Rules for Ring Closure: Ring Formation by Conjugate Addition of Oxygen Nucleophiles

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The formation of rings by the closure of acyclic precursors is a fundamental process in organic chemistry. In a recent communication,[2] a set of rules for ring closure was described which allows the prediction of the relative facility of various ring closure reactions. These rules promise to be of utility to organic chemists in the design and execution of syntheses. To establish more precisely the validity and limitations of these rules, a systematic investigation of ring closure reactions has been initiated in these laboratories. The preliminary results of some of these investigations have been described in several communications.[3] In the present paper we wish to present the results of our studies on the ring closure by nucleophilic attack of oxygen on conjugated double and triple bonds.

In a preliminary description of these rules for ring closure,[2] ring-forming reactions are designated by a numerical prefix which denotes the ring size, followed by either the term exo or endo depending on whether the breaking bond is exocyclic or endocyclic to the smallest so-formed ring, and finally by one of the suffixes tet, trig or dig describing the hybridization of the carbon atom undergoing the closure reaction (tetrahedral, trigonal, or diagonal, respectively). This classification system is exemplified by the possibilities for five-membered rings as shown in Scheme I. Examination of the rules suggests that a careful study of the closure of five- and six-membered rings should provide a critical test of the utility of these concepts since it is these ring sizes that provide the borderlines between favored and disfavored processes[4] in nucleophilic trigonal cyclizations.

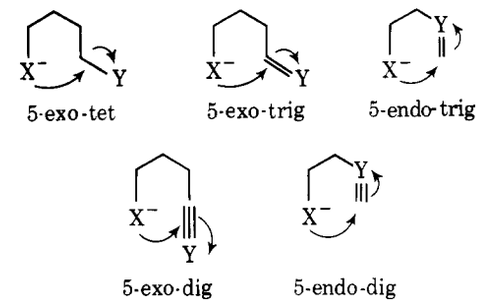
All of the exocyclic closures that generate five- or six-membered rings are favored reactions.[5] In the formation of five-membered rings via endocyclic closures, however, the hybridization of the atoms involved is predicted by the rules to have a dramatic effect on the reaction. Thus, the 5-endo-digonal closure is a favored process whereas 5-endo-trigonal closures are disfavored. The disfavored 5-endo-trigonal reaction is further contrasted by the favored nature of the corresponding 6-endo-trigonal process. It is these predicted differences in reactivity that we have chosen to exemplify via an investigation of cyclizations with oxygen nucleophiles.

5-Endo-Trigonal Closures. The first of these ring-forming reactions to be investigated was the disfavored 5-endo-trigonal closure. A number of hydroxy enones were prepared as models for this process, as outlined in Scheme II. Enone 1 was prepared from 3-hydroxy-3-methyl-2-butanone by condensation with benzaldehyde in a manner similar to that reported by Nazarov.[6] The synthesis of the cyclohexyl analogues **3a** and **3b** was accomplished by similar condensation of 1-acetylcyclohexan-1-ol (**2**) (prepared by the method of Baldwin, Höfle, and Lever[7]) with the requisite aldehydes.

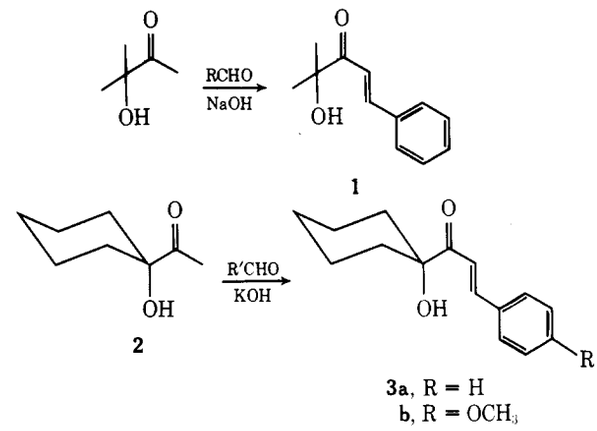
All attempts to cyclize enones **1**, **3a**, and **3b** in a base-catalyzed reaction failed as anticipated. The starting materials were recovered unchanged on exposure to a variety of basic reaction conditions (e.g., sodium methoxide–methanol or sodium hydride–tetrahydrofuran). It remained to be shown, however, that this failure to cyclize was not merely a consequence of poor nucleophilicity of the alkoxide in the desired conjugate addition and that the lack of closure was a kinetic phenomenon and not the result of an unfavorable equilibrium.

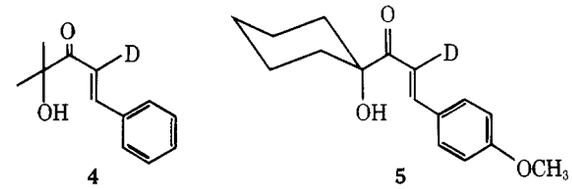
The susceptibility of these systems to conjugate addition of alkoxide nucleophiles was verified by conducting the attempted cyclizations with sodium methoxide in methanol-*o*-*d*. Under these reaction conditions, hydroxy enones **1** and **3b** failed to cyclize as before and afforded on work-up their α-deuterated analogues **4** and **5**, respectively. The incorporation of a deuterium atom α to the carbonyl was rationalized as a consequence of reversible addition of the methoxide anion giving an adduct such as **6** which underwent deuterium ex-

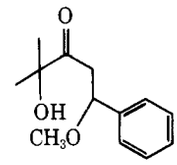
Scheme I



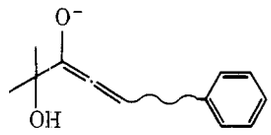
Scheme II







change and subsequent elimination of methanol.[8] The alternative explanation, i.e., that exchange occurs through direct enolization to 7, is rendered unlikely by the observation that



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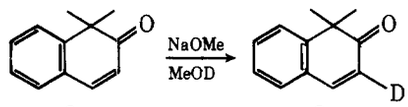
cyclic enone 8[9] undergoes a similar rapid exchange to 9, under the above conditions. Clearly, an allenic enolate derived from 8 should be a highly strained system.



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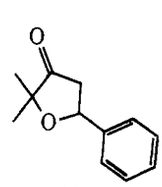
To establish that failure to observe closure of these hydroxyenones was not due to an unfavorable equilibrium, we prepared the corresponding furanones 10, 11a, and 11b via



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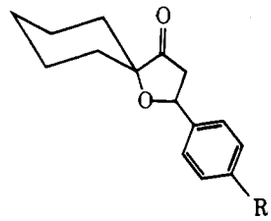
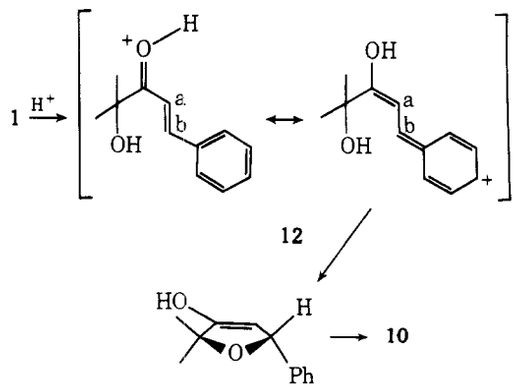


11a, R = H
b, R = OCH_3

acid-catalyzed cyclization[6] of the hydroxy enones. Furanones 11a and 11b were recovered unchanged on treatment with sodium hydride in tetrahydrofuran. More dramatically, furanones 10 and 11b were found to exchange their α-hydrogen atoms on treatment with sodium methoxide in methanol-*O*-*d*. Thus it was shown that the furanones and their derived enolates, the potential immediate products of the 5-endo-trigonal closure, were stable to ring opening under the attempted cyclization conditions.

