shown by proton NMR and IR to be identical with *trans*-1,2-diethyl-1,2-dimethylcyclobutane reported by Barlett and Porter.[22] IR (film) 2990, 1460, 1365 cm^{-1}; NMR (CCl_4) δ 1.7-1.2 (m, 8 H), 1.02 (s, 6 H), 0.9-0.6 (t, 6 H).

Photodecomposition of 1, 2, and 3. Degassed chromatographed solution of **1**, **2**, and **3** were sealed in base-washed, argon-purged, precooled (-78 °C) 5-mm NMR tubes. Sensitizers were added to the tubes before addition of 1,1-diazene. In all photochemical decompositions two identical samples were prepared; one was photolyzed at -78 °C and the other remained in the dark at -78 °C. ^1H NMR spectra (-60 °C) were taken before and after photolysis to ensure that all decomposition of diazene arose from photolysis. In addition, the 1,1-diazenes were shown to be stable to partial photodecomposition. Photolyses were carried out at -78 °C (hexane, dry ice) in an evacuated quartz dewar. For direct photolyses of 1,1-diazene **1** and **2** a water filter, Pyrex filter, and two Corning glass filters, CS-370 and CS-496, were used (466-610 nm). For sensitized photolyses of **1** and **2**, a water filter, Pyrex filter, and Corning glass filter CS2-59 (>608 nm) were used. For direct studies on 1,1-diazene **3** Corning filter CS-251 was used. For sensitized photolysis, **1** and **2** were irradiated in the absence of azulene at >608 nm and shown to be photostable. All solution were photolyzed with a 1000-W argon arc lamp until the diazene had completely decomposed. Tetrazene/hydrocarbon ratios were determined by ^1H NMR (-60 °C). Hydrocarbon ratios were determined by a combination of 0.125-in. analytical VPC and capillary VPC. Solutions of 1,2-diazene **9** in $CFCl_3$ were degassed by three freeze-pump-thaw cycles in 5-mm NMR tubes and sealed. Photolyses were done at -78 °C (hexane/dry ice) in an evacuated quartz dewar using a water filter, Pyrex filter, and WF-335 Schott filter (>330 nm). Photolyses were halted at approximately 50% completion and analyzed in a manner identical with that of **1**. Triplet-sensitized photolyses were done in an identical manner with 0.05 M thioxanthone as a sensitizer.

Registry No. 1, 73331-62-1; *dl*-**2**, 83350-57-6; **3**, 66337-86-8; *dl*-**11**, 83350-62-3; *meso*-**11**, 83350-67-8; *dl*-**12**, 83350-64-5; *meso*-**13**, 83350-58-7; *dl*-**13**, 83350-66-7; (+)-**13**·HCl, 83350-70-3; (+)-**13**, 83350-68-9; (+)-**13**·(*d*)-tartrate, 83350-69-0; **20**, 83350-65-6; *dl*-ethyl-5-nitrohexan-2-one, 83350-59-8; 2-nitrobutane, 600-24-8; methyl vinyl ketone, 78-94-4; *dl*-2,5-dimethyl-2-ethyl-Δ^5-pyrroline oxide, 83350-60-1; ethyl bromide, 74-96-4; *dl*-1-hydroxy-2,5-diethyl-2,5-dimethylpyrrolidine, 83350-61-2; *dl*-2,5-diethyl-2,5-dimethylpyrrolidine, 83350-63-4; azulene, 275-51-4; thiaxanthene, 492-22-8; 3,4,5,6-tetrahydro-3,3,6,6-tetramethylpyridazine, 19403-24-8.

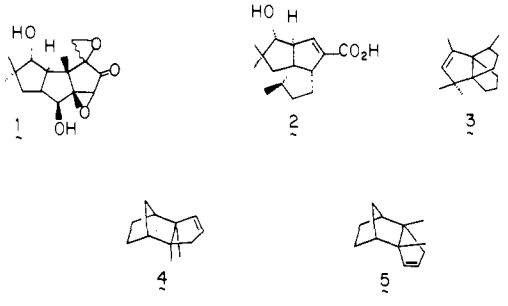
Palladium-Mediated Cycloaddition Approach to Cyclopentanoid Natural Products. (±)-Albene

Barry M. Trost* and Patrice Renaut

Contribution from the McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received March 24, 1982*

Abstract: A five-step synthesis of (±)-albene from 2,3-dicarbomethoxynorbornene utilizes the palladium-catalyzed cycloaddition of 2-((trimethylsilyl)methyl)-3-acetoxy-1-propene as the key reaction. Deoxygenation to the hydrocarbon takes advantage of the treatment of phosphoramidates with lithium. This procedure nicely resolves the problems of conversion of a ketone to an olefin and a neopentyl ester to a methyl group, which permits both types of modifications in a single stroke.

Polycondensed cyclopentanoid natural products represent an increasingly important class. In the tricycles, several different ring fusions occur among the sesquiterpenes as represented by **1**-**4**.[1-6] Outside of the hirsutanes as illustrated by coriolin **1**, none of these carbon skeletons were known among natural products prior to 1972.[7] The growing recognition of their importance mandates the development of efficient synthetic strategies. A cycloaddition approach to these as well as other cyclopentanoid



1 2 3 4 5

(1) Takahashi, S.; Naganawa, H.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Tetrahedron Lett.* **1971**, 1955. Nakamura, H.; Takita, T.; Umezawa, H.; Mamuru, K.; Yuga, N.; Iitaka, Y. *J. Antibiot.* **1974**, *27*, 301.

(2) Seto, H. Sasaki, T.; Uzawa, J.; Takeuchi, S.; Yonehara, H. *Tetrahedron Lett.* **1978**, 4411.

(3) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D. *J. Chem. Soc., Chem. Commun.* **1978**, 420.

