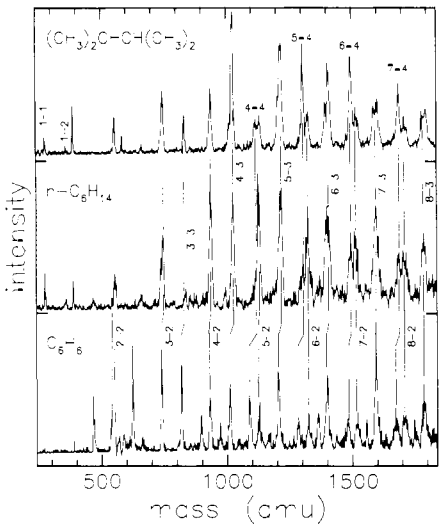

Figure 3. Time-of-flight mass spectra of platinum cluster reactions with benzene, *n*-hexane (0.22%), and 2,3-dimethylbutane (0.42%). The bis(benzene)diplatinum peak is off scale. The nomenclature is the same as in Figure 2. The extensive degree of dehydrogenation is emphasized by the connecting lines between the similar cluster adducts in the three spectra.

(3) A dramatic increase in the extent of chemisorption occurs between Pt_3 and Pt_4 for *n*-hexane and 2,3-dimethylbutane, so that by Pt_4 the triadduct dominates and by Pt_5 the tetraadduct is of comparable intensity. (4) For Pt_2–Pt_8 with *n*-hexane and 2,3-dimethylbutane, the degree of dehydrogenation increases with cluster size. This is extensive, as evidenced by the similar mass of products for Pt_4–Pt_8 with *n*-hexane and with benzene. The branched hexane also dehydrogenates but retains on the average two–four more hydrogens. These highly dehydrogenated adduct peaks have widths that indicate a distribution of losses.

The platinum dimer favors the production of a bis(benzene) complex which most likely results from an enhanced stability, due to π-type bonding similar to bis(arene) complexes[4] and chemisorbed benzene.[5] However, at these temperatures (300–600 K), platinum insertion into C–H bonds cannot be ruled out.[6]

The propensity of cyclohexane chemisorption on platinum clusters is similar to benzene, except for the lack of an intense $Pt_2(C_6D_6)_2$ signal. This behavior and the extent of dehydrogenation suggest benzene formation and are seen even on the Pt atom. The distinct change in the multiple chemisorption behavior, as function of cluster size, for *n*-hexane and 2,3-dimethylbutane and the onset of benzene dehydrogenation we take as evidence of an enhanced reactivity for Pt_4 and larger clusters.

Benzene dehydrogenates on Pt_3 and larger, with a maximum hydrogen loss of eight atoms on $Pt_8(adduct)_3$. Reversible C–H bond breaking is observed above 370 K in benzene on the Pt(111) surface,[3] suggesting these small metal clusters have at least the same activity toward C–H. The similarity between *n*-hexane and 2,3-dimethylbutane dehydrogenation suggests that *n*-hexane does not produce aromatic species on these unsupported clusters. However, we note that the area occupied by three and four hexane or benzene molecules lying flat as found on surfaces, significantly exceeds the small-cluster surface area[7,8] requiring these species to be quite different from the surface chemistry analogues.

In conclusion, our observations are consistent with a qualitative model in which Pt clusters seek to become coordinatively saturated by activation of sufficient C–H bonds and subsequent loss of hydrogen.

Registry No. Pt, 7440-06-4; hexane, 110-54-3; 2,3-dimethylbutane, 79-29-8; cyclohexane, 110-82-7; benzene, 71-43-2.

(4) Power, W. J.; Ozin, G. A. *Adv. Inorg. Chem. Radiochem.* **1980**, *23*, 79–175.
(5) Tsai, M.; Muetterties, E. L. *J. Am. Chem. Soc.* **1982**, *104*, 2534–2539.
(6) Klabunde, K. J.; Tanaka, Y. *J. Mol. Catal.* **1983**, *21*, 57–79.
(7) Lehwald, S.; Ibach, H.; Demuth, J. E. *Sur. Sci.* **1978**, *78*, 577–590.
(8) Firment, L. E.; Somorjai, G. A. *J. Chem. Phys.* **1977**, *66*, 2901–2913.