These acid-catalyzed cyclizations deserve comment. At present, we attribute the success of these reactions to the reduction in the rotational barrier around the enone double bond, C_a–C_b in 12, allowing thereby access to conformations



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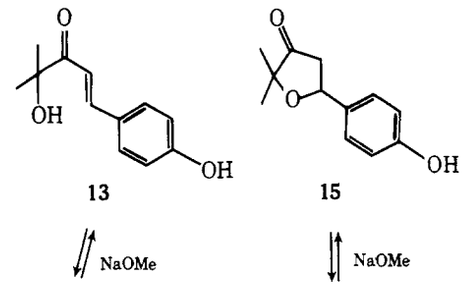
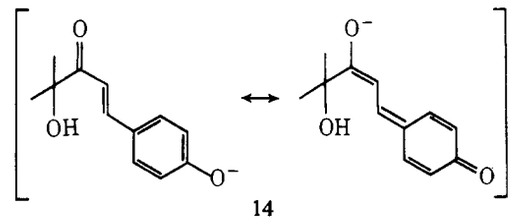
geometrically similar to the product, as shown. The reduction of the rotational barrier is clarified by resonance as in 12.

As a follow-up to these experiments and to provide support for our rationale regarding the acid-catalyzed closure of enone 1, we have examined the chemistry of the related phenolic enone (13). If our hypothesis is correct, then we might expect *base*-catalyzed closure in the case of 13 via contributions from resonance structures, as 14.



13 15



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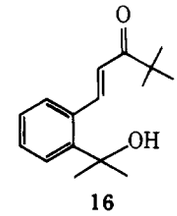
Phenolic enone 13 was prepared, but was recovered unchanged from treatment with sodium methoxide in refluxing methanol. Suspecting that this lack of closure was probably the result of an unfavorable equilibrium due to the stability of the highly conjugated phenolate anion, we prepared furanone 15 from 13 via the acid-catalyzed route. Thus, the unfavorable equilibrium was demonstrated by then submitting 15 to the basic reaction conditions when it smoothly opened to give the enone isomer (13).

These experiments establish that the nucleophilic ring closure by conjugate addition to a *neutral* enone, in an *endocyclic* sense is a relatively unfavorable process for forming five-membered cycles. It has also been established that the stereoelectronic restraint implicit in these reactions can be overcome by protonation of the enone, perhaps as a result of reduction of the rotational barrier.

5-Exo-Trigonal Closures. To demonstrate the contrasting facility of 5-exo-trigonal mode of cyclization, we desired a model system that, as nearly as possible, possessed the same steric and electronic properties displayed by 1, the model for endocyclic closure. A recent report by Johnson and co-workers[10] suggested a simple synthetic approach to hydroxy enone 16. Closure of 16 would require attack of a tertiary alcohol on



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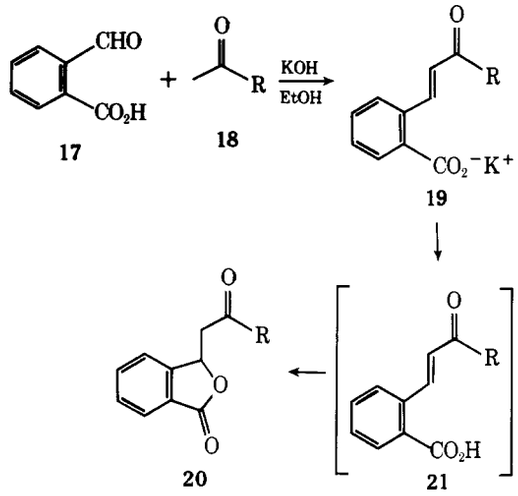
a β-phenyl-substituted enone system as was required in the closure of 1. The differences in reactivity of enones 1 and 16 can therefore be attributed to the endocyclic vs. exocyclic nature of the closure.

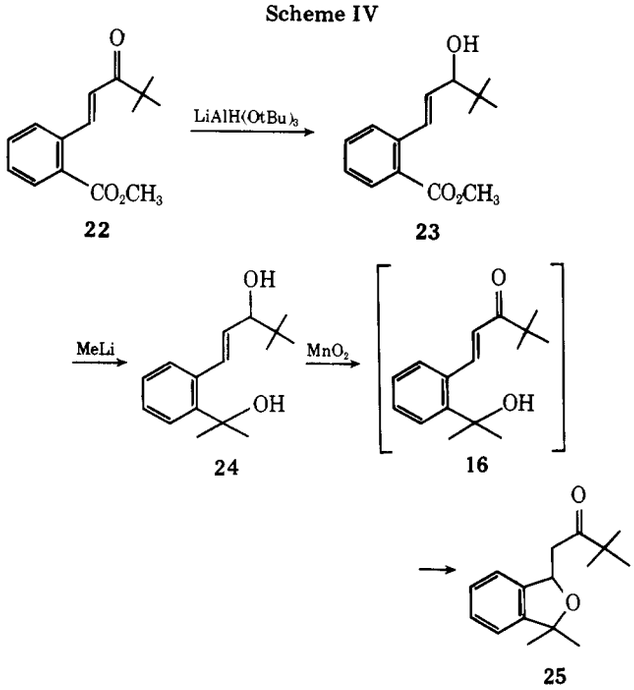
Johnson[10] described the base-catalyzed condensation of phthalaldehydic acid (17) with a variety of methyl ketones (18) (Scheme III). They found that the initial condensation products could be isolated as the crystalline carboxylate salts (19), but on protonation of these salts, the isolated product was the phthalide (20), not the corresponding carboxylic acid (21), attesting to the facility of the 5-exo-trigonal closure.

In the cases cited with aryl methyl ketones as substrates, the yields of phthalide were good to excellent. In the case at hand, however, with 18 being pinacolone, the reported yield of phthalide was only 8%. We have repeated this work and have confirmed the high yields of aryl phthalides 20 (R = aryl). On attempting the reaction with pinacolone we found the major product on acidification of the reaction mixture to be

Scheme III



Scheme IV

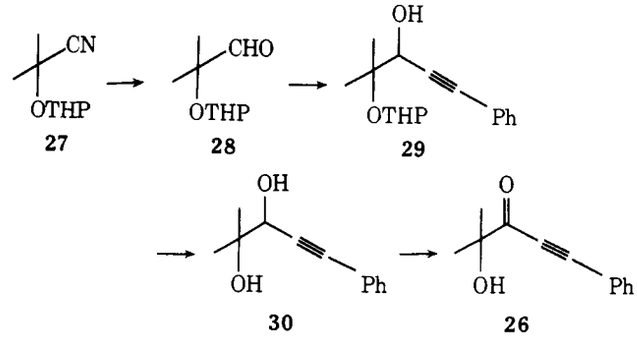


uncyclized carboxylic acid **21** (R = *tert*-butyl), thus explaining the poor yield reported by Johnson. The reasons for the failure of this acid to close to phthalide are unclear since we subsequently found closures of **19** (R = *tert*-butyl) to be quite easy (vide infra). We have also determined that the carboxylate salts (**19**) can conveniently be trapped in the open form by alkylation with methyl iodide, generating the corresponding methyl esters.

The remainder of the synthetic sequence leading to enone **16** is depicted in Scheme IV. Methylation of carboxylate salt **19** (R = *tert*-butyl) gave ester **22**. Selective reduction of the enone carbonyl afforded allylic alcohol **23**, which with methyllithium gave diol **24**. Oxidation of diol **24** with carefully neutralized active manganese dioxide[11] provided the dihydroisobenzofuran **25** directly in quantitative yield. The choice of manganese dioxide oxidation as the final step leading to the not isolable **16** was made on the basis of the mildness and essentially neutral conditions of this method.