(4) Hochmannova, J.; Novotny, L.; Herout, V. *Collect. Czech. Chem. Commun.* **1962**, *27*, 2711. Vokac, K.; Samek, Z.; Herout, V.; Sorm, F. *Tetrahedron Lett.* **1972**, 1665. Lansbury, P. T.; Boden, R. M. *Tetrahedron Lett.* **1973**, 5017. Kreiser, W.; Janitschke, L. *Chem. Ber.* **1979**, *112*, 408. Kreiser, W.; Janitschk, L.; Voss, W.; Ernst, L.; Sheldrick, W. S. *Ibid.* **1979**, *112*, 397. Baldwin, J. E.; Barden, T. C. *J. Org. Chem.* **1981**, *46*, 2442.

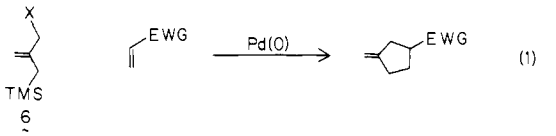
(5) Such a strategy employed by Baldwin and Barden depended upon the separation of the exo and endo adducts in unstated yields. See ref 4.

(6) For some recent synthetic efforts, see: (hirsutane family) (a) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 7380. (b) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *Ibid.* **1981**, *103*, 3460. (c) Shibasaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1980**, 3587. Iseki, K.; Yamazaki, M.; Shibasaki, M.; Ikegami, S. *Tetrahedron* **1981**, *37*, 4411. (d) Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Antibiot.* **1980**, *23*, 100; *Tetrahedron* **1981**, *37*, 4365. (e) Trost, B. M.; Shuey, C. D.; DiNinno, F. *J. Am. Chem. Soc.* **1979**, *101*, 1284. (f) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 2795. (g) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Ibid.* **1978**, 1991. (h) Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1979**, *101*, 6116. (i) Greene, A. E. *Tetrahedron Lett.* **1980**, 3059. (j) Hudlicky, T.; Kutchan, T.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351. (k) Little, R. D.; Muller, G. W. *Ibid.* **1981**, *103*, 2744. (l) Little, R. D.; Carroll, G. L. *Tetrahedron Lett.* **1981**, *22*, 4389. (m) Stevens, K. E.; Paquette, L. A. *Ibid.* **1981**, *22*, 4393. (pentalene-iscomene family) (n) Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1835. (o) Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103. (p) Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82. (q) Oppolzer, W.; Battig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493. (r) Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. F. *J. Am. Chem. Soc.* **1979**, *101*, 7020. (s) Parsons, W. H.; Schlessinger, R. H.; Quesada, M. L. *Ibid.* **1980**, *102*, 889. (t) Plavai, F.; Heathcock, C. H. *Tetrahedron Lett.* **1979**, 2115. (u) Wender, P. A.; Dreyer, G. B. *Tetrahedron* **1981**, *37*, 4445. (modhephene family) (v) Schostarez, H.; Paquette, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 722; *Tetrahedron* **1981**, *37*, 4431. (w) Karpf, M.; Dreiding, A. S. *Tetrahedron Lett.* **1980**, 4569. (x) Oppolzer, W.; Marazza, F. *Helv. Chim. Acta* **1981**, *64*, 1575. (y) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017.

(7) Devon, T. K.; Scott, A. I. "Handbook of Naturally Occurring Compounds"; Academic Press: New York, 1972; Vol. II.

0002-7863/82/1504-6668$01.25/0

natural products offers the hope of streamlining synthetic designs with accompanying control of stereochemistry.[8-10] In pursuing such a goal, we have focused on the general reaction outlined in eq 1.[11,12] The bifunctional conjunctive reagent **6** (X = I) has



(1)

proved its value in a *stepwise* sequence directed toward coriolin (**6**).[5a] On the other hand, a key question remains to be answered. Does such a cycloaddition approach toward cyclopentanoid natural products offer a unique insight in retrosynthetic analysis?

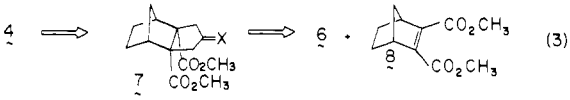
In considering this goal, albene **4** represents a tempting target.[4] Early investigations that assigned structure **5** to this natural product made a sequence based upon Diels–Alder reactions with 2,3-dimethylmaleic anhydride attractive—the key strategy emanating from the existence of a six-membered ring in the molecule. With the establishment of **4** as the structure, such strategies clearly become less attractive.[5] On the other hand, the intrinsic preference for norbornyl systems to undergo exo attack would make a sequence based upon a cycloaddition of the type represented in eq 2 very attractive. Thus, the complementary stereochemical fea-


(2)

tures of the [4 + 2] vs. [3 + 2] approaches makes albene a valid challenge for this cycloaddition as outlined in eq 1.

We report (1) that not only does the cycloaddition methodology resolve this stereochemical problem but also offers the simplest approach to this family, (2) the first case of such a transition-metal-mediated (TMM) strategy in natural products synthesis, and (3) the applicability of deoxygenation methodology to the classical problem of conversion of vicinal neopentyl diesters to methyl groups.

Equation 3 delineates the retrosynthetic analysis. In choosing



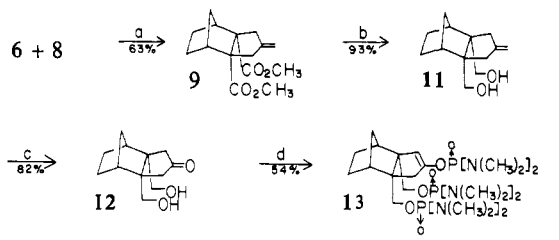
(3)

a ketone as an antecedent of the endocyclic olefin of albene, we rely on the ready interconversion of a ketone and an exocyclic methylene group to generate **7**, (X = CH_2). Conversion of the methyl groups of albene to carboalkoxy groups recognizes the need for an electron-withdrawing group for the cycloaddition. With the deduction that **7** represents a logical albene precursor, it is then straightforward to deduce that a cycloaddition between **6** and **8** should initiate this synthesis.

