was brought to pH 9 and carefully maintained at this value by addition of 3 N aqueous sodium hydroxide.[14] After 90 min (60 min for D-glucose),[15] the pH was carefully raised to 7 by addition of 3 N HCl (typically only 2–4 mL were necessary), and the solvents were eliminated under reduced pressure. Azeotropic removal of pyridine with toluene (3 × 200 mL) gave a semisolid that was triturated with absolute ethanol and filtered through florisil (200-mesh size from Aldrich Chemical Co.), typically a pad ~14 cm wide and 5 cm deep. Impurities, which show up as a brown residue, were not allowed to penetrate through the pad. Washing with ethanol was continued until the filtrate was free of sugar derivatives (TLC, ~2 L EtOH). Rotary evaporation of the solvent afforded the desired crude 1,6-anhydro sugars **3a** and **3b**, which were dried under high vacuum and derivatized to the crystalline derivatives **4** and **5**, respectively.

1,6-Anhydro-2,3-isopropylidene-β-D-mannopyranose (4). 1,6-Anhydro-β-D-mannopyranose (**3a**), obtained as described above, was treated with acetone (reagent grade, 800 mL) and stirred with heating until only a free-flowing solid remained (~30 min). Dimethoxypropane (300 mL) and *p*-toluenesulfonic acid (5 g) were added, and the mixture was stirred until no mannosan **3a** was detected by TLC. After basification with triethylamine (pH 8) and filtration to remove the white solid, the solvents were rotary evaporated, and the residue was taken in ethyl acetate and filtered through florisil. Removal of the solvents under reduced pressure afforded the crude acetonide **4**, which was recrystallized from ethyl acetate as clear needles (32 g, 29% from **1a**, R_f (80% EtOAc/hexane) = 0.48); mp 157 °C (lit.[11b] mp 161–162 °C). Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.59; H, 7.16.

2,3,4-Tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (5). To the crude 1,6-anhydro-β-D-glucopyranose (**3b**), obtained as described above, were added acetic anhydride (314 mL, 3.3 mol, 2 equiv), (*N*,*N*-dimethylamino)pyridine (6.80 g, 56 mmol, 0.1 equiv), and ethyl acetate (300 mL), and the mixture was stirred until no **3b** was detected by TLC. The reaction mixture was quenched with ethanol (125 mL) and treated with solid sodium bicarbonate until CO_2 evolution ceased (additional ethyl acetate (~1 L) was added to facilitate stirring). Filtration through florisil and evaporation of the solvents under reduced pressure gave crude triacetate **5**, which was crystallized from methyl *tert*-butyl ether (24 g, 15%, R_f (40% acetone/hexane) = 0.37). Concentration of the mother liquors and column chromatography on silica gel (eluent: 60% diethyl ether–hexanes), followed by recrystallization, afforded another 15 g of **5**, raising the yield to 24%: mp 106 °C (lit.[10] mp 108–109 °C).

Registry No. **3a**, 14168-65-1; **3b**, 498-07-7; **4**, 14440-51-8; **5**, 13242-55-2; D-mannose, 3458-28-4; D-glucose, 50-99-7.

(14) During this process the reaction color changes from pale yellow to deep yellow, at which stage a white precipitate begins to form. Further addition of sodium hydroxide causes the precipitate to redissolve, with development of a deep red color. This color formation was found to be indicative of a pH of 9.

(15) At this point the main product by TLC is the 1,6-anhydro sugar **3a** or **3b**: R_f (**3a**, 20% MeOH/CH_2Cl_2) = 0.38; R_f (**3b**, 20% MeOH/CH_2Cl_2) = 0.43.