While this ring closure presumably proceeds via formation of enone **16**, this intermediate was not observed in the reaction mixture. The extremely facile nature of this exo closure had been anticipated in analogy to the chemistry of the aryl keto

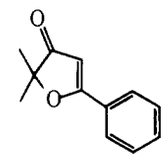
Scheme V



acids (**21**). The slower cyclization of *tert*-butyl keto acid **21** (R = *tert*-butyl) is surprising, but it should be noted that some closure to phthalide **20** (R = *tert*-butyl) occurred during the preparation of **21** (R = *tert*-butyl) and during its subsequent esterification.

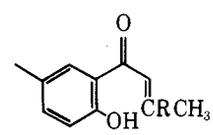
5-Endo-Digonal Closures. For the final five-membered ring forming reaction to be studied in the digonal series, we sought a model compound with steric and electronic properties as similar to **1** and **16** as possible. Hydroxy ynone **26** was chosen as the best candidate and its synthesis is shown in Scheme V. Protection of acetone cyanohydrin as its tetrahydropyranyl ether **27** followed by partial reduction with lithium triethoxyaluminum hydride[12] gave aldehyde **28**. Addition of lithium phenylacetylide followed by removal of the protecting group proceeded smoothly affording diol **30** in good yield. Oxidation of **30** with active manganese dioxide completed the synthesis of ynone **26**.

Simple refluxing of **26** in methanol was insufficient to effect the cyclization;[13] however, treatment of **26** with sodium methoxide in methanol at reflux provided the natural product bullatenone[15] (**31**) in excellent yield, establishing the favored

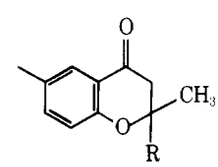


nature of this 5-endo-digonal mode of closure in contrast to the 5-endo-trigonal reactions described above. This cyclization could also be effected more slowly under acidic conditions (*p*-toluenesulfonic acid in refluxing methanol).

6-Endo-Trigonal Closures. To extend our study we examined the 6-endo-trigonal case by the well known chalcone to chromanone conversion. Chalcones **32a** and **32b** were



32a, R = H
b, R = CH_3



33

therefore prepared via the procedure of von Auwers and Lämmerhirt,[16] and their reactivity under basic reaction conditions was studied. In each instance, treatment with either aqueous sodium hydroxide or methanolic sodium methoxide effected smooth cyclization to the corresponding chromanones **33a** and **33b** attesting to the relative facility of this mode of closure.

Conclusion

In the present study of a series of structurally related unsaturated hydroxy ketones we have found experimental

support for the suggestion[2] that there are substantial differences in the ease of nucleophilic ring closures, strongly dependent on ring size, geometry of reacting terminus, and the endo or exo nature of the reactions. In those examples we examined, 5-exo-trigonal closures were facile, whereas the alternative 5-endo-trigonal processes did not proceed under similar conditions. On the other hand, the *endocyclic* cyclizations could be readily induced in 6-membered systems (6-endo-trigonal) and in acetylenic systems (5-endo-digonal). Finally, the stereoelectronic barriers to the 5-endo-trigonal reactions could be overcome by acid catalysis, an effect we presently attribute to a reduction in the rotational barriers in protonated enones.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 700 spectrophotometer. NMR spectra were recorded on either a Varian Associates T-60, a Hitachi Perkin-Elmer R20B, or a Hitachi Perkin-Elmer R22 spectrometer. Ultraviolet spectra were obtained using a Perkin-Elmer Coleman 124 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6 mass spectrometer.

Tetrahydrofuran (THF), diethyl ether, and benzene were distilled from sodium–benzophenone ketyl under nitrogen. Methanol was dried by distillation from magnesium methoxide.

(*E*)-2-Methyl-3-oxo-5-phenylpent-4-en-2-ol (1).[6] To a solution of 6.7 g (65.9 mmol) of 3-hydroxy-3-methyl-2-butanone and 13.9 mL (131.7 mmol) of benzaldehyde in 100 mL of ethanol was added 26 mL (130 mmol) of 5 N sodium hydroxide. The reaction mixture was stirred for 6 h at room temperature and the ethanol was removed in vacuo. Ether was added and the solution was washed with water and brine. The ether layer was dried over $MgSO_4$ and the solvent was removed in vacuo to give an orange oil. Filtration through silica gel (25% EtOAc/hexane) gave 8.1 g (43.6 mmol, 65%) of pale yellow solid. Recrystallization from pentane gave colorless needles: mp 39–40 °C (lit.[6] 39–40 °C); IR (melt) 3420, 3050, 3020, 2975, 1680, 1600, 1570 cm^{-1}; NMR ($CDCl_3$) δ 7.87 (d, J = 16 Hz, 1, vinyl), 7.40 (m, 5, aromatic), 7.07 (d, J = 16 Hz, 1, vinyl), 4.0 (s, 1, OH), 1.48 (s, 6, CH_3); mass spectrum m/e 190, 172, 157, 147, 132, 131, 105, 77, 59.

1-Cinnamoylcyclohexanol (3a). To a solution of 6.22 g (44.4 mmol) of 1-acetylcyclohexanol (**2**)[7] in 5 mL of methanol was added 10 mL of 60% aqueous potassium hydroxide and 4.64 g (44.4 mmol) of benzaldehyde. The mixture was stirred 15 min at room temperature, diluted to 50 mL with methanol, and poured onto 250 mL of a 3:1 mixture of ice and hydrochloric acid. The solution was extracted with ether and the ethereal solution was dried (brine, $MgSO_4$). Removal of solvents in vacuo afforded 8.7 g (37.8 mmol, 85%) of **3a** as a viscous oil: IR (neat) 3400, 2950, 1680, 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.4 (m, 7, aromatic and vinyl), 3.8 (broad s, 1, OH), 1.7 (m, 10, CH_2).

1-*p*-Methoxycinnamoylcyclohexanol (3b). To a solution of 5.16 g (36.4 mmol) of 1-acetylcyclohexanol[7] in 5 mL of methanol was added 10 mL of 60% aqueous potassium hydroxide and 5.02 g (26.9 mmol) of *p*-methoxybenzaldehyde. The mixture was shaken 15 min at room temperature, diluted to 50 mL with methanol, and poured onto 250 mL of 3:1 ice–hydrochloric acid. The solution was extracted with ether and the combined ethereal layers were washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo afforded 8.97 g of yellow crystals (95% crude yield). Recrystallization from hexane–ether afforded white crystals: mp 89–90 °C; IR (KBr) 3370, 2930, 2850, 1660, 1580, 1510, 1265, 1180, 1040, 1025, 995, 825, 800 cm^{-1}; NMR ($CDCl_3$) δ 7.83 (d, J = 16 Hz, 1, vinyl), 7.57 and 6.94 (AB quartet, J_{AB} = 9 Hz, 4, aromatic), 7.10 (d, J = 16 Hz, 1, vinyl), 3.96 (s, 1, OH), 3.85 (s, 3, OCH_3), 1.80 (m, 10, $-CH_2-$); mass spectrum m/e 260, 162, 161, 134, 99, 81.