Results

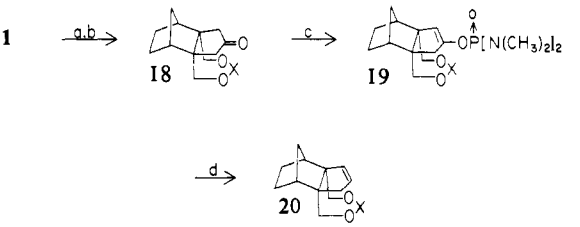
Scheme I outlines the synthesis from **6** (X = OAc) and **8**.[13] The cycloaddition generated a single crystalline adduct **9** whose homogeneity is established by both ^1H and ^{13}C NMR spectroscopy. This high stereocontrol contrasts with the palladium-catalyzed

Scheme I. Synthesis of (±)-Albene



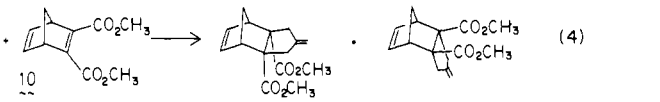
[a] (i-$C_3H_7O)_3P$, $Pd(OAc)_2$, THF, reflux. [b] LAH, ether, 0 °C. [c] O_3, CH_2Cl_2, CH_3OH, −78 °C, then $(CH_3)_2S$. [d] $KN(Me_3Si)_2$, DME, HMPA, $[(CH_3)_2N]_2P(O)Cl$, 0 °C. [e] Li, $C_2H_5NH_2$, THF, t-C_2H_5OH, −5 °C.

Scheme II. Formation of Endocyclic Disubstituted Olefin



[a] $(CH_3)_2C(OCH_3)_2$, $(CH_3)_2CO$, camphosulfonic acid, room temperature, 84%. [b] O_3, CH_2Cl_2, CH_3OH, −78 °C, then $(CH_3)_2S$, 69%. [c] LDA, THF, −78 °C, then $[(CH_3)_2N]_2P(O)Cl$, HMPA, 0 °C, 80%. [d] Li, $C_2H_5NH_2$, t-C_4H_9OH, THF, −5 °C, 92%.

cycloaddition to 2,3-dicarbomethoxynorbornadiene (**10**), which generated a 4:1 exo:endo mixture (eq 4).[14] We attribute the

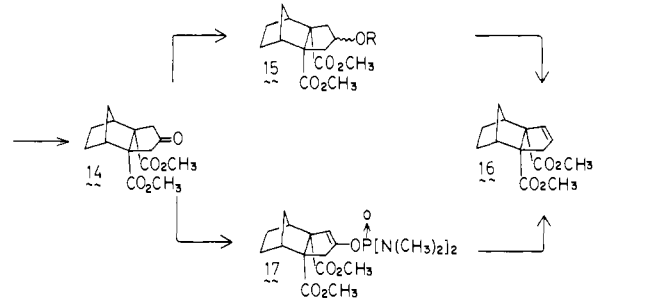


(4)

difference to a partial prior coordination of palladium with the norbornadiene unit of **10**, thereby delivering the TMM unit on the endo side. An alternative explanation invoking a smaller steric bias for exo attack in the case of **10** cannot be dismissed.

Several palladium(0) catalysts were explored including tetrakis(triphenylphosphine)palladium and a mixture of this palladium complex with 1,2-bis(diphenylphosphino)ethane. Both indeed gave the desired cycloadduct **9**. However, best results were obtained by using tetrakis(triisopropyl phosphite)palladium prepared in situ from triisopropyl phosphite and palladium acetate. Work in these laboratories suggests this new catalyst to be preferred for this type of cycloaddition.[15]

Conversion of **9** to albene requires two separate structural modifications—the conversion of the exocyclic methylene group to a disubstituted endocyclic olefin with loss of the exocyclic carbon and of the ester groups to methyl groups. Ozonolysis of **9** led smoothly to the ketone **14**. Reduction to the alcohol and deh-



(8) For reactions via diyls, see: Berson, J. A. *Acc. Chem. Res.* **1978**, *11*, 446. Little, R. D.; Carroll, G. L. *J. Org. Chem.* **1979**, *44*, 4720. Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1979**, *101*, 7129. Little, R. D.; Muller, G. W.; Venegas, M. G.; Carroll, G. L.; Bukhari, A.; Patton, L.; Stone, K. *Tetrahedron* **1981**, *37*, 4371. Also see ref 5, k and l.

(9) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604.

(10) For reactions via alkylidenecyclopropanes and transition-metal catalysts, see: Noyori, R.; Yamakawa, M.; Takaya, H. *Tetrahedron Lett.* **1978**, 4823. Noyori, R.; Odagi, T.; Takaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780. Binger, P. *Synthesis* **1973**, 427. Binger, P.; Germer, A. *Chem. Ber.* **1981**, *114*, 3325. Binger, P.; Schuchardt, U. *Ibid.* **1981**, *114*, 3313; **1980**, *113*, 3334.

(11) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429, 6432; **1980**, *102*, 6359; **1981**, *103*, 5972.

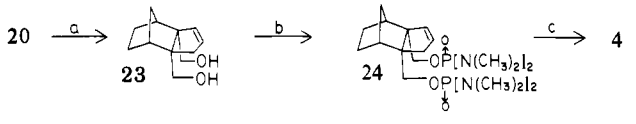
(12) Cf.: Knapp, S.; O'Connor, U.; Mobilio, D. *Tetrahedron Lett.* **1980**, 4557.

(13) Zalkow, L. H.; Hill, R. H. *Tetrahedron* **1975**, *31*, 831.

(14) Chan, D. M. T.; unpublished observations in these laboratories.

(15) Nanninga, T., unpublished observations in these laboratories.