Total Synthesis of (±)-*O*-Methylorantine

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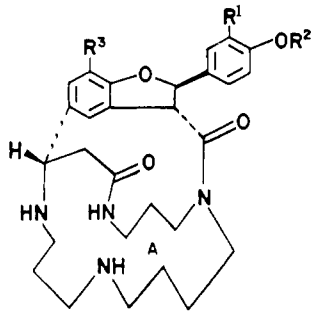
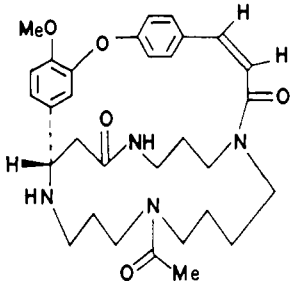
Among the most complex of the macrocyclic polyamine alkaloids are the ephedradines A (**1**), B (**2**), C (**3**), and D (**4**), hy-





1, $R^1 = R^2 = R^3 = H$ (ephedradine A, orantine) 6
2, $R^1 = OCH_3$; $R^2 = R^3 = H$ (ephedradine B)
3, $R^1 = OCH_3$; $R^2 = CH_3$; $R^3 = H$ (ephedradine C)
4, $R^1 = R^2 = H$; $R^3 = OCH_3$ (ephedradine D)
5, $R^1 = H$; $R^2 = CH_3$; $R^3 = H$ (*O*-methylorantine)

potensive components of the crude Chinese drug "mao-kon" prepared from the roots of *Ephedra* plants. The structures of these compounds, established by the X-ray crystallographic work of Hikino,[1-4] are characterized by the presence of a substituted dihydrobenzofuran grouping which bridges a 17-membered lactam ring (ring A) containing a spermine nucleus. The same dihydrobenzofuran system is found in the antifungal agent, hordatine A,[5] and in the closely related alkaloids, aphelandrine[6,7] and *O*-methylorantine (**5**),[7,8] isolated by Hesse from species of *Aphelandra* and *Chaenorhinum*, respectively.[9]

We now report the first total synthesis of (±)-*O*-methylorantine (**5**) by a convergent pathway paralleling routes previously employed in the formation of the spermine alkaloids chaenorhine (**6**)[10] and verbascenine.[11] The synthesis illustrates the generality of

(1) Tamada, M.; Endo, K.; Hikino, H.; Kabuto, C. *Tetrahedron Lett.* **1979**, 873.
(2) Tamada, M.; Endo, K.; Hikino, H.; *Heterocycles* **1979**, *12*, 783.
(3) Konno, C.; Tamada, M.; Endo, K.; Hikino, H. *Heterocycles* **1980**, *14*, 295.
(4) Hikino, H.; Ogata, M.; Konno, C. *Heterocycles* **1982**, *17*, 155.
(5) (a) Stoessl, A. *Tetrahedron Lett.* **1966**, 2287. (b) Stoessl, A. *Can. J. Chem.* **1967**, *45*, 1745.
(6) (a) Bosshardt, H.; Guggisberg, A.; Johne, S.; Hesse, M. *Pharm. Acta Helv.* **1978**, *53*, 355. (b) Datwyler, P.; Bosshardt, H.; Bernhard, H.; Hesse, M. *Helv. Chim. Acta* **1978**, *61*, 2646.
(7) Datwyler, P.; Bosshardt, H.; Johne, S.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 2712.
(8) Bosshardt, H.; Guggisburg, S.; Johne, S.; Veith, H.-J.; Hesse, M.; Schmid, H. *Pharm. Acta Helv.* **1976**, *51*, 371.
(9) "Orantine", obtained by Hesse from the base-catalyzed isomerization of aphelandrine, is identical in all respects with ephedradine A (**1**).
(10) Wasserman, H.; Robinson, R.; Carter, C. *J. Am. Chem. Soc.* **1983**, *105*, 1697.
(11) Wasserman, H.; Robinson, R. *Tetrahedron Lett.* **1983**, 3669.
(12) Schwartz, M.; Rose, B.; Holton, R.; Scott, S.; Vishnuvajjala, B. *J. Am. Chem. Soc.* **1977**, *99*, 2571.
(13) While the ^1H NMR spectrum of **11** indicated that only one stereoisomer was formed, it was not originally clear whether this possessed a cis or trans relationship between the substituents of the dihydrobenzofuran ring. This uncertainty, also encountered by Stoessl during the structural determination of hordatine A,[5] arose because there is no reliable correlation between the stereochemistry of coumarans and the coupling constant between the protons at C2 and C3 (J_{23}) in these systems. (For both hordatine (cis) and compound **11** (trans), J_{23} = 7.5 Hz.) In the present work, the coumaran **11** has been converted to *O*-methylorantine, which, in turn, has been correlated with ephedradine A (stereochemistry established by an X-ray determination). It therefore seems clear that **11** has the same trans stereochemistry as *O*-methylorantine.
(14) (a) Fowler, F.; Hassner, A.; Levy, L. *J. Am. Chem. Soc.* **1967**, *89*, 2077. (b) Hassner, A.; *Acc. Chem. Res.* **1971**, *4*, 9.