Attempted Base-Catalyzed Cyclization of 1. Sodium metal (30 mg, 1.3 mmol) was allowed to react with 10 mL of dry methanol, and 210 mg (1.10 mmol) of hydroxy enone 1 was added. The solution was heated at reflux for 19 h and the methanol was removed in vacuo. Ether was added and the solution was washed with water and brine. The ethereal solution was dried ($MgSO_4$) and the solvent was removed in vacuo to afford 206 mg (98% recovery) of pale yellow oil. Analysis of IR, NMR, and TLC established the identity of the product with the starting material.

Attempted Sodium Hydride Catalyzed Cyclization of 3a. To a suspension of 96 mg (2.00 mmol) of 50% sodium hydride dispersion in 7.5 mL of dry THF stirred at 0 °C under nitrogen was added a solution of 339 mg (1.47 mmol) of enone **3a** in 2.5 mL of THF. The mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched by the addition of 20% aqueous ammonium chloride. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic phases were dried (brine, $MgSO_4$) and solvent was removed in vacuo to give a viscous oil. Preparative TLC on silica gel (20% EtOAc/hexane) gave 303 mg (1.32 mmol, 90%) of **3a** which was shown to be identical with the starting material by IR and NMR.

Attempted Sodium Hydride Catalyzed Cyclization of 3b. To a suspension of 51 mg (1.06 mmol) of 50% sodium hydride dispersion in 8.5 mL of THF stirred at 0 °C under nitrogen was added a solution of 251 mg (0.97 mmol) of enone **3b** in 3.5 mL of THF. The reaction mixture was stirred 9 h at room temperature and quenched by the addition of 20% aqueous ammonium chloride. The solution was extracted with ether and the ethereal solution was dried (brine, $MgSO_4$). Removal of the solvent in vacuo gave a viscous oil. Preparative TLC on silica gel (10% EtOAc/hexane) gave 239 mg (0.92 mmol, 95%) of a thick oil with IR and NMR spectra identical with those of the starting material.

Attempted Sodium Methoxide Catalyzed Cyclization of 3b. Sodium metal (119 mg, 5.16 mmol) was allowed to react with 25 mL of methanol, and 714 mg (2.75 mmol) of enone **3b** was added. The solution was heated at reflux for 15 h. The reaction mixture was cooled and adjusted to pH 5 with 1 N HCl. The mixture was poured into 300 mL of water and extracted with ether. The extracts were dried (brine, $MgSO_4$) and solvent was removed in vacuo to afford 670 mg (2.58 mmol, 94%) of crystalline solid. The IR and NMR spectra of the product were identical with those of the starting material.

(*E*)-2-Methyl-3-oxo-4-deuterio-5-phenylpent-4-en-2-ol (4). To a solution of 1.17 mmol of sodium methoxide in 7 mL of methanol-*O*-*d* was added 207 mg (1.09 mmol) of enone **1**. The solution was heated at reflux for 18 h and the methanol was removed in vacuo. Ether was added and the solution was washed with water. The solution was dried over $MgSO_4$ and the solvent was removed in vacuo to yield 197 mg (1.02 mmol, 94%) of enone **4** as a pale yellow oil: IR (neat) 3440, 3060, 3020, 2980, 1675, 1600, 1575 cm^{-1}; NMR ($CDCl_3$) δ 7.86 (broad s, 1, vinyl), 7.3–7.7 (5, aromatic), 4.15 (s, 1, OH), 1.50 (s, 6, CH_3); mass spectrum m/e 191, 173, 158, 148, 133, 132, 106, 77, 59. The NMR, IR, and TLC showed no evidence of any formation of furanone **10**.

Deuterium Incorporation with Hydroxy Ketone 3b. Sodium metal (11.5 mg, 0.50 mmol) was allowed to react with 6 mL of freshly distilled methanol-*O*-*d* and 100 mg (0.38 mmol) of hydroxy ketone **3b** was added. The reaction mixture was heated at reflux for 19 h, taken up in 25 mL of ether, and washed with brine. The ether layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo to give 92 mg of pale yellow solid (92% recovery). Analysis by IR, NMR, and TLC established the identity of the product to the starting material with incorporation of one deuterium. Recrystallization from hexane gave white crystals: mp 88–89 °C; IR (KBr), 3400, 1660, 1580, 1560, 1515 cm^{-1}; NMR ($CDCl_3$) δ 7.78 (broad s, 1, vinyl), 7.54 and 6.90 (AB quartet, J_{AB} = 8 Hz, 4, aromatic), 3.85 (s, 4, OCH_3 and OH), 1.4–2.1 (m, 10, CH_2); mass spectrum m/e 261, 163, 162, 135, 99, 81.

1,1-Dimethyl-2-oxo-3-deuterio-1,2-dihydronaphthalene (9). To a solution of 2.6 mmol of sodium methoxide in 7 mL of methanol-*O*-*d* was added 356 mg (2.06 mmol) of enone 8.[9] The solution was heated at reflux for 18 h and the methanol was removed in vacuo. Ether was added and the solution was washed with D_2O and dried over $MgSO_4$. Removal of solvent in vacuo gave 331 mg (1.91 mmol, 93%) of enone **9** as a pale yellow liquid: IR (neat) 2970, 1660, 1650, 770, 740 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.5 (m, 5, aromatic and vinyl), 1.48 (s, 6, CH_3). Subsequent experiments have shown the exchange to be complete in ca. 1.5 h.

2,2-Dimethyl-5-phenyltetrahydro-3-furanone (10). A solution of 2.0 g (10.5 mmol) of enone **1** and 500 mg (2.64 mmol) of *p*-toluenesulfonic acid monohydrate in 75 mL of 1,2-dichloroethane was heated at reflux for 24 h. The solution was diluted with methylene chloride and washed with dilute sodium hydroxide, water, and brine. The solution was dried over $MgSO_4$ and the solvent was removed in vacuo to afford 2.3 g of viscous oil. Filtration through 60 g of silica gel gave 1.60 g (8.4 mmol, 80%) of pale yellow solid: mp 34–36 °C (lit.[6] 35–36 °C); IR (neat) 2980, 1750, 1180, 1120, 780, 720 cm^{-1}; NMR ($CDCl_3$) δ 7.34 (broad s, 5, aromatic), 5.13 (d of d, X of ABX, J_{AX} = 7 Hz, J_{BX} = 10 Hz, 1, methine), 2.85 and 2.35 (AB of ABX, J_{AX} = 7 Hz, J_{BX} = 10 Hz, J_{AB} = 18 Hz, 2, methylene), 1.38 (s, 3, CH_3), 1.30 (s, 3, CH_3); mass spectrum m/e 190, 172, 162, 132, 104, 78, 77.

Furanone 11a. A solution of 1.23 g (5.35 mmol) of enone **3a** and 150 mg (0.79 mmol) of *p*-toluenesulfonic acid monohydrate in 25 mL of benzene was heated at reflux for 24 h. The solution was neutralized

with aqueous sodium bicarbonate and the organic phase was separated. The aqueous phase was extracted with ether and the combined organic phases were dried (brine, $MgSO_4$). Removal of the solvent in vacuo followed by chromatography on Florisil (10% $CHCl_3$/hexane) gave **11a** as a viscous oil in 10% yield: IR (neat) 2950, 2860, 1745, 1450, 1070, 780, 720 cm^{-1}; NMR ($CDCl_3$) δ 7.4 (m, 5, aromatic), 5.2 (m, 1, methine), 2.7 (m, 2, CH_2), 1.80 (m, 10, ring CH_2).