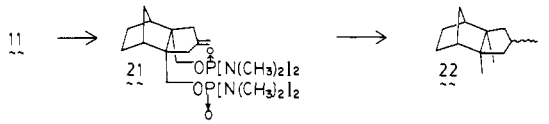
Scheme III. Conversion of Carbomethoxy to Methyl Group



[a] TsOH, CH_3OH, room temperature, 91%. [b] CH_3Li, ether–DME–TMEDA, $[(CH_3)_2N]_2P(O)Cl$, room temperature, 30%. [c] Li, $C_2H_5NH_2$, THF, t-C_4H_9OE, -5 °C, 90%.

ydration proved disappointing. The best achieved was treatment of the corresponding mesylate **15** (R = SO_2CH_3) with tetra-*n*-butylammonium oxalate in acetone to give **16** in 28% yield.[16] Examination of the reaction mixture by NMR spectroscopy revealed that only the minor mesylate isomer reacted, accounting for the low conversion. Attempts to use more forcing conditions were fruitless. Assuming the source of the reluctance for an E_2 reaction stemmed from steric hindrance, we focused our attention on the use of enol derivatives. Selective reduction of the phosphoramidate **17**, albeit risky because of the other functionality present, could alleviate the problem.[17] However, fears of the stability of the ester groups to lithium in ethylamine indeed were well-founded. This problem was easily alleviated by use of **18**, available in straightforward fashion from **11** as shown in Scheme II. Indeed, dissolving-metal reduction of the corresponding phosphoramidate **19** proceeded in excellent yield to give the desired olefin **20**.

Concurrent with the above, a sequence for ester to methyl group transformation was explored. Such a sequence gained prominence in the synthesis of cantharidine.[18] Attempts to follow a similar sequence from diol **11** were set aside when the propensity of the exocyclic double bond to migrate was discovered. For this reason, the phosphoramidate method appeared most promising. Indeed **21**, available from **11** [KH, DME, $[(CH_3)_2N]_2P(O)Cl$, room temperature], permitted smooth deoxygenation with lithium [$C_2H_5NH_2$, THF, t-C_4H_9OH] but was accompanied by double-bond reduction to give **22**.[19] Sensing that the undesired olefin



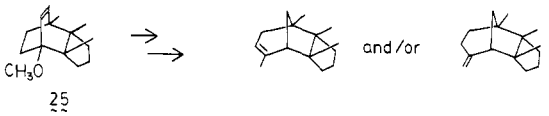
reduction was in part due to the high reactivity of the exocyclic double bond and that it would be controlled, we felt the endocyclic olefin of the diol **23** derived from **20** as shown in Scheme III would survive. Indeed, subjection of the bis(phosphoramidate) **24** to lithium in ethylamine gave crystalline **4** in 90% yield, whose spectral data proved identical with the published data.

Since the phosphoramidate method proved the most satisfactory for both types of deoxygenations, convergence into a much simpler operation was envisioned (see Scheme I). Thus, the keto diol **12** was converted into its tris(phosphoramidate) **13**, which, in a single stroke, loses all oxygen upon exposure to lithium in ethylamine to give the crystalline and volatile hydrocarbon (±)-albene.

Discussion

The entire carbon skeleton of the tricyclic albene arises from two cycloadditions—a Diels–Alder reaction and a TMM–Pd(O) reaction. The result is a seven-step synthesis from cyclopentadiene and dimethyl acetylenedicarboxylate or a five-step synthesis from **6**. The overall yield of approximately 21% is clearly not optimized. While optimization of the cycloaddition of **6** and **8** has been attempted, no such efforts have been made for any other transformation in Scheme I. Combined with certain mechanical losses due to the high volatility of albene, this overall yield should be considered a minimum.

In addition to highlighting the utility of this type of cycloaddition in synthesis, this route also provides a more practical solution to the conversion of the bis(neopentyl)-type esters to methyl groups. Such transformations are frequently encountered. For example, a recent approach to the α- and β-barbatenes invokes **25** as an intermediate[20]—a type of structure nicely broached by this cycloaddition and deoxygenation methodology.



Experimental Section

General Methods. Melting points were determined in capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Acculab 7 spectrometer with $CDCl_3$ solutions. ^1H NMR spectra were recorded in $CDCl_3$ at 270 MHz on a Bruker WH270 instrument and reported in δ. ^{13}C NMR spectra were recorded at 15.1 MHz on a JEOLCO-FX-60 spectrometer and reported in δ. High-resolution mass spectra were determined on an AEI-MS 902 mass spectrometer with an ionizing current of 70 eV. Combustion analyses were performed by Spang Microanalytical Labs., Eagle Harbor, MI. Unless otherwise specified, all reactions were performed under nitrogen. THF and DME were distilled from sodium and benzophenone. Ethylamine was distilled from lithium. Glassware was flame-dried under nitrogen. Preparative TLC employed Macherey Nagel P/UV_{254} silica gel that had been activated by heating at 120 °C for 2 h. Flash chromatography employed Merck EM silica gel 60 (230–400 mesh). Standard column chromatography employed Grace silica gel, Grade 62 (60–200 mesh).

Preparation of 2-((Trimethylsilyl)methyl)-3-acetoxy-1-propene (6).[11,21] A 500-mL three-necked flask was charged with *n*-BuLi (1.45 M in hexane, 170 mL, 246 mmol); the bulk of hexane was removed in vacuo, and 135 mL of anhydrous ether and TMEDA (40 mL, 264 mmol) were added. 2-Methyl-2-propen-1-ol (8.7 g, 121 mmol) was then added dropwise over 15 min at 0 °C, whereby the yellow solution turned quite cloudy. THF (60 mL) was then added, and the solution turned clear again. The reaction was then allowed to warm very slowly to room temperature over 13 h with mechanical stirring and then was stirred for an additional 9 h. The reaction was quenched with chlorotrimethylsilane (65 mL, 512 mmol) at 0 °C. The dark reaction mixture was allowed to stir for 10 min before being diluted with 1 L of ether. The ether solution was then washed with saturated $NaHCO_3$ (1 × 250 mL), water (1 × 250 mL), saturated $CuSO_4$ (2 × 250 mL), water (1 × 100 mL), and saturated NaCl (1 × 200 mL), dried (anhydrous K_2CO_3), and then distilled to give 2-((trimethylsilyl)methyl)-3-(trimethylsiloxy)-1-propene as a colorless oil (14.5 g, 55% yield): bp 76–79 °C (5 mmHg); IR (neat) 2943, 1641, 1245, 1081, 880, 836 cm^{-1}; ^1H NMR δ 4.92 (m, 1 H), 4.63 (m, 1 H), 3.95 (br s, 2 H), 1.49 (br s, 2 H), 0.13 (s, 9 H), 0.03 (s, 9 H). Calcd for $C_{10}H_{24}OSi_2$: 216.1358. Found: 216.1363.