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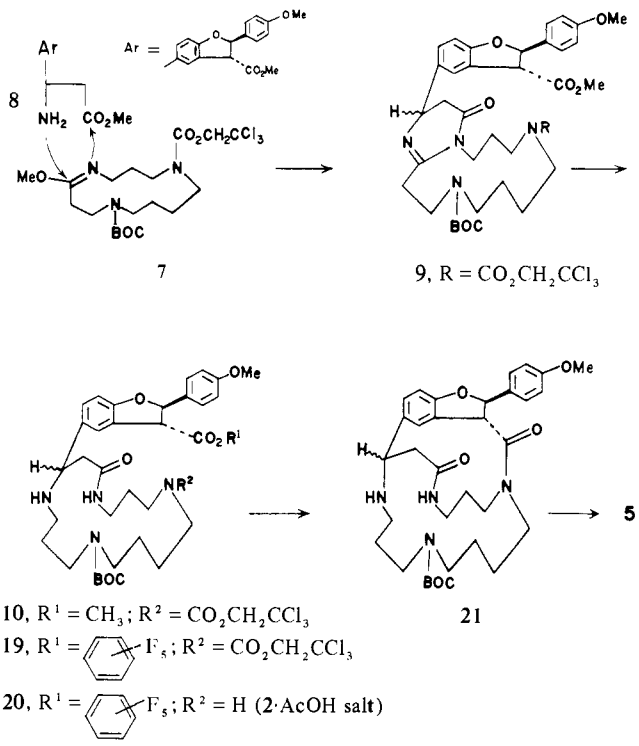
Scheme I



7 9, R = $CO_2CH_2CCl_3$

10, $R^1 = CH_3$; $R^2 = CO_2CH_2CCl_3$

19, R^1 = C_6F_5; $R^2 = CO_2CH_2CCl_3$

20, R^1 = C_6F_5; R^2 = H (2·AcOH salt)

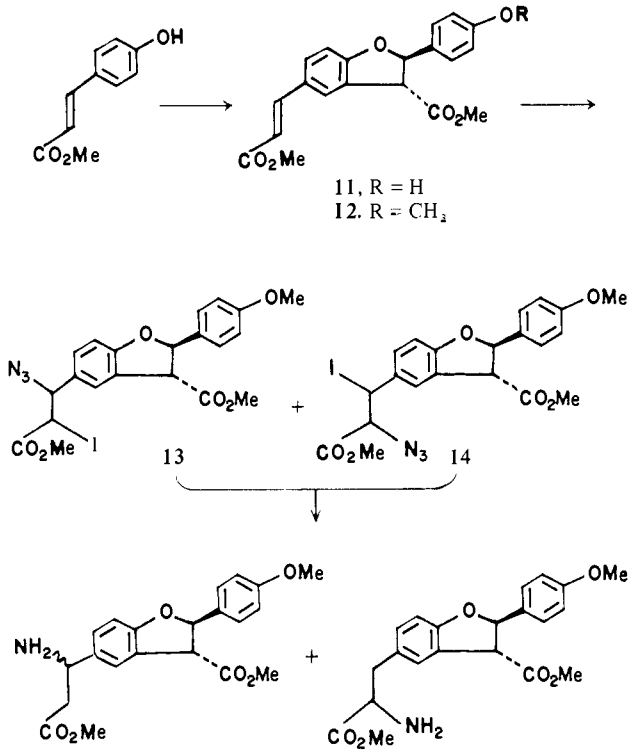
21 5

the lactam ring expansion method for the formation of complex bicyclic polyamine systems.

The formation of **5** is summarized in Scheme I showing the use of two key fragments, the 13-membered lactim ether **7** and the substituted β-amino ester **8**. The method involves coupling of components **7** and **8** to form **9**, followed by reductive opening of **9** to **10**, the monocyclic precursor to *O*-methylorantine. The lactim ether **7**,[20] employed previously in the synthesis of **6**,[10] provides within the nonaromatic 17-membered lactam all but one nitrogen atom of the spermine residue. An important feature of the key intermediate **7** is the differential protection of the amino groups necessary to ensure selective acylation during the macrocyclization step.