Furanone 11b. A solution of 390 mg (1.50 mmol) of enone **3b** and 293 mg (1.54 mmol) of *p*-toluenesulfonic acid monohydrate in 10 mL of benzene was heated at reflux overnight. The reaction mixture was neutralized with aqueous sodium bicarbonate and the organic phase was separated. The aqueous layer was extracted with ether and the combined organics were dried (brine, $MgSO_4$). Removal of the solvent in vacuo followed by preparative layer chromatography (20% EtOAc/hexane) afforded 180 mg (0.69 mmol, 46%) of furanone **11b** as a viscous oil: IR (neat) 2950, 2870, 1745, 1520, 1260, 845 cm^{-1}; NMR ($CDCl_3$) δ 7.40 and 6.96 (AB quartet, J = 9 Hz, 4, aromatic), 5.20 (X of ABX, J_{AX} = 6 Hz, J_{BX} = 9 Hz, 1, methine), 3.86 (s, 3, OCH_3), 2.5 and 2.9 (AB of ABX, J_{AB} = 18 Hz, J_{AX} = 6 Hz, J_{BX} = 9 Hz, 2, CH_2), 1.70 (m, 10, ring CH_2).

Attempted Base-Catalyzed Ring Opening of Furanone 11a. A solution of 66 mg (0.29 mmol) of furanone **11a** in 2.5 mL of dry THF was added to a suspension of 98 mg (2.05 mmol) of 50% sodium hydride dispersion in 7.5 mL of THF stirred under nitrogen at 0 °C. The reaction mixture was allowed to react 4 h at room temperature and then 4 h at reflux. The mixture was quenched with 20% aqueous ammonium chloride and extracted with ether. The ether layers were washed with brine and dried over $MgSO_4$. Removal of solvent in vacuo followed by preparative layer chromatography (20% EtOAc/hexane) gave 59 mg (90% recovery) of a viscous oil whose spectral properties were identical with the starting material.

Attempted Base-Catalyzed Ring Opening of Furanone 11b. A solution of 310 mg (1.2 mmol) of furanone **11b** in 5 mL of THF was added to a suspension of 63.3 mg (1.32 mmol) of 50% sodium hydride dispersion in 5 mL of THF stirred under nitrogen at 0 °C. The mixture was stirred 4 h at room temperature and 4 h at reflux followed by quenching with 20% aqueous ammonium chloride. The reaction mixture was extracted with ether and the organic phase was dried (brine, $MgSO_4$). Removal of solvent in vacuo gave a 98% recovery of product with spectral data identical with the starting material.

Base-Catalyzed Deuterium Incorporation with Furanone 10. To a solution of 1.6 mmol of sodium methoxide in 7 mL of methanol-*O*-*d* was added 168 mg (0.89 mmol) of furanone **10**. The solution was heated at reflux 17 h and the methanol was removed in vacuo. Ether was added and the solution was washed with D_2O and dried over $MgSO_4$. Removal of solvent in vacuo gave 143 mg (0.75 mmol, 85%) of product as a light yellow oil: IR (neat) 2980, 1750, 1180, 1120, 770, 710 cm^{-1}; NMR ($CDCl_3$) δ 7.34 (broad s, 5, aromatic), 5.13 (broad s, 1, methine), 1.38 (s, 3, CH_3), 1.30 (s, 3, CH_3); mass spectrum *m/e* 192, 172, 164, 134, 133, 132, 106, 80, 79, 78, 77. The Nmr, IR, and TLC showed no evidence of any formation of enone 1.

Base-Catalyzed Deuterium Incorporation with Furanone 11b. Sodium metal (58.2 mg, 2.53 mmol) was allowed to react with 10 mL of methanol-*O*-*d*, and 100 mg (0.38 mmol) of furanone **11b** was added. The mixture was refluxed 19 h and acidified to pH 3 with 1 N HCl, poured into water, and extracted with ether. The extracts were dried with brine and $MgSO_4$. Removal of the solvent in vacuo afforded 60 mg (60% recovery) of the deuterated product: NMR ($CDCl_3$) δ 7.4 and 6.95 (AB quartet, J_{AB} = 9 Hz, 4, aromatic), 5.2 (broad s, 1, methine), 3.80 (s, 3, OCH_3), 1.65 (m, 10, CH_2).

(*E*)-2-Methyl-3-oxo-5-[4-hydroxyphenyl]pent-4-en-2-ol (13). A solution of 2.1 g (20.8 mmol) of 3-hydroxy-3-methyl-2-butanone, 2.54 g (20.8 mmol) of 4-hydroxybenzaldehyde and 8.4 mL (42 mmol) of 5 N sodium hydroxide in 30 mL of ethanol was stirred for 10 days at room temperature. The ethanol was removed in vacuo and the mixture was taken up in ether and water. The aqueous layer was acidified to pH 3 and extracted with ether. Removal of the solvent in vacuo gave 4.0 g of yellow solid. Recrystallization from ether gave pale yellow crystals: mp 154–156 °C, IR (KBr) 3340, 3240, 2980, 1675, 1590, 1515, 1445, 1285, 1180, 1090, 995, 970, 850, 825 cm^{-1}; NMR (Me_2SO-d_6) δ 7.3 and 7.5 (AB, J_{AB} = 16 Hz, 2, vinyl), 7.6 and 6.8 (A_2B_2, J_{AB} = 8 Hz, 4, aromatic), 5.25 (s, 1, OH), 3.3 (s, 1, OH), 1.27 (s, 6, CH_3).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.76; H, 7.04.

2,2-Dimethyl-5-[4-hydroxyphenyl]tetrahydro-3-furanone (15). A solution of 395 mg (1.92 mmol) of enone **13** and 100 mg (0.53 mmol) of *p*-toluenesulfonic acid monohydrate in 40 mL of 1,2-dichloroethane was heated at reflux for 4 h. The cooled solution was diluted with dichloromethane and washed with water and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo to give 408 mg of yellow solid. Chromatography on 30 g of silica gel (10% ether/CH_2Cl_2) gave 360 mg (1.75 mmol, 91%) of **15** as a pale yellow solid. Recrystallization from ether–hexane gave an analytical sample as white crystals: mp 101–102 °C; IR ($CHCl_3$) 3570, 3300, 3000, 1750, 1175 cm^{-1}; NMR ($CDCl_3$) δ 7.23 and 6.75 (A_2B_2, J_{AB} = 8 Hz, 4, aromatic), 6.45 (s, 1, OH), 5.14 (d of d, X of ABX, J_{AX} = 7 Hz, J_{BX} = 10 Hz, 1, methine), 2.9 and 2.5 (AB of ABX, J_{AX} = 7 Hz, J_{BX} = 10 Hz, J_{AB} = 18 Hz, 2, methylene), 1.40 (s, 3, CH_3), 1.32 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.98; H, 7.02.

Base-Catalyzed Cleavage of Furanone 15. To a solution of 1.17 mmol of sodium methoxide in 10 mL of methanol was added 104 mg (0.505 mmol) of furanone **15**. The solution was heated at reflux for 72 h. The methanol was removed in vacuo, ether and water were added, and the aqueous layer was acidified with 10% HCl. The ether layer was dried with brine and $MgSO_4$ and the solvent was removed in vacuo to afford 105 mg (100%) of enone **13** as a pale yellow solid. Analysis by NMR and IR showed the cleavage to be complete. No trace of the starting furanone was observed.