To a solution of 2-((trimethylsilyl)methyl)-3-(trimethylsiloxy)-1-propene (13.5 g, 62 mmol) in 130 mL of THF was added 30 mL of 1 N aqueous sulfuric acid. The mixture was then stirred for 30 min and the bulk of the THF removed in vacuo. The residue was taken up in 500 mL of ether, washed with saturated $NaHCO_3$ (100 mL) and saturated NaCl (100 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation to yield 9.3 g (100%) of crude colorless alcohol, which was carried on to the next step without further purification. A sample was purified by preparative VPC: IR ($CHCl_3$) 3602, 3560–3340, 2950, 1638, 1247, 1038, 857 cm^{-1}; ^1H NMR δ 4.91 (m, 1 H), 4.67 (m, 1 H), 3.98 (br, 2 H), 1.55 (br, 1 H), 1.54 (s, 2 H), 0.03 (s, 9 H). Calcd for $C_7H_{16}OSi$: 144.0963. Found: 144.0962.

To a solution of 2-((trimethylsilyl)methyl)-3-hydroxy-1-propene (7.7 g, 53 mmol) in pyridine (15 mL, 185 mmol) and 60 mL of CH_2Cl_2 at 0 °C was added acetyl chloride (6.5 mL, 91 mmol) dropwise over a period of 10 min. The mixture was then stirred for 30 min and diluted with 500 mL of ether. The ether solution was washed with saturated $NaHCO_3$ (2 × 150 mL), saturated $CuSO_4$ (3 × 100 mL), water (1 × 100 mL), and saturated NaCl (1 × 100 mL), dried over K_2CO_3, and then

(16) Corey, E. J.; Terashima, S. *Tetrahedron Lett.* **1972**, 111.
(17) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.
(18) Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6893. Stork, G.; van Tamelen, E. E.; Friedman, L. J.; Burgstahler, A. W. *Ibid.* **1953**, *75*, 384.
(19) Cf.: Whitesides, G. M.; Ehmann, W. J. *J. Org. Chem.* **1970**, *35*, 3565 and references therein.
(20) Ito, S. "Proceedings of 4th Asian Symposium on Medicinal Plants and Spices"; Bangkok, Thailand, Sept 15–19, 1980; pp 284–292. Kodama, M.; Kurihara, T.; Sasaki, J.; Ito, S. *Can. J. Chem.* **1979**, *57*, 3343.
(21) Taken from Trost, B. M.; Chan, D. M. T.; Nanninga, T. *Org. Synth.*, in press.

distilled to give 9.1 g (92% yield) of the desired acetate as a colorless liquid: bp 95 °C (7 torr); IR (neat) 3070, 2945, 2885, 1753, 1643, 1372, 1250, 1044, 840 cm^{-1}; ^1H NMR δ 4.88 (m, 1 H), 4.72 (br s, 1 H), 4.44 (br s, 2 H), 2.09 (s, 3 H), 1.55 (s, 2 H), 0.05 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.4, 141.7, 109.6, 67.84, 23.61, 20.86, −1.43; mass spectrum, (*m/e*, %) 186 (5), 147 (13), 143 (18), 129 (11), 117 (34), 75 (40), 73 (100), 54 (42), 43 (18). Calcd for $C_9H_{18}O_2Si$: 186.1075. Found: 186.1075.

Preparation of *endo*-2,6-Dicarbomethoxy-4-methylenetricyclo-[5.2.1.0^{2,6}]decane (9). Under an argon atmosphere, a solution of 0.200 g (0.89 mmol) of palladium acetate, 1.112 g (5.34 mmol) of triisopropyl phosphite, 6.27 g (29.85 mmol) of diester **8**, and 5.56 g (29.85 mmol) of 2-((trimethylsilyl)methyl)-3-acetoxy-1-propene in 42 mL of dry THF was heated to reflux for 3.5 h. After cooling, the solution was concentrated in vacuo. The resulting yellow syrup was purified by flash chromatography (8:2 (v:v) hexane–ether) to give 4.98 g (63%) of pure **9** as a colorless crystalline solid: mp 52.5–53.0 °C (ether–pentane); IR 3000, 2960, 2880, 1735, 1085 cm^{-1}; ^1H NMR δ 4.75 (br s, 2 H), 3.62 (s, 6 H), 3.05 (d, J = 18 Hz, 2 H), 2.43 (d, J = 18 Hz, 2 H), 2.27 (br s, 2 H), 1.98 (d, J = 10.7 Hz, 1 H), 1.64 (m, 2 H), 1.37 (m, 2 H), 1.17 (d, J = 10.7 Hz, 1 H); ^{13}C NMR δ 174.37, 150.53, 104.34, 62.82, 51.15, 48.12, 46.08, 35.35, 25.22. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; M_r, 264.1361. Found: C, 68.25; H, 7.63; M_r, 264.1362.

Preparation of *endo*-2,6-Bis(hydroxymethyl)-4-methylenetricyclo-[5.2.1.0^{2,6}]decane (11). To a well-stirred slurry of 0.43 g (11.4 mmol) of LAH in 12 mL of dry ether at 0 °C was added dropwise during 25 min a solution of 1.0 g (3.81 mmol) of **9** in 12 mL of dry ether. The resulting mixture was stirred for 25 min at 0 °C and then carefully hydrolyzed with 20 mL of ether saturated with a solution of 10% sodium bisulfate in water at 0 °C and then 150 mL of 10% sodium bisulfate in water. The aqueous layer was extracted with 4 × 50 mL of ether. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford 0.737 g (93%) of **11** as a colorless solid: mp 125–126 °C (ethyl acetate); IR 3620, 3440, 3070, 2960, 2940, 2880, 1650, 1025, 1010 cm^{-1}; ^1H NMR δ 4.76 (s, 2 H), 3.85 (d, J = 11 Hz, 2 H), 3.52 (d, J = 11 Hz, 2 H), 2.82 (d, J = 16.4 Hz, 2 H), 2.78 (s, 2 H), 2.20 (d, J = 16.4 Hz, 2 H), 2.02 (s, 2 H), 1.98 (d, J = 10.8 Hz, 1 H), 1.47 (m, 2 H), 1.31 (m, 2 H), 1.09 (d, J = 10.8 Hz, 1 H). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; M_r, 208.1463. Found: C, 75.04; H, 9.75; M_r, 208.1463.