Novel Synthesis of Cyclohexa-2,4-dien-1-ones. Its Use in a Partial Synthesis of the Chromophore Portion of Phomenoic Acid

Ravindra Satish Topgi†

Department of Chemistry, Columbia University, New York, New York 10027

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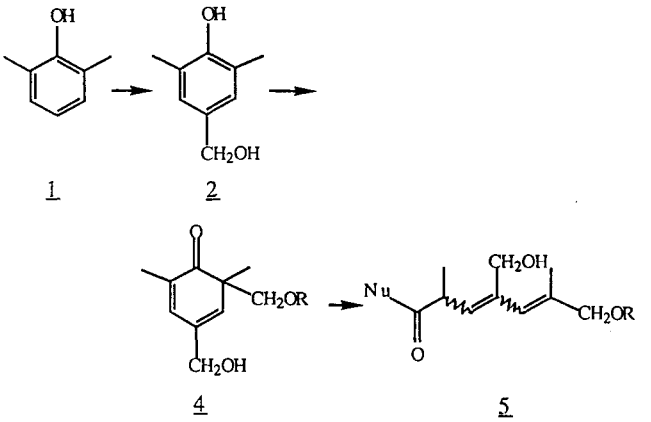
The interesting structural feature of phomenoic acid[1] and phomenolactone[2] isolated from the mycelium of the fungus *Phoma lingum* Tode lies in the diene system. Hence the partial synthesis of this unit containing the diene system was undertaken, hoping to establish a general method for such diene fragments.

Scheme I



The photochemical cleavage of cyclohexa-2,4-dien-1-ones is well established.[3] Based on the same principle Scheme I was considered.

Hydroxymethylation of 2,6-dimethylphenol **1** to give phenol **2** can be easily accomplished by formaldehyde and base.[4] However further hydroxymethylation leading to the cyclohexadienone **4** is not known. Our efforts in using *tert*-butyl alcohol–potassium *tert*-butylate as the medium, chloromethyl methyl ether as a hydroxymethyl equivalent, and phenol **3** as a substrate led to the formation of cyclohexadienone **6** in trace quantities. However, when this method was applied to phenol **2**, formation of cyclohexadienone **4** was not observed.

Alkali metal phenolates are known to give ethers when treated with chloromethyl methyl ether.[5] In aryl metalation studies the methoxymethyl group allows regiospecific aryl metalation and subsequent reaction with a variety of electrophiles in good yields.[6] Coordinative and inductive effects are operative in ortho-lithiation of alkylaryl ethers.[7] This indicates the methoxymethyl group's ability to bind alkali metals and its pronounced binding capability toward lithium. Taking into consideration of these facts, when lithium phenolate **3** was treated with chloromethyl methyl ether, cyclohexadienone **6** was obtained in 65% yield. Similarly when the same phenolate **3** was treated with chloromethyl benzyl ether, the cyclohexadienone **7** was obtained in 75% yield. When the above method was applied to the lithium salt of phenol **2** using chloromethyl benzyl ether, cyclohexadienone **8** was obtained in 66% yield (see Table I).

Furthermore, the advantage of lithium as an efficient phenolate counter cation and its enhanced ability to complex with the methoxymethyl group as well as the (ben-

† Present address: Department of Chemistry, Texas A&M University, College Station, TX 77843.

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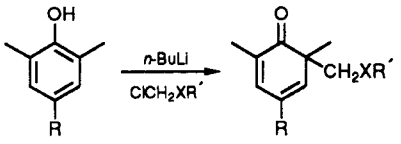
Table I. Conversion of Phenols to Cyclohexa-2,4-dien-1-ones



compd	phenol R	substrate X	substrate R'	product	yield,[a] %
1	H	O	CH_3	13	65
	H	O	$CH_2C_6H_5$	14	70
	H	O	$CH_2CH_2OCH_3$	15	80
	H	O	$CH_2CH_2Si(CH_3)_3$	16	85
	H	S	CH_3	17	95
	H	S	C_6H_5	18	85
2	CH_2OH	O	$CH_2C_6H_5$	8	66
3	CH_3	O	CH_3	6	65
	CH_3	O	$CH_2C_6H_5$	7	75
	CH_3	O	$CH_2CH_2OCH_3$	19	85
	CH_3	O	$CH_2CH_2Si(CH_3)_3$	20	85
	CH_3	S	CH_3	21	95
	CH_3	S	C_6H_5	22	85

[a] Based on the conversion of the starting phenol.