***o*-((*E*)-3-Oxo-4,4-dimethyl-1-pentenyl)benzoic Acid (21) (R = *tert*-Butyl).** A solution of 6.1 g (92.8 mmol) of potassium hydroxide in 20 mL of 50% aqueous ethanol was added dropwise to a rapidly stirred solution of 4.64 g (46.4 mmol) of pinacolone and 6.96 g (46.4 mmol) of phthalaldehydic acid in 30 mL of ethanol. The mixture was stirred for 2 h at room temperature and the solvent was removed in vacuo. The resulting pale yellow paste was dissolved in 200 mL of water and acidified with 10% HCl. The resulting precipitate was extracted with ether. The ether layer was dried (brine, $MgSO_4$), and the solvent was removed in vacuo. Recrystallization from ethanol gave a first crop of 3.0 g of white needles: mp 138–140 °C; IR (KBr) 2200–3600 (CO_2H), 1690, 1675, 1600 cm^{-1}; NMR (acetone-d_6) δ 8.52 (d, J = 16 Hz, 1, vinyl), 7.5–8.2 (m, 4, aromatic), 7.25 (d, J = 16 Hz, 1, vinyl), 1.24 (s, 9, *tert*-butyl). The acid proton was not observable in the NMR spectrum.

Methyl *o*-((*E*)-3-Oxo-4,4-dimethyl-1-pentenyl)benzoate (22). To a solution of 2.2 g (9.5 mmol) of acid **21** in 200 mL of methanol was added 1.31 g (9.5 mmol) of potassium carbonate and 2.95 mL (47.5 mmol) of methyl iodide. The resulting suspension became a homogeneous solution after 30 min and the mixture was heated at reflux for 20 h. The methanol was removed in vacuo and the residue was taken up in methylene chloride and washed with dilute sodium bicarbonate. The aqueous phase was extracted with methylene chloride and the combined organic layers were washed with saturated sodium bicarbonate and dried over $MgSO_4$. Removal of the solvent in vacuo gave 2.48 g of an orange oil. Chromatography on 75 g of silica gel with 10% EtOAc/hexanes gave 1.75 g (7.1 mmol, 75%) of ester **22** followed by 470 mg (2.02 mmol, 21%) of phthalide **20**, R = *tert*-butyl.[10] Recrystallization of the ester from hexane gave white crystals: mp 54–56 °C; IR ($CHCl_3$) 2970, 1720, 1680, 1605, 1090 cm^{-1}; NMR ($CDCl_3$) δ 8.40 (d, J = 16 Hz, 1, vinyl), 7.9 (m, 1, aromatic) 7.5 (m, 3, aromatic), 6.98 (d, J = 16 Hz, 1, vinyl), 3.93 (s, 3, OCH_3), 1.24 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.94; H, 7.39.

Methyl *o*-((*E*)-3-Hydroxy-4,4-dimethyl-1-pentenyl)benzoate (23). To a suspension of 1.27 g (5.02 mmol) of lithium tri-*tert*-butoxyaluminum hydride in 100 mL of ether was added a solution of 1.03 g (4.18 mmol) of enone **22** in 10 mL of ether. The reaction mixture was stirred for 5 min at room temperature and quenched by the addition of 20 mL of pH 7 buffer and 20 mL of water. The layers were separated and the ether layer was washed with 20 mL of water. The total aqueous layer was acidified with 10% HCl until the solids had all dissolved and this solution was extracted three times with methylene chloride. The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave 1.03 g of colorless oil. Chromatography on 35 g of silica gel with 10% EtOAc/hexanes gave 190 mg of light orange oil which was assigned to be the product of 1,4 reduction by spectral methods, followed by 890 mg (3.58 mmol, 86%) of alcohol **23**: IR (neat) 3470, 1720, 1275 cm^{-1}; NMR ($CDCl_3$) δ 7.85 (m, 1, aromatic), 7.30 (m, 4, aromatic and vinyl), 6.1 (d of d, J_A = 16 Hz, J_B = 7 Hz, 1, vinyl), 3.96 (broadened d, J = 7 Hz, 1, methine), 3.83 (s, 3, OCH_3), 2.57 (s, 1, OH), 0.99 (s, 9, *tert*-butyl).

2-(*o*-(*E*)-3-Hydroxy-4,4-dimethyl-1-pentenylphenyl)-2-propanol (24). To a solution of 800 mg (3.22 mmol) of hydroxy ester **23** in 25 mL of ether stirred at 0 °C was added 10 mL (12.9 mmol) of a 1.3 M solution of methyllithium in ether. The reaction mixture was stirred for 30 min at 0 °C and allowed to warm to room temperature. Ether (40 mL) and 20 mL of water were added and the phases were separated. The aqueous phase was extracted with more ether and the

combined ether layers were dried (brine, $MgSO_4$). Removal of the solvent in vacuo gave 804 mg of viscous yellow oil. Chromatography on 40 g of silica gel with 25% EtOAc/hexane gave 239 mg of a mixture of **24** and the acetophenone derivative resulting from addition of a single molecule of organometallic to the ester, followed by 400 mg of pure diol **24** as an extremely viscous gum: IR ($CHCl_3$) 3570, 3420, 1475, 1365, 1000 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (m, 5, aromatic and vinyl), 6.04 (d of d, J_A = 16 Hz, J_B = 6 Hz, 1, vinyl), 3.90 (broadened d, J = 6 Hz, 1, methine), 2.4 (s, 2, OH), 1.64 (s, 6, CH_3), 0.98 (s, 9, *tert*-butyl).

1-*H*-1-(2-Oxo-3,3-dimethylbutyl)-3,3-dimethyldihydroisobenzofuran (25). To a solution of 132 mg (0.53 mmol) of diol **24** in 10 mL of methylene chloride was added 0.75 g (8.6 mmol) of manganese dioxide. The reaction mixture was stirred for 1.5 h at room temperature, filtered through celite, and the solid was washed with more methylene chloride. Removal of the solvent in vacuo gave 130 mg (0.53 mmol, 100%) of **25** as a colorless oil: IR (neat) 2980, 1705 cm^{-1}; NMR ($CDCl_3$) δ 7.18 (m, 4, aromatic), 5.7 (t, J = 7 Hz, 1, methine), 2.92 (AB of ABX, J_{AB} = 17 Hz, J_{AX} = J_{BX} = 7 Hz, 2, methylene), 1.52 (s, 3, CH_3), 1.43 (s, 3, CH_3), 1.17 (s, 9, *tert*-butyl).

The 2,4-dinitrophenylhydrazone derivative was prepared and recrystallized from ether to afford orange crystals: mp 166–167.5 °C; IR ($CHCl_3$) 2950, 1605, 1580, 1340, 1315 cm^{-1}; NMR ($CDCl_3$) δ 11.6 (s, 1, NH), 9.03 (d, J = 2 Hz, 1, aromatic), 8.30 (½ of AB, J_{AB} = 15 Hz, further splitting J = 2 Hz, 1, aromatic), 8.05 (½ of AB, J_{AB} = 15 Hz, 1, aromatic), 7.4 (m, 4, aromatic), 5.48 (d of d, J_{AX} = 8 Hz, J_{BX} = 3 Hz, 1, methine), 3.10 (AB of ABX, J_{AB} = 14 Hz, J_{AX} = 8 Hz, J_{BX} = 3 Hz, 2, methylene), 1.68 (s, 3, CH_3), 1.44 (s, 3, CH_3), 1.38 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{22}H_{26}N_4O_5$: C, 61.96; H, 6.15; N, 13.14. Found: C, 62.07; H, 6.21; N, 13.09.