Preparation of *endo*-2,6-Bis(hydroxymethyl)tricyclo[5.2.1.0^{2,6}]decan-4-one (12). A slow stream of ozone was bubbled into a solution of 0.25 g (1.2 mmol) of **11** in 3 mL of methanol and 3 mL of methylene chloride at −78 °C. The stream of ozone was maintained until a slight blue color persisted. After removal of excess ozone with a stream of nitrogen, 2 mL of dimethyl sulfide was added at −78 °C. The mixture was then allowed to warm to room temperature during 1 h. Evaporation of solvents afforded a crude product, which was purified on silica gel (6:4 (v:v) hexane–acetone) to give 0.207 g (82%) of **12** as a crystalline solid: mp 225–230 °C; IR 3600, 3400, 2940, 2880, 1735, 1390, 1195, 1125, 1030, 1020 cm^{-1}; ^1H NMR δ 4.40 (br s, 2 H), 4.18 (d, J = 11.39 Hz, 2 H), 3.47 (d, J = 11.39 Hz, 2 H), 3.12 (d, J = 19.48 Hz, 2 H), 2.03 (d, J = 19.48 Hz, 2 H), 2.02 (s, 2 H), 1.65 (d, J = 11.03 Hz, 1 H), 1.56 (m, 2 H), 1.36 (m, 2 H), 1.28 (d, J = 11.03 Hz, 1 H). Calcd for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1256.

Preparation of Tris(phosphoramidate) 13. To a solution of 6 mmol of potassium hexamethyldisilazide (6.9 mL of a 0.87 M solution in DME) and 0.87 mL of dry HMPA cooled to −50 °C was added dropwise over 30 min to a solution of 0.207 g (1 mmol) of **12** in 3 mL of dry DME. The mixture was stirred for 1 h at −50 °C, 1 h at −35 °C, and 1 h at −15 °C. The resulting solution was then cooled to −60 °C, 1.47 mL (10 mmol) of bis(dimethylamino)chlorophosphoramidate added, and the solution allowed to warm to room temperature overnight. Then 10 mL of a saturated aqueous solution of sodium bicarbonate was added at 0 °C. After stirring the solution for 30 min at room temperature, enough water was added to make a homogeneous solution, and the aqueous layer was extracted four times with ethyl acetate. The organic layers were dried over potassium carbonate and concentrated, affording a crude oil. This crude product was purified on silica gel (elution was done with acetone and then a mixture of acetone–methanol with an increasing content of methanol; the end of the elution was done with pure methanol) to give 0.335 g (54%) of pure **13** as a yellow syrup: IR 2955, 2870, 2830, 2790, 1655, 1450, 1300, 1205, 1030, 985 cm^{-1}; ^1H NMR δ 5.13 (d, J = 1.5 Hz, 1 H), 4.13 (dd, J = 9.55, 5.14 Hz, 1 H), 4.01 (dd, J = 9.55, 4.04 Hz, 1 H), 3.86 (dd, J = 9.55, 4.4 Hz, 1 H), 3.75 (dd, J = 9.55, 3.6 Hz, 1 H), 2.79 (d, J = 16.91 Hz, 1 H), 2.65 (m, 36 H), 2.34 (d, J = 16.91 Hz, 1 H), 2.15 (br s, 1 H), 2.12 (br s, 1 H), 1.90 (d, J = 10.29 Hz, 1 H), 1.73–1.34 (m, 4 H), 1.21 (d, J = 10.29 Hz, 1 H). Calcd for $C_{24}H_{51}N_6O_6P_3$: 612.3082. Found: 612.3081.

Preparation of (±)-Albene. (A) From 13. To a mixture containing lithium (0.112 g, 16.0 mmol) in 15 mL of dry ethylamine under argon at −5 °C was added dropwise a solution of 0.612 g (1.00 mmol) of **13** in 5 mL of dry ether and 0.56 mL of dry *tert*-butyl alcohol over 50 min. After an additional 10 min at −5 °C, sufficient solid ammonium chloride was added to destroy excess lithium. Water and distilled pentane was added, and the mixture was allowed to warm to room temperature. The aqueous layer was extracted three times with distilled pentane. The organic layers were washed with a cold aqueous 0.5 N solution of hydrochloric acid and brine and dried over magnesium sulfate. The filtered solution is carefully concentrated by an atmospheric pressure distillation using a 20-cm Vigreux column to leave 0.135 g (82%) of an extremely volatile colorless solid, (±)-albene: mp 107–108 °C (after sublimation); IR 3040, 2920, 2880, 1630 cm^{-1}; ^1H NMR δ 5.56 (dt, J = 5.8, 2.2 Hz, 1 H), 5.26 (dt, J = 5.8, 2.2 Hz, 1 H), 2.23 (dt, J = 16.9, 2.20 Hz, 2 H), 1.65–1.22 (m, 8 H), 0.94 (s, 6 H); ^{13}C NMR δ 139.6, 128.3, 56.5, 51.7, 50.3, 47.0, 46.6, 34.1, 23.8, 20.7, 18.1; mass spectrum, *m/e* 162, 147, 134, 133, 121, 119, 105. Calcd for $C_{12}H_{20}$: 162.1409. Found: 162.1409. These data agree with the published data.[4]

(B) Via 24. To a solution of 0.026 g (0.134 mmol) of **23** in 0.6 mL of dry THF and 0.15 mL of dry TMEDA was added dropwise 0.236 mL (0.294 mmol) of a 1.25 M solution of methyllithium in ether. The mixture was stirred for 2 h at room temperature. To the heterogeneous mixture was added 0.228 g (1.34 mmol) of bis(dimethylamino)chlorophosphoramidate. The mixture was stirred overnight at room temperature. At this time, enough saturated aqueous sodium bicarbonate solution was added to result in a homogeneous mixture that was stirred for 20 min. The resulting mixture was partitioned between water and ethyl acetate, and the aqueous layer was extracted three times with ethyl acetate. The organic layers were washed with a saturated aqueous solution of cupric sulfate, dried over potassium carbonate, and concentrated. The resulting oil was purified on silica gel (acetone, then 1:1 (v:v) acetone–methanol) to give 0.019 g (30%) of **24** as a colorless oil.