In considering the synthesis of the β-amino ester **8**, we noted the possibility of forming the dihydrobenzofuran system by the oxidative coupling of *p*-hydroxycinnamic acid units. Precedent for the coupling reaction may be found in a number of such oxidations carried out in vitro,[5] including the oxidation used by Stoessl to prepare hordatine A. Accordingly, the first step in the synthesis of **8** was the reaction of methyl *p*-hydroxycinnamate with potassium ferricyanide in a two-phase mixture of aqueous Na_2CO_3 and chloroform[12] forming the trans coupling product **11** (57%) (Scheme II).[13]

Scheme II



11, R = H
12. R = CH_3

13 14

8 15

The coumaran **11** was converted to the β-amino ester **8** as follows: Alkylation (MeI/acetone/25 °C) yielded the methyl ether **12** (74%), which was then treated with iodo azide[14] (NaN_3, ICl/MeCN/0 °C) to form a mixture (90%) of the adduct **13** and the regioisomer **14**. The ratio of **13** to **14** was somewhat variable but generally favored (5:1) the desired isomer **13**. Direct conversion of the iodo azide adducts to **8**[15] could be accomplished by reaction of the mixture with an excess of tributyltin hydride (benzene/25 °C/20 h; benzene/80 °C/1 h). The regioisomeric α-amino ester **15** formed from the adduct **14** was readily separated from **8** by flash chromatography. The overall yield of the β-amino ester **8**[16,20] from **12** was 48%.

Coupling of the β-amino ester **8** with the 13-membered lactim ether **7** was accomplished[10] by heating a concentrated solution of the reactants in chlorobenzene (132 °C/9 h). The product **9**[16] (32%) was then reductively opened to the 17-membered lactam **10**[16] (3 equiv of $NaBH_3CN$/AcOH, 25 °C/2 h, 50 °C/1 h, 25 °C/12 h) (90%).[10,11]

To complete the conversion of **10** to *O*-methylorantine, mild conditions were required because of the sensitivity of the dihydrobenzofuran residue toward oxidation, acid, and base.[17] Accordingly, the methyl ester, **10** was hydrolyzed by using barium hydroxide in a mixture of THF and methanol.[18] Subsequent treatment of the acid with pentafluorophenol and DCC gave the activated ester **19** which was allowed to react with powdered zinc in acetic acid, cleaving the protecting (2,2,2-trichloroethoxy)carbonyl group and forming the diacetate **20** (75% from **12**).

In the cyclization step, a solution of **20** in dry, degassed DMF was slowly added (dropwise via syringe pump over a period of 10 h) to a solution of *N,N*-diisopropylethylamine (12.4 equiv) and 1-hydroxybenzotriazole (7 equiv) in the same solvent[18] at 40 °C, yielding the cyclized product as a mixture of diastereoisomers **21** (ca. 1:1) (17% from **20**). Treatment of this mixture with HCl gas in methylene chloride (-10 to 0 °C) removed the BOC protecting group in quantitative yield, affording crude **5** which was purified by column chromatography (basic Al_2O_3) eluted by 2% CH_3OH in $CHCl_3$. Preparative silica gel TLC developed by CH_3OH:$CHCl_3$:NH_4OH = 30:10:1 then yielded pure (±)-*O*-methylorantine (**5**). Our synthetic product was identical in all respects (250-MHz ^1H NMR, FT-IR, TLC, and mass spectrum) with a sample of the natural product provided by Hesse.[9,19]

(15) The assignment of structure **8** to this compound is consistent with the ^1H NMR spectrum: (90 MHz, $CDCl_3$) δ 7.37–7.19 (7, 4 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.1 Hz, 1 H), 6.05 (d, *J* = 7.9 Hz, 1 H), 4.40 (t, *J* = 6.8 Hz, 1 H), 4.25 (d, *J* = 7.9 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.69 (s, 3 H), 2.64 (d, *J* = 6.8 Hz, 2 H), 1.85 (br s, 2 H).

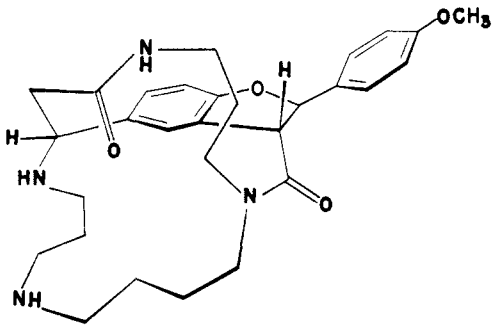
(16) A mixture of diastereomers that could not be separated at this stage.

