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TOTAL SYNTHESIS OF CATALPALACTONE

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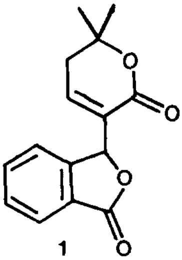
ABSTRACT: The first synthesis of catalpalactone (1) is reported.[1] The key steps are the coupling of the selenenylated lactone 8 with bromophthalide (9) and the selenoxide elimination of 14 to give catapalactone with very high regioselectivity.

Catalpalactone (1) is a dilactone isolated from the ornamental tree, Catalpa ovata G. Don. It contains two lactone rings, derived from an allylic and a tertiary alcohol, so it is an acid-sensitive molecule. Its propensity for 1,4 elimination, to give the conjugated compound 2, renders it also base-sensitive.[2]



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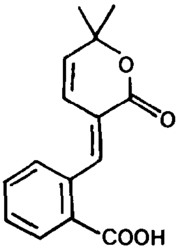

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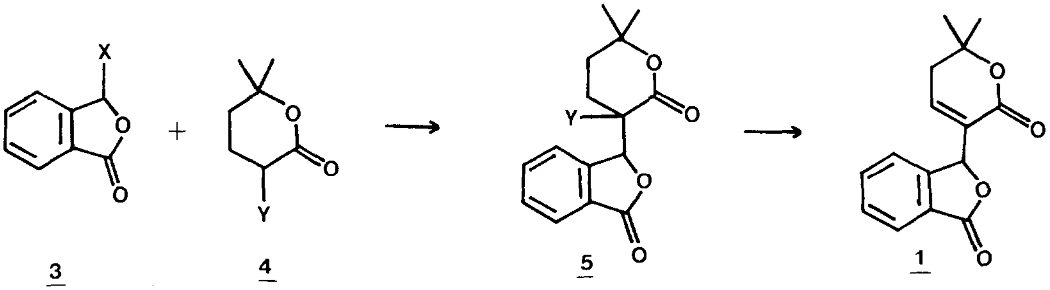
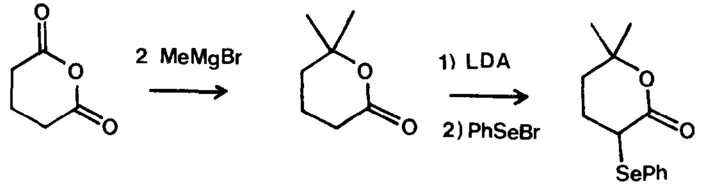
We wish to report the first synthesis of catalpalactone, via a coupling reaction followed by an elimination reaction. The route is short, fairly efficient, and highly regioselective when X = Br, Y = PhSe.

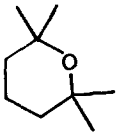


Addition of MeMgBr in THF to glutaric anhydride gave δ, δ-dimethylvalerolactone (6), bp 44-46° (0.26 mm). The literature yield[3] (15%) was increased to 43% by inverse addition of the Grignard reagent and by improved extraction procedures (ether) of the somewhat water-soluble product. The tetramethyl ether 7 was a small but persistent by-product in all preparations of 6.

Treatment of 6 with lithium diisopropyl amide (LDA) in THF at -78°, followed by addition of PhSeBr, gave the selenenylated lactone 8, 90%, mp 33-35° (MeOH-H_2O), NMR: ($CDCl_3$) δ 1.32 (3 H,s); 1.38 (3 H, s); 1.67-2.40 (4 H, m); 3.96 (1 H, t, J = 6); 7.31 (3 H, m); 7.70 (2 H, m); IR: (KBr) 1700, 1380, 1365, 1270, 1115 cm^{-1}.



6 8



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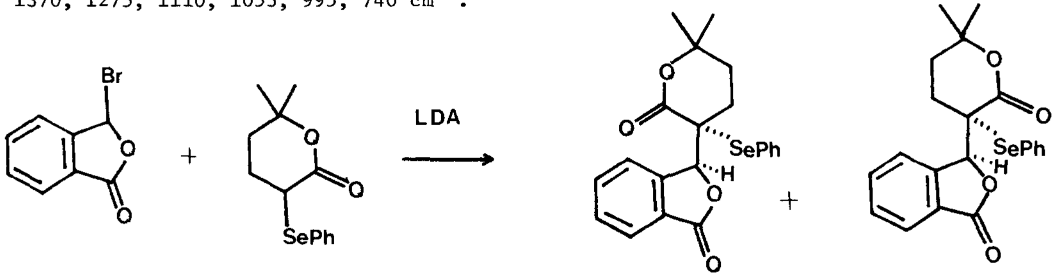
The coupling reaction between the enolate ion of 8 and bromophthalide (9)[4] proceeded as desired, to give a 3:1 mixture (47% yield) of the diastereomeric compounds 10 and 11. These were separated by chromatography on silica gel. The major isomer had mp 192-195° (CH_2Cl_2-ether); NMR ($CDCl_3$): δ 1.37 (3 H, s); 1.45 (3 H, s); 1.42-2.5 (4 H, m); 6.09 (1 H, s); 7.23-8.04 (8 H, m); 8.45 (1 H, dd, J = 10, 2): IR (KBr): 2925, 1740, 1685, 1375, 1360, 1265, 1095, 1025, 955, 725 cm^{-1}. The minor diastereomer had mp 168-172° (CH_2Cl_2-ether); NMR ($CDCl_3$): δ 1.02 (3 H, s); 1.45 (3 H, s); 1.38-2.40 (4 H, m); 5.90 (1 H, s); 7.28-8.00 (9 H, m); IR (KBr): 2970, 1760, 1690, 1385, 1370, 1275, 1110, 1055, 995, 740 cm^{-1}.