2-Methyl-2-[tetrahydropyran-2-yloxy]propionitrile (27). To a solution of 16.0 g (0.188 mol) of acetone cyanohydrin and 25 mL (0.28 mol) of dihydropyran in 100 mL of methylene chloride was added ca. 50 mg of *p*-toluenesulfonic acid. A violently exothermic reaction began immediately. The reaction mixture was stirred for 1.5 h at room temperature. The solution was diluted with 500 mL of ether and extracted with water. The formation of emulsions complicated this extraction and much material was lost in this manner. The organic phase was dried over $MgSO_4$, the solvent was removed in vacuo, and the residue was distilled to afford 18.1 g (0.107 mol, 57%) of product as a light yellow liquid: bp 65–68 °C (1.0 mm); IR (neat) 2950, 2870, 1180, 1130, 1080, 1050, 1035, 1000 cm^{-1};[17] NMR ($CDCl_3$) δ 5.0 (m, 1, methine), 3.3–4.1 (m, 2, $-OCH_2-$), 1.3–1.7 (m, 12, $-CH_2-$ and $-CH_3$).

2-Methyl-2-(tetrahydropyran-2-yloxy)propionaldehyde (28). To 30 mL (33.0 mmol) of a 1.1 M solution of lithium aluminum hydride in ether was added 4.84 mL (49.5 mmol) of ethyl acetate while vigorously stirring and cooling to 0 °C. The resulting suspension of lithium triethoxyaluminum hydride was stirred for 15 min at 0; 3.72 mL (2.0 mmol) of nitrile **27** was added and stirring at 0 °C was continued for 45 min. The mixture was quenched by the addition of 50 mL of 10% H_2SO_4 and 50 mL of ether. The layers were separated and the aqueous phase was further extracted with ether. The combined organic phases were washed with water and brine, dried over $MgSO_4$, and the solvent was removed in vacuo to afford 2.7 g of colorless liquid. Chromatography on 50 g of silica gel (petroleum ether/ethyl acetate) gave 1.28 g of the desired aldehyde **28** which was molecularly distilled (kugelrohr) at 100 °C (10 mm), giving a colorless liquid: IR (neat) 2950, 2860, 2700, 1725 cm^{-1}; NMR ($CDCl_3$) δ 9.6 (s, 1, –CHO), 4.7 (m, 1, methine), 3.5 and 3.95 (m, 2, $-OCH_2-$), 1.6–2.1 (m, 6, CH_2), 1.38 (s, 3, CH_3), 1.33 (s, 3, CH_3); MS 172, 171, 143, 85, 71, 29.

1-Phenyl-4-methyl-4-[tetrahydropyran-2-yloxy]pent-1-yn-3-ol (29). A solution of 296 mg (2.9 mmol) of phenylacetylene in 10 mL of dry THF was cooled to −78 °C and treated by dropwise addition of 1.31 mL (2.9 mmol) of a 2.2 M solution of *n*-butyllithium in hexane. The mixture was stirred for 15 min at 0 °C and 480 mg (2.78 mmol) of aldehyde **28** was added. The mixture was stirred 30 min at 0 °C and the THF was removed in vacuo. The residue was taken up in ether and washed with water and brine. The ether solution was dried over Na_2SO_4 and the solvent was removed in vacuo to give 800 mg of yellow oil. Chromatography on 20 g of activity III neutral alumina (hexane/ethyl acetate) gave 680 mg (2.48 mmol, 86%) of alcohol **29** as a pale yellow oil: IR (neat) 3400, 2950, 2870 cm^{-1}; NMR ($CDCl_3$) (mixture of diastereomers) δ 7.2 (m, 5, aromatic), 4.5 (m, 1, THP methine), 4.32 and 4.37 (2s, 1, methine), 4.0 (broad s, 1, OH), 3.8 and 3.5 (m, 2, $-OCH_2-$), 1.2–2.0 (12, $-CH_2-$ and $-CH_3$).

1-Phenyl-4-methylpent-1-yne-3,4-diol (30). To a solution of 118 mg (0.43 mmol) of tetrahydropyranyl ether **29** in 3 mL of THF was added 5 mL of 50% aqueous acetic acid. The reaction mixture was stirred for 4 h at room temperature. The pH was adjusted to 7 with 5% sodium hydroxide and the solution was extracted twice with ether. The ether solution was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave 88 mg of yellow oil, which was purified by preparative layer chromatography on silica gel (50% EtOAc/hexane) to give 65 mg (0.34 mmol, 80%) of diol **30** as a colorless oil: IR (neat) 3370, 2250, 1600, 770, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.1–7.6 (m, 5, aromatic), 4.41 (broad s, 1, methine), 3.6 (broad s, 1, OH), 2.95 (broad s, 1, OH), 1.40 (s, 6, CH_3), mass spectrum *m/e* 190, 157, 131, 77, 59.

2-Methyl-3-oxo-5-phenylpent-4-yn-2-ol (26). To a solution of 260 mg (1.37 mmol) of diol **30** in 20 mL of methylene chloride was added 1.27 g (14.7 mmol) of active manganese dioxide. The reaction mixture was stirred for 30 min at room temperature, filtered, and the precipitate was washed with more methylene chloride. Removal of the solvent in vacuo gave 196 mg (1.04 mmol, 82%) of **26** as a pale yellow oil: IR (neat) 3430, 2230, 1660 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.8 (m, 5, aromatic), 3.6 (s, 1, OH), 1.56 (s, 6, CH_3).

2-Phenyl-4-oxo-5,5-dimethyldihydrofuran (31). To a solution of 84 mg (0.44 mmol) of ynone **26** in 5 mL of methanol was added 12 mg (0.50 mmol) of oil-free sodium hydride. The solution was heated at reflux for 2 h, cooled, and the methanol was removed in vacuo. The residue was partitioned between water and methylene chloride. The organic phase was dried over $MgSO_4$ and solvent was removed in vacuo to afford 77 mg (0.41 mmol, 93%) of 31 as a pale yellow solid. Recrystallization from hexanes gave an analytical sample: mp 66–67 °C (lit.[15] 67.5–68.5 °C; IR ($CHCl_3$) 3000, 1680, 1605, 1590, 1565 cm^{-1}; NMR ($CDCl_3$) δ 7.4–8.0 (m, 5, aromatic), 5.98 (s, 1, vinyl), 1.50 (s, 6, CH_3); UV λ_{max} (EtOH) 215, 242, 298, ϵ_{298} = 17 750.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.69; H, 6.54.

A similar reaction sequence using a catalytic amount of *p*-toluenesulfonic acid in place of the sodium methoxide gave a 79% yield of **31** after 19 h at reflux in methanol.

2-Crotonyl-4-methylphenol (32a). To 16 mL of carbon disulfide in a dry nitrogen purged flask equipped with a magnetic stirrer and a reflux condenser was added 3.66 g (30 mmol) of *p*-methyl anisole and 3.06 (30 mmol) of crotonyl chloride. The resulting solution was stirred at room temperature while 3.92 g (30 mmol) of anhydrous aluminum chloride was added slowly, causing a vigorous evolution of hydrogen chloride. After the addition was complete, the mixture was stirred for 1 h at room temperature. An additional 3.92 g (30 mmol) of anhydrous aluminum chloride was added and the mixture was refluxed on a steam bath until gas evolution ceased; it was then cooled to room temperature and allowed to stand for 4 h. The mixture was cautiously quenched into concentrated hydrochloric acid/ice, and the resulting yellow oily aqueous phase was decanted from red tarry by-products, extracted into ether, and washed five times with water, once with brine, dried ($MgSO_4$), and concentrated to give a red oil which crystallized from petroleum ether containing a small amount of methanol to yield 1.53 g (29%) yellow needles: mp 65 °C (lit.[16] 65–66 °C); IR (CCl_4) 2800–3300 (m), 1665 (s), 1640 (s), 1600 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.02 (d, 3 H, J = 5 Hz), 2.35 (s, 3H), 6.67–7.5 (m, 5H), 12.75 (s, 1H).