(17) Studies on model systems, namely, **12**, its hydrogenation product, and the *N*-BOC derivative of **10**, have shown that special care must be taken to prevent decomposition of the dihydrobenzofuran ring by the action of bases (e.g., IN NaOH/MeOH/THF; imidazole/120 °C) or strong nucleophiles (e.g., LiI/DMF; NaSEt/DMF).

(18) Nutt, R. F.; Chen, K.-M.; Joullie, M. M. *J. Org. Chem.* **1984**, *49*, 1013. High dilution conditions were used (0.4 mol/mL) with a minor modification of the method reported by M. M. Joullie.

(19) Along with *O*-methylorantine, we isolated a product believed to be a diastereomer, epimeric at C11. This product was not identical (^1H NMR) with *O*-methylaphelandrine. ^1H NMR (250 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.5 Hz, 2 H), 7.37 (s, 1 H), 7.5 (d, *J* = 7.8 Hz, 1 H), 6.94 (d, *J* = 8.5 Hz, 2 H), 6.85 (br s, 1 H), 6.78 (d, *J* = 7.8 Hz, 1 H), 6.20 (d, *J* = 11.5 Hz, 1 H), 4.41 (d, *J* = 11.5 Hz, 1 H), 4.10 (m, 1 H), 3.83 (s, 3 H).

(20) Satisfactory elemental analyses and/or high-resolution mass spectra were obtained.



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Novel Cyclization of Type II Biradicals from α,β-Acetylenic Ketones

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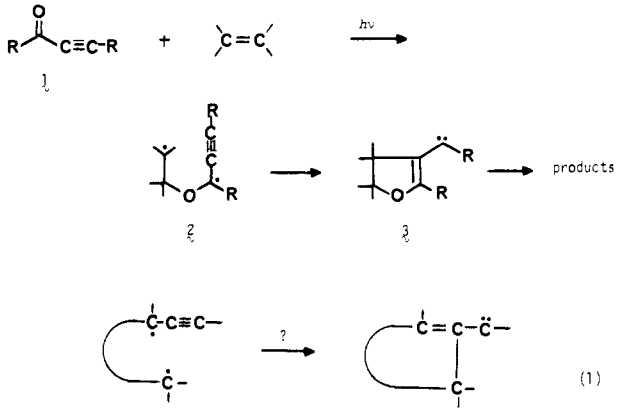
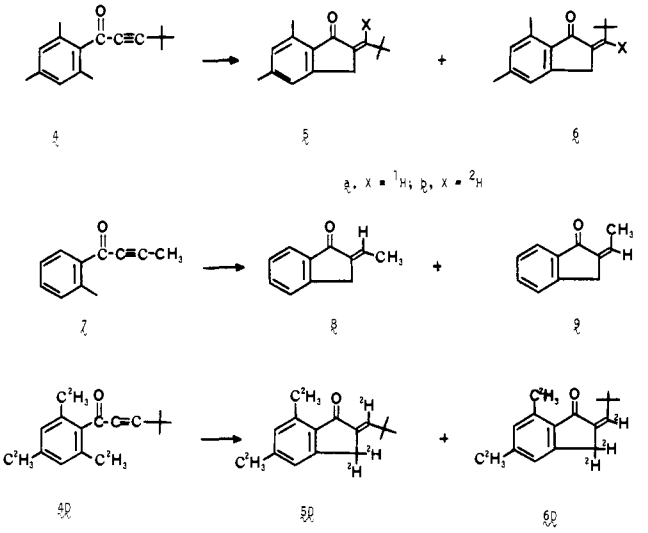
There is a good evidence[1] that the photochemical [3 + 2] cycloaddition between α,β-acetylenic ketones (**1**) and simple olefins proceeds through reaction of the ketone triplet with olefin to form biradical **2** that then closes to carbene **3**. Products are formed from **3** by way of various hydrogen shifts or cyclization to the cyclopropene.[1-3] Biradical **2** from the excited singlet of **1** closes in the [2 + 2] manner to form alkynyloxetane.[1] The closure of **2** to **3** implies that other types of alkyl propargyl biradicals could also cyclize to vinyl carbenes (eq 1). We have now confirmed



(1)

this possibility for several examples of the all-carbon system through a new photochemical reaction of α,β-acetylenic ketones. Irradiation of the mesityl alkynyl ketone **4** leads efficiently to indanone **5a**, and labeling experiments show that the simplest mechanism for this isomerization involves formation of the type II biradical and its cyclization according to eq 1. Details of this and analogous reactions are given below.