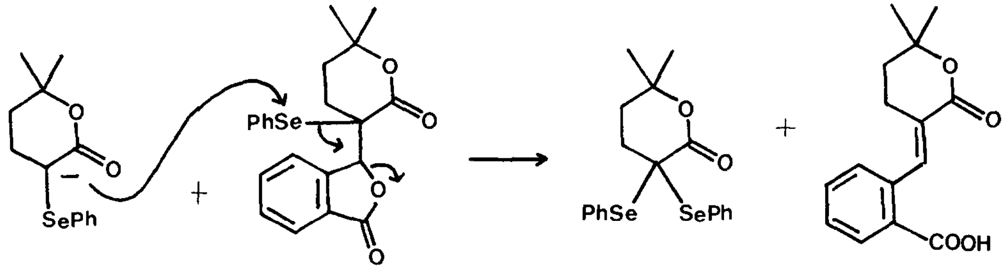


9 8 10 11

The two diastereomers 10 and 11 each have one NMR signal in an unusual position. The major one (10) has the peri H signal shifted ca. 1.0 ppm downfield, which appears to be due to deshielding by the carbonyl group. The minor isomer (11) has one methyl group signal shifted ca. 0.3 ppm upfield, which appears to be due to shielding by the phthalide π system. Unambiguous assignments of stereochemistry were not made, but the assignments given by means of the formulas seem to fit the NMR data, as judged by molecular models.

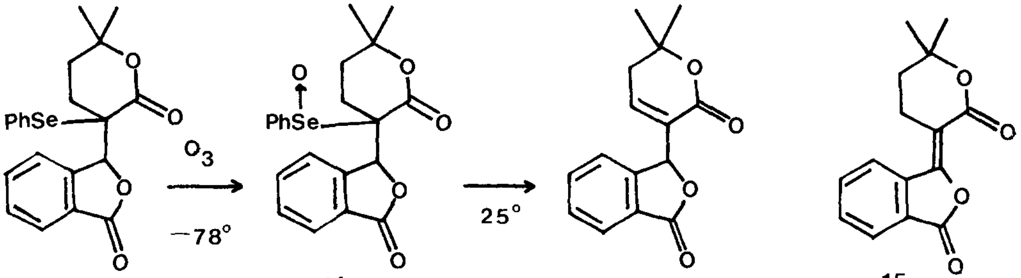
Two side products were isolated from the coupling reaction, the bis-phenylselenenyl compound 12, mp 92-94° (ether), and the conjugated lactone 13, mp 149-151° (MeOH); NMR ($CDCl_3$): δ 1.46 (6 H, s); 1.79 (2 H, m); 3.04 (2 H, ddd, J = 5, 4, 2); 6.35 (1 H, dd, J = 2, 1); 7.5-8.0 (4 H,m).

These products presumably arise by attack of the anion of 8 on selenium in the product 10 or 11, followed by an eliminative deselenylation, as shown. In support of this, treatment of 10 with one equivalent of the anion of 8 under the coupling conditions slowly gave 12 and 13 as the only detectable products.



8 10 or 11 12 13

Treatment of either compound 10 or 11 with O_3 at -78°, followed by addition of Et_3N and warming to room temperature gave a high yield (96% crude yield after chromatography, 87% crystalline, mp 109-110° from ether) of catalpalactone (1), identical[5] with an authentic sample.[6]



10 or 11 14 1 15

It was of considerable interest to determine the regiospecificity of this key elimination reaction, since compound 15, the product of the alternative elimination mode, has the double bond conjugated with the aromatic ring, and is presumably more stable than catalpalactone. Investigation by NMR spectroscopy of the material in the mother liquors from the crystallization of catalpalactone showed small amounts of unidentified compounds, but no peaks in the δ 1.5 - 1.6 region, which would be expected for the methyl signals for 15 (compare compound 13). It was estimated that ca. 0.5% of 15 could have been detected easily. While it is possible that a small amount of 15 was formed in the reaction but did not survive the work-up conditions, the selenoxide elimination route to produce catalpalactone is at least highly regioselective and is probably regiospecific.

The successful use of the selenoxide elimination method to yield the double bond in the position required for catalpalactone is presumably due to the known propensity for this reaction to eliminate away from heteroatoms.[7,8] The fact that both diasteromers 10 and 11 give identical results suggests that conformational factors, even in these sterically congested molecules, are not important in determining the direction of the elimination reaction.

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References and Notes

1. Presented at the 183rd National ACS meeting, Las Vegas, March 28, 1982, Abstract ORGN 29.
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4. I. A. Koten and R. J. Sauer, Org. Syn., 42, 26 (1962); Coll. Vol. V, 145 (1973).
5. Natural catalpalactone is reported[2] to be optically inactive at all wavelengths. Whether this is an artifact of the isolation procedure or not is unclear.
6. We wish to thank Professor Hiroyuki Inouye for an authentic sample of catalpalactone.
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