In identical fashion to part A, 19 mg (0.041 mmol) of **24** in 3 mL of dry ethylamine, 0.7 mL of dry THF, and 0.023 mL of dry *tert*-butyl alcohol was reduced with 3.0 mg (0.41 mmol) of lithium to give 6 mg (90%) of albene, identical with the above.

Preparation of Acetonide of 11. To a stirred solution of 0.35 g (1.68 mmol) of the diol **11** in 10 mL of dry acetone was added 0.02 g of camphorsulfonic acid followed by 0.35 g (3.36 mmol) of 2,2-dimethoxypropane. After stirring the solution at room temperature for 2 h, 50 mg of sodium carbonate was added, followed by 20 mL of water. The mixture was extracted five times with ether. The combined organic layers were concentrated, and the crude oil was taken up in ether and dried over potassium carbonate. The evaportion of ether afforded an oil that was chromatographed on silica gel (10:1 (v:v) hexane–ether) to give 0.350 g (84%) of acetonide, isolated as an oil that crystallizes in the freezer: IR 3080, 2990, 2950, 2890, 1655, 1385, 1255, 1195, 1090, 1055, 1035 cm^{-1}; ^1H NMR δ 4.72 (s, 2 H), 4.11 (d, J = 12.9, 2 H), 3.39 (d, J = 12.9 Hz, 2 H), 2.88 (d, J = 16.2 Hz, 2 H), 2.48 (d, J = 10.7 Hz, 1 H), 2.44 (d, J = 16.2 Hz, 2 H), 1.92 (s, 2 H), 1.62 (m, 2 H), 1.46 (s, 3 H), 1.29 (m, 2 H), 1.1 (d, J = 10.7 Hz, 1 H). Calcd for $C_{16}H_{24}O_2$: 248.1776. Found: 248.1777.

Preparation of Keto Acetonide 18. A slow stream of ozone was bubbled into a solution of 0.371 g (1.49 mmol) of the acetonide of **11** in 3 mL of methanol and 3 mL of methylene chloride at −78 °C. The stream of ozone was maintained until a slight blue color persisted. After removal or excess ozone with a stream of nitrogen, 3 mL of dimethyl sulfide was added at −78 °C. The mixture was then allowed to warm to room temperature during 1 h. Evaporation of solvents afforded an oil that was partitioned between water and ether. The aqueous layer was extracted three times with ether. The organic layers were washed with brine, dried over potassium carbonate, and concentrated to afford 0.37 g of an oil. Purification of this crude product by flash chromatography (1:1 (v:v) hexane–ether) afforded 0.257 g (69%) of **18** as a colorless solid: mp 65–67 °C; IR 2980, 2940, 2880, 1725, 1380, 1240, 1190, 1080, 1055, 1030 cm^{-1}; ^1H NMR δ 4.26 (d, J = 13.9 Hz, 2 H), 3.43 (d, J = 13.9 Hz, 2 H), 3.08 (d, J = 19.9 Hz, 2 H), 2.10 (d, J = 19.9 Hz, 2 H), 2.02 (s, 2 H), 1.8–1.3 (m, 6 H), 1.55 (s, 3 H), 1.49 (s, 3 H).

Preparation of Acetonide of *endo*-2,6-Bis(hydroxymethyl)tricyclo-[5.2.1.0^{2,6}]dec-3-ene (20). A solution of 0.056 g (0.224 mmol) of the ketone **18** in 1 mL of dry THF was added dropwise to a solution of 0.274 mmol of lithium diisopropylamide in 1 mL of dry THF cooled to −78 °C. The mixture was stirred for 30 min at −78 °C and then warmed to 0 °C, at which time 48 mg (0.27 mmol) of dry HMPA was added. The resulting mixture was stirred at 0 °C for 20 min, and then 76.4 mg (0.45 mmol) of bis(dimethylamino)chlorophosphoramidate was added. The mixture was stirred for 20 h at room temperature. A saturated aqueous solution of sodium bicarbonate was added, the mixture stirred vigorously for 30 min at room temperature, and then enough water added to produce a homogeneous solution. The aqueous layer was extracted four times with ether. The organic layers were dried over potassium carbonate and

then concentrated to afford 0.085 g of a crude oil, which was purified on silica gel (1:1 (v:v) hexane–acetone) to give 0.069 g (80%) of **19** as a colorless oil. Calcd for $C_{19}H_{33}N_2O_4P$: 384.2177. Found: 384.2178.

To a blue solution of lithium (0.013 g, 1.85 mmol) in 5 mL of dry ethylamine under argon at 0 °C was added dropwise a solution of 0.068 g (1.77 mmol) of **19** in 1 mL of dry THF and 0.02 mL of *tert*-butyl alcohol. The resulting mixture was stirred at 0 °C for 20 min, and then enough solid NH_4Cl was added to destory the excess lithium. Water was added, the mixture warmed to room temperature, and extracted four times with ether. The ethereal layers were dried over potassium carbonate and concentrated to afford 0.038 g (92%) of **20** as an oil: IR 3040, 2990, 2930, 2880, 1630, 1380, 1080, 1030 cm^{-1}; ^1H NMR δ 5.79 (dt, J = 5.88, 2.2 Hz, 1 H), 5.30 (dt, J = 5.88, 2.2 Hz, 2 H), 4.10 (m, 2 H), 3.50 (m, 2 H), 2.72 (d, J = 16.9 Hz, 1 H), 2.07 (dt, J = 16.9, 2.2 Hz, 1 H), 1.88 (s, 2 H), 1.8–1.7 (m, 3 H), 1.44 (s, 3 H), 1.33 (s, 3 H), 1.4–1.3 (m, 2 H), 1.09 (d, J = 9.9 Hz, 1 H). Calcd for $C_{15}H_{22}O_2$: 234.1619. Found 234.1619.