zyloxy)methyl group, so as to direct these groups to the ortho-position leading to cyclohexa-2,4-dien-1-one, was studied with phenol 1. In these cases the yields of cyclohexadienones 13 and 14 were 65% and 70%, respectively. In general ortho-alkylation is preferred over para-alkylation. However, cyclohexa-2,5-dien-1-ones are isolated in higher yields than cyclohexa-2,4-dien-1-ones, indicating that cyclohexa-2,4-dien-1-ones are less stable than cyclohexa-2,5-dien-1-ones.[8] But in our method, no formation of cyclohexa-2,5-dien-1-ones were observed. The yields of cyclohexa-2,4-dien-1-ones, on the other hand, are good to acceptable. These results support our views regarding the role of lithium and the complexing ability of methoxy-(benzyloxy)methyl group.

Alkali metal cation and phenoxide are present in ion pairs. The role of cation as a binder to oxygen of the methyleneoxy group allows one to suppose the transition state as represented in Figure 1, predicting the possible reaction path via a quasi six-membered ring transition state.[8]

Accordingly, when (2-methoxyethoxy)methyl chloride (MEM chloride), where the oxygen α to the chloromethyl group is available for the complexation, was reacted with lithium phenolates of 1 and 3, cyclohexadienones 15 and 19 were obtained in 80% and 85% yields, respectively. Similarly when [2-(trimethylsilyl)ethoxy]methyl chloride (SEM chloride) was used in place of MEM chloride, the corresponding cyclohexadienones 16 and 20 were obtained in 85% yield from lithium phenolates 1 and 3, respectively. [(Methylthio)methyl]cyclohexadienones are useful organic intermediates, and many methods are available for their synthesis.[9,10] The present novel cyclohexadienone synthetic methodology was extended to their synthesis, where the lithium cation will play the same role with phenoxide anion, and the sulfur atom of the (methylthio)methyl group will exhibit complexation capability analogous to that of the oxygen atom. Thus, when lithium phenolates 1 and 3 were treated with chloromethyl methyl sulfide, cyclohexadienones 17 and 21 were obtained in 95% yield, respectively.

Cyclohexadienones are known to rearrange under different conditions.[11] Cyclohexadienone 21 was observed to rearrange in agreement with Moffatt et al.[9] However, cyclohexadienone 22 is more stable than cyclohexadienone 21 to silica gel purification. Apparantly these cyclohexadienones were very sensitive to acidic conditions and were unstable under these conditions. For these reasons the yields were based on ^1H NMR spectroscopy. In $CDCl_3$ or methanol certain cyclohexadienones showed dimerization. Carbon tetrachloride was found to be a more suitable solvent. Reverse-phase chromatographic purification proved to be the method of choice.

The cyclohexadienones 6 and 7 were irradiated with a medium-pressure UV lamp in the presence of morpholine for 4 h. The quantitative cleavage led to the formation of dienes 9 and 10, respectively. Similarly the photocleavage of cyclohexadienone 8 led to the formation of two diene isomers 11 and 12, which possibly represent the diene system in phomenoic acid and phomenolactone (Figure 2).

This novel cyclohexadienone synthetic principle can further be extended to the synthesis of *o*-methoxyalkyl(aryl), *o*-(methylthio)methyl(alkyl/aryl), and related simple phenols. After we completed this work, introduction of functionalized alkyl groups into the ortho position of phenols has been published.[12]