2-(3-Methylcrotonyl)-4-methylphenol (32b). A solution of 3.66 g (30 mmol) of *p*-methyl anisole and 3.54 g (30 mmol) of dimethylacryloyl chloride in 16 mL of carbon disulfide was reacted exactly as for **32a**. Extractive work-up yielded a crystalline product which was recrystallized from petroleum ether twice to yield 2.50 g (44%) yellow crystals: mp 49–50 °C (lit.[16] 50 °C); IR (CCl_4) 2800–3300 (m), 1660 (s), 1600 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 6.65 (br s), and 6.80 (s, 2H total), 7.0–7.2 (m, 1H), 7.4 (m, 1H), 12.60 (s, 1H).

Sodium Hydroxide Catalyzed Cyclization of 32b. A solution of **32b** in aqueous base was prepared by dissolving 0.150 g (0.78 mmol) of **32b** in 10 mL of 5% aqueous sodium hydroxide. The resulting bright yellow solution rapidly faded to become colorless, and after standing at room temperature for 2 h, the solution was diluted with water and extracted twice with ether, which was subsequently washed with brine and dried ($MgSO_4$) to give 0.100 g (65%) of **33b** as a light yellow oil: IR (CCl_4) 2990 (s), 1695 (s), 1620 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.52 (s, 6H), 2.33 (s, 3H), 2.7 (s, 2H), 6.7 (d, 1H, J = 8 Hz), 7.18 (2d, 1 H, J = 2 Hz, 8 Hz), 7.58 (br d, 1 H, J = 2 Hz).

Sodium Hydroxide Catalyzed Cyclization of 32a. A solution of 0.150 g (0.85 mmol) of **32a** in 10 mL of 5% aqueous sodium hydroxide at room temperature was prepared as above. The bright yellow solution became clear and deposited a tan precipitate during the course of the reaction. After 2 h the solid was removed by filtration, washed with water, and dried in vacuo at room temperature to yield after recrystallization from petroleum ether 0.120 g (80%) of **33a** as white prisms: mp 54 °C (lit.[16] 54–55 °C); IR ($CHCl_3$) 3000 (w), 1685 (s), 1620

(s), 1500 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.5 (d, 3H, J = 6 Hz), 2.23 (s, 3H), 2.65 (d, 2H, J = 7 Hz), 4.1 (m, 1H), 6.72 (d, 1H, J = 8 Hz), 7.15 (br d, 1H, J = 7 Hz), 7.60 (br s, 1H).

Sodium Methoxide Catalyzed Cyclization of 32a. Compound **32a** (0.150, g, 0.85 mmol) and 0.100 g (1.85 mmol) of commercial sodium methoxide was dissolved in 5 mL of anhydrous methanol under nitrogen. The solution was allowed to stand for 4 h at room temperature and was then neutralized to pH 5 with 1 N hydrochloric acid. The solution was concentrated and the residue was extracted into ether, which was subsequently washed twice with water, once with brine, then dried ($MgSO_4$) and concentrated to give 0.140 g (93%) of tan crystals which were recrystallized from petroleum ether to give a product identical with that from closure in aqueous sodium hydroxide.

Sodium Methoxide Catalyzed Cyclization of 32b. A solution of 0.150 g (0.78 mmol) of **32b** and 0.100 g (1.85 mmol) of sodium methoxide in 5 mL of anhydrous methanol was treated exactly as above to yield 0.100 g (65%) light yellow oil, indistinguishable from the product obtained from the closure in aqueous sodium hydroxide.

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Registry No.—**1**, 63677-96-3; **2**, 1123-27-9; **3a**, 61541-23-9; **3b**, 20099-78-9; **4**, 63677-97-4; **5**, 63677-98-5; **8**, 23230-52-6; **9**, 63677-99-6; **10**, 63678-00-2; **11a**, 61541-24-0; **11b**, 61541-25-1; **13**, 63678-01-3; **15**, 63678-02-4; **17**, 119-67-5; **18** (R = *t*-Bu), 75-97-8; **21** (R = *t*-Bu), 63678-03-5; **22**, 63678-04-6; **23**, 63678-05-7; **24**, 63678,06-8; **25**, 63678-07-9; **25** DNP, 63678-08-0; **26**, 15495-23-5; **27**, 63678-09-1; **28**, 63678-10-4; **29** isomer A, 63678-11-5; **29** isomer B, 63678-12-6; **30**, 63678-13-7; **31**, 493-71-0; **32a**, 5631-63-0; **32b**, 24114-55-4; **33a**, 51423-95-1; **33b**, 63678-14-8; 3-hydroxy-3-methyl-2-butanone, 115-22-0; benzaldehyde, 100-52-7; *p*-methoxybenzaldehyde, 123-11-5; methanol-*O*-*d*, 1455-13-6; 4-hydroxybenzaldehyde, 123-08-0; acetone cyanohydrin, 75-86-5; dihydropyran, 110-87-2; phenylacetylene, 536-74-3; *p*-methyl anisole, 104-93-8; crotonyl chloride, 10487-71-5; dimethylacryloyl chloride, 3350-78-5.

References and Notes

(1) (a) National Cancer Institute Postdoctoral Trainee, Grant No. T32 CA09112, Sept 1, 1976–Mar 31, 1977; National Cancer Institute Postdoctoral Fellow, Grant No. F32 CA05968-01, Apr 1, 1977 to present; (b) National Science Foundation Predoctoral Fellow, 1977.

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(4) The adjectives *favored* and *disfavored* were deliberately chosen to describe ring closures of acyclic molecules, which after suitable rotations around single bonds (conformations), can or cannot attain the necessary geometry for bond formation, dictated by the stereoelectronic requirements of the reaction. For example, reactions of tetrahedral systems by displacements require the collinear arrangement of reacting atoms, characteristic of the S_N2 transition state. If by rotation around single bonds in the acyclic precursor this geometry cannot be reached, e.g., in endo-tetrahedral processes, then these are disfavored and vice versa.

(5) References to these and other favored closures may be found in ref 2.

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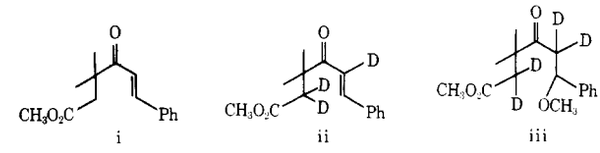

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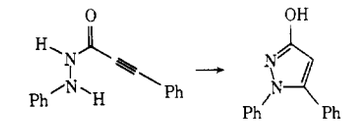

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Syntheses and Relative Stability of (D_3)-Trishomocubane (Pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane), the Pentacycloundecane Stabilomer[1]

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(D_3)-Trishomocubane (**1**) can be synthesized easily by aluminum bromide catalyzed isomerization of the "one-winged" bird-cage hydrocarbon **2** or by skeletal rearrangement during aqueous HI iodination of corresponding diol **11**, followed by dehalogenation. Syntheses of several derivatives of **1** and **2** including trishomocubanone (**14**) are also described. The isomerization results are in good agreement with predictions based on empirical force-field calculations on various $C_{11}H_{14}$ isomers which show that **1** is the pentacycloundecane stabilomer.

The trishomocubane (**1**) has two noteworthy features not explicitly mentioned by Underwood and Ramamoorthy in their account of the synthesis of this molecule.[3] First, **1** is one of the rare rigid organic molecules belonging to chiral point group D_3.[4] Second, **1** is the only structure possessing neither three- or four-membered rings nor other strained features among the large number of possible $C_{11}H_{14}$ pentacyclic isomers, and is thus likely to be the pentacycloundecane "sta-