and 15 Hz, 1 H, olefinic), 9.30 (d,  $J = 8.0$  Hz, 1 H, CHO); IR (neat): 1710 and 1690  $\text{cm}^{-1}$ ] The enal 11 was treated for 1 h at 0°C under nitrogen with 1.2 equiv. of trimethylsilyl cyanide in the presence of a catalytic amount of zinc iodide<sup>13)</sup> to give 12. Removal of trimethylsilyl group in 12 with 0.1 N-HCl in THF at 0°C and protection of the resulting cyanohydrin with ethyl vinyl ether gave the protected cyanohydrin 13 in 90% overall yield.

The cyclization of 13 was carried out in the following way. The protected cyanohydrin 13 (100 mg, 0.2 mmol) in THF (7 mL) was added, using a Hershberg dropping funnel, over 30 min at 40°C under nitrogen to sodium hexamethyldisilazane (0.6 mmol) in THF (8 mL). The reaction mixture was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  solution. The cyclized product was isolated in 75% yield after short column chromatographic purification. Acid treatment (1 N-HCl/THF, at 0°C, 1 h) of the cyclized product 14 gave the corresponding cyanohydrin, which was dissolved in ether and shaken vigorously for 1 min with 2% KOH in a separatory funnel. Dehydroxy-*trans*-resorcyllide (15) was isolated in 90% yield after chromatography. [NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  1.35 (d,  $J = 6.0$  Hz, 3 H,  $\text{CH}_3$ ), 3.4 (d,  $J = 13$  Hz, 1 H, ArCH), 4.8 (d,  $J = 13$  Hz, 1 H, ArCH), 4.9-5.3 (m, 1 H, OCOCH), 5.92 (d,  $J = 17$  Hz, olefinic), 6.8 (ddd,  $J = 5.7$ , 8.6, and 17 Hz, olefinic), 7.12-7.48 (m, 4 H, aromatic); IR (neat): 1720 and 1670  $\text{cm}^{-1}$ ; MS  $m/e$  258 ( $\text{M}^+$ )] The *trans* configuration of the double bond was fully confirmed by the NMR spectrum.

Further application of this cyclization method to the syntheses of *trans*- and *cis*-resorcyllides and monorden are in progress.

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