Experimental Section

Chloromethyl methyl ether, benzyl chloromethyl ether, and chloromethyl methyl sulfide were distilled just before use. The handling of these carcinogens were done under a well-ventilated hood, and all the precautions were taken to avoid the inhalation of the vapors. Other reagents were used as received from the commercial suppliers. All solvents were dried by standard procedures. Thin-layer chromatography was performed on Merck silica gel plates (60 F-254) or Whatman KC-18-F plates. HPLC was effectuated on a Perkin-Elmer Series-2 liquid chromatograph. Various columns were used: (1) Whatman Partisil M9 10/50 ODS-2, 500 mm × 9.4 mm; (2) Whatman Partisil 10-C8 M9, 500 mm × 9.4 mm. (3) Chrompack LiChrosorb Si-60-10, 250 mm × 9 mm; (4) Chrompack LiChrosorb 10 RP-18, 250 mm × 9 mm; 70 eV E.I. mass spectra were recorded on either an AEI-MS9 or an AEI-MS50 apparatus. Infrared spectra were recorded with either a Perkin-Elmer 297 or 257 spectrophotometer. Ultraviolet spectra were recorded on Jobin-Yvon type Duospac 203 or Perkin-Elmer Lambda 5 UV/vis spectrophotometer. ^1H NMR spectra were recorded at 60 MHz with either a Varian T-60 or EM-360 spectrometer; 200- and 400-MHz spectra were obtained with a Bruker WM 200 spectrometer and a Bruker WM 400 spectrometer, respectively. Chemical shifts are in ppm downfield from tetramethylsilane.

General Procedure for the Cyclohexadienone Synthesis. The phenol (5 mmol) was dissolved in 25 mL of solvent under an inert atmosphere and cooled in ice water bath. Through a syringe was added 1.6 N *n*-butyllithium solution in hexane (5.5 mmol), and the mixture was allowed to warm the room temperature gradually. After 1 h of stirring at room temperature, the phenolate solution was cooled in ice water bath. Chloromethyl reagent (6.0 mmol) was added dropwise. The temperature of the reaction mixture was allowed to warm to room temperature very slowly. After the reaction mixture was stirred at room temperature for 2–4 h, ice-cold water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The combined organic phases were washed with water, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography and HPLC were used for the isolation and purification of the cyclohexadienone. In most cases solvents such as pentane, hexane, benzene, and toluene were used satisfactorily.

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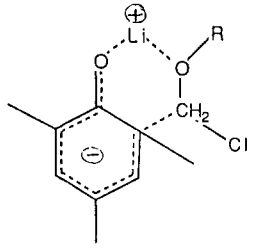
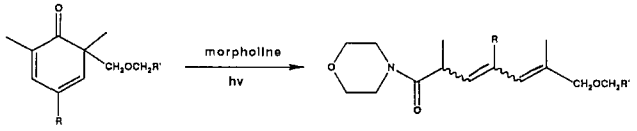


Figure 1.



6	R = CH_3	R' = H	9	R = CH_3	R' = H
7	R = CH_3	R' = C_6H_5	10	R = CH_3	R' = C_6H_5
8	R = CH_2OH	R' = C_6H_5	11 &12	R = CH_2OH	R' = C_6H_5

Figure 2.

2,4,6-Trimethylcyclohexa-2,4-dien-1-one (6). Cyclohexadienone **6** was obtained as per the general procedure from 2,4,6-trimethylphenol and chloromethyl methyl ether. The concentrate was applied on C18 reverse-phase column. By use of a gradient of methanol in water, cyclohexadienone was obtained as a colorless liquid: 65% yield; R_f 0.88 (C18 reverse-phase; MeOH–H_2O, 90:10); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.12 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 1.99 (s, 3 H, CH_3), 3.29 (s, 3 H, OCH_3), 3.33–3.68 (d, 2 H, system AB, J_{AB} = 9 Hz, CH_2), 6.03 (s, 1 H), 6.82 (s, 1 H); UV λ (CCl_4) 315 nm (3436); IR (neat) 2850, 1660 cm^{-1}; MS m/z 180 (M^+, 87), 148 (100), 135 ($M^+ - CH_2OCH_3$, 25). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.54; H, 9.07.

General Procedure for the Photochemical Cleavage of the Cyclohexa-2,4-dienones. The cyclohexa-2,4-dien-1-one (0.2 mmol) dissolved in dry ether (20 mL) was placed in a Pyrex tube. Morpholine (500 μL) was added. Oxygen from the reaction mixture was expelled by bubbling an inert gas. Then the reaction tube was irradiated with UV lamp (Hanovia, medium-pressure, 100 W). The reaction was followed by either UV absorption measurements or TLC. After complete consumption of the starting material, which required nearly 4 h, solvent and the morpholine were removed under reduced pressure, and the concentrate was subjected to flash chromatography.