Ketone **4**,[4] prepared by reaction of mesitaldehyde with the Grignard reagent from *tert*-butylacetylene and subsequent Jones oxidation,[5] was irradiated in benzene solution (~0.02 M; λ ≥ 340 nm) for 6 h to yield 74% of an 84:16 mixture of **5a**[4] and **6a**,[4] which



were separated and purified by preparative gas chromatography. Photolysis of **7**,[4] available through acylation[6] of 1-(trimethylsilyl)propyne with *o*-toluyl chloride, yielded a 78:22 mixture of **8** and **9**.[7,8]

We performed several experiments to clarify the mechanism of these transformations. In the first, irradiation of **4** as above, but in benzene saturated with deuterium oxide,[10] furnished **5a** and **6a** carrying ~45% deuterium at the olefinic hydrogen (as **5b** and **6b**) and no deuterium at other positions. A second labeling experiment employed ketone **4D**, which was prepared from mesitoic acid-d_9.[11] Photolysis of **4D**, using glassware and solvent benzene that had been carefully dried, led to **5D** and **6D**, accompanied by some loss of the olefinic deuterium atom. Recovered **4D** had lost no deuterium. In dry solvent, then, the benzylic positions of **4** provide the olefinic hydrogen of **5a** and **6a**, but in the presence of water one of these benzylic hydrogens can be lost from some intermediate and the olefinic hydrogen is then derived from solvent. The time course of the rearrangement of **4** indicated that **5a** is a primary product but that essentially all of **6a** arises from secondary photolysis. The related isomerization of **8** to **9** under similar conditions is known to be efficient.[7] Quenching of the isomerization of **4** (0.01 M in cyclohexane) at low conversion by 2,3-dimethyl-1,3-butadiene was examined over the range 0.0–3.2 M quencher and was found to follow Stern–Volmer kinetics[12] with

(1) Saba, S.; Wolff, S.; Schröder, C.; Margaretha, P.; Agosta, W. C. *J. Am. Chem. Soc.* **1983**, *105*, 6902.
(2) Hussain, S.; Agosta, W. C. *Tetrahedron* **1981**, *37*, 3301.
(3) Wolff, S.; Agosta. W. C. *J. Am. Chem. Soc.* **1984**, *106*, 2363.

(4) Characterization data for **4**, **5a**, **6a**, **7**, **13a,b**, **14a,b**, **15a**, and **16b** have not been reported previously; each gave appropriate infrared and ^{1}H nuclear magnetic resonance spectra, as well as satisfactory elemental analysis or molecular ion in its high-resolution mass spectrum. Complete data are available as supplementary material.
(5) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. *J. Chem. Soc.* **1953**, 2548. Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.
(6) Birkofer, L.; Ritter, A.; Uhlenbrauk, H. *Chem. Ber.* **1963**, *96*, 3280.
(7) The spectroscopic properties and mp's of **8** and **9** agreed with those recorded for these substances: Newsoroff, G. P.; Sternhell, S. *Aust. J. Chem.* **1972**, *25*, 1669 and references cited therein.
(8) The yield of **8** and **9** was ~10%. It is well-known in other cases that *o*-tolyl ketones undergo reversible photoenolization rather than the photochemical reactions typical of similar 2,6-dimethylphenyl ketones; for details, see ref 9.
(9) Wagner, P. J. *Pure Appl. Chem.* **1977**, *49*, 259 and references cited therein.
(10) The solubility of water in benzene at 20 °C is 0.021 M: Joris, G. G.; Taylor, H. S. *J. Chem. Phys.* **1948**, *16*, 45.
(11) This was available (~95% d_9) through base-catalyzed exchange of sodium mesitoate with deuterium oxide: Atkinson, J. G.; Csakvary, J. J.; Herbert, G. T.; Stuart, R. S. *J. Am. Chem. Soc.* **1968**, *90*, 498. Hydride reduction and reoxidation furnished labeled mesitaldehyde.
(12) Wagner, P. J. In "Creation and Detection of the Excited State"; Marcel Dekker: New York, 1971; Vol. 1, Part A, p 173.

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