Photochemical Cleavage of 2,4,6-Trimethylcyclohexa-2,4-dien-1-one (6). Cyclohexadienone **6** was subjected to photochemical cleavage as per the general procedure. After 4-h irradiation, complete consumption of the starting material and appearance of single reaction product were observed. The usual workup afforded diene **9** as a colorless liquid in quantitative yield: R_f 0.22 (ethyl acetate–hexane, 50:50); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.17 (d, 3 H, J = 7 Hz, 10-CH_3), 1.67 (s, 3 H, 8-CH_3), 1.82 (s, 3 H, 9-CH_3), 3.2–3.8 (m, 8 H, morpholine), 3.37 (s, 3 H, OCH_3), 3.40 (dq, 1 H, J = 10 and 7 Hz, 2-H), 3.88 (s, 2 H, CH_2O), 5.40 (d, 1 H, J = 10 Hz, 3-H), 5.93 (s, H, 5-H); UV λ (MeOH) 206 nm (20482); IR (neat) 2850, 1655, 1440, 1200–1000 cm^{-1}; MS m/z 268 ($(M + 1)^+$, 39), 253 (9), 237 ($(M + 1)^+ - OCH_3$, 9), 121 (100), 114 (48).

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Registry No. 1, 576-26-1; 2, 4397-14-2; 3, 527-60-6; 6, 123674-61-3; 7, 123674-62-4; 8, 123674-63-5; 9, 123674-64-6; 10, 123674-65-7; 11 & 12, 123674-66-8; 13, 123674-67-9; 14, 123674-68-0; 15, 123674-69-1; 16, 123674-70-4; 17, 16184-95-5; 18, 123674-71-5; 19, 123674-72-6; 20, 123674-73-7; 21, 16184-96-6; 22, 123674-74-8; phomenoic acid, 83652-15-7; phomenolactone, 83652-16-8; morpholine, 110-91-8.

Stereochemistry of Hydrogen Loss on Formation of the Vinyl Group in the Biosynthesis of Ravidomycin

Robert F. Keyes and David G. I. Kingston*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061-0212

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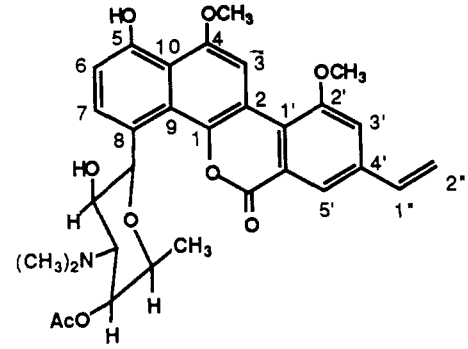
The antibiotic ravidomycin was isolated from *Streptomyces ravidus*[1] and shown to have structure **1** by Findlay and his collaborators.[2] Its aglycone unit is identical with that of the related antibiotics chrysomycin V[3] (albacarcin V,[4] virenomycin V[5]) and toromycin[6] (gilvocarin V[7]).



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Ravidomycin shows significant antitumor activity against P388 lymphocytic leukemia and colon 38 and CD8F1 mammary tumors in mice.[1] The vinyl group appears to be essential for effective antitumor activity. Thus gilvocarcin V, like ravidomycin, shows significant antitumor activity in P388 lymphocytic leukemia,[8,9] but gilvocarcin M, in which the vinyl group is replaced by a methyl group, is significantly less active in this system. Similarly, dihydroravidomycin is less effective against P388 than is ravidomycin, although the difference in this case seems to be associated with increased toxicity of the dihydro antibiotic at higher doses in this assay.[10] Interestingly, it has been shown that gilvocarcin V is activated by low doses of visible light to induce bacteriophage λ in *Escherichia coli*, while gilvocarcin M fails to show this activation even though it has a similar absorption spectrum.[11] These results thus suggest that the vinyl group of antibiotics of the ravidomycin/toromycin/gilvocarcin type is essential for effective antitumor activity.

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