Preparation of *endo*-2,6-Bis(hydroxymethyl)tricyclo[5.2.1.0^{2,6}]dec-3-ene (23). A mixture of 0.071 g (0.3 mmol) of **20**, 0.01 g of *p*-toluenesulfonic acid, and 1.5 mL of dry methanol was stirred under nitrogen for 1 h at room temperature. The methanol was then evaporated, and the residue was partitioned between ethyl acetate and a saturated aqueous solution of sodium bicarbonate and the resulting aqueous layer extracted four times with ethyl acetate. The organic layers were dried over magnesium sulfate and concentrated to give 0.053 g (91%) of **23** as a colorless solid: mp 193–194 °C dec; IR 3600, 3400, 3040, 2960, 2940, 2880, 1630, 1060, 1040 cm^{-1}; ^1H NMR δ 5.95 (dt, J = 5.9, 2.2 Hz, 1 H), 5.34 (dt, J = 5.9, 2.2 Hz, 1 H), 4.03 (d, J = 11.4 Hz, 1 H), 3.98 (d, J = 11.4 Hz, 1 H), 3.5 (br s, 1 H), 2.97 (d, J = 11.4 Hz, 1 H), 2.97 (dt, J = 17.28, 2.2 Hz, 1 H), 2.8 (br s, 1 H), 2.03 (dt, J = 17.28, 2.2 Hz, 1 H), 1.94 (s, 2 H), 1.74 (d, J = 9.9 Hz, 1 H), 1.6–1.3 (m, 4 H), 1.04 (dt, J = 9.9, 1.47 Hz, 1 H). Calcd for $C_{12}H_{18}O_2$: 194.1306. Found: 194.1307.

Acknowledgment. We thank the National Institutes of Health–General Medical Sciences for their generous support of our programs. We express our thanks to Laboratories Fournier SA for making it possible for P.R. to spend this time in our laboratories.

Registry No. (±)-**4**, 67180-07-8; **6** (X = OAc), 72047-94-0; **6** (X = Me_3SiO), 83378-96-5; **6** (X = OH), 81302-80-9; **8**, 17931-56-5; **9**, 83378-86-3; **11**, 83378-87-4; **11** acetonide, 83378-88-5; **12**, 83378-89-6; (±)-**13**, 83378-90-9; **18**, 83378-91-0; (±)-**19**, 83378-92-1; (±)-**20**, 83378-93-2; (±)-**23**, 83378-94-3; (±)-**24**, 83435-70-5; $[(i\text{-}PrO)_3P]_4Pd$, 82838-61-7; $[(CH_3)_2N]_2P(O)Cl$, 1605-65-8; $(Ph_3P)_4Pd$, 14221-01-3; 2-methyl-2-propen-1-ol, 513-42-8.

Tautomerism of Phenindione, 2-Phenyl-1,3-indandione, in Dipolar Aprotic/Hydrocarbon Solvent Mixtures[1]

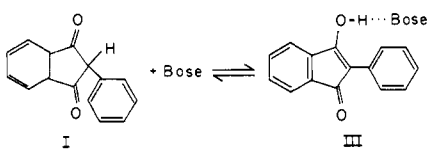
J. D. Pipkin[2b] and V. J. Stella*[2a]

Contribution from the Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas 66045. *Received October 13, 1981*

Abstract: Phenindione, 2-phenyl-1,3-indandione, exists in its diketo form in hydrocarbon solvents but enolizes in the presence of dipolar aprotic molecules. The enolization could be easily quantitated since it results in a large spectral shift to longer wavelength. In dilute solutions of phenindione, 5×10^{-4} M, and various bases, 0–2 M in cyclohexane, a 1:1 interaction constant could be determined that correlated well with other measures of basicity. The interaction was attributed to a hydrogen bond between the enolic hydrogen and the base. Phenindione is, therefore, proposed as a possible indicator molecule as its tautomerism is very sensitive to changes in solvent basicity and quantitation of the interactions can be determined rapidly by use of simple spectrophotometric measurements.

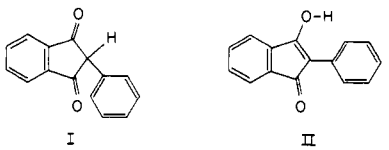
In the course of various investigations into the simultaneous solid to liquid mass transport and ionization of various carbon acids[3-6] including phenindione[5,6] (I), some interesting nonaqueous aprotic chemistry of a phenindione analogue was uncovered.[7] Phenyl-1,3-indandiones appeared to enolize in the presence of dipolar aprotic bases to an extent that qualitatively followed the expected basicity of the interacting bases. Such observations have also been qualitatively observed with other cyclic and acyclic 1,3-diketones.[8-16]

Scheme I



I III

On the basis of these observations, a quantitative study was undertaken to investigate the prototropic equilibrium between the diketo (I) and enol (II) isomers of the cyclic 1,3-dicarbonyl carbon



I II

acid, phenindione (2-phenyl-1,3-indandione), in a saturated hydrocarbon solvent, cyclohexane, in the presence of increasing

(1) This work was supported by NIH Grant GM22357 and the University of Kansas General Research Funds.
(2) (a) Address inquires to this author. (b) Current address: Squibb Institute for Medical Research, New Brunswick, NJ 08903.
(3) V. Stella, *J. Pharm. Sci.*, **64**, 706 (1975).
(4) V. Stella and J. D. Pipkin, *J. Pharm. Sci.*, **65**, 1161 (1976).
(5) V. J. Stella and R. Gish, *J. Pharm. Sci.*, **68**, 1042 (1979).
(6) V. J. Stella and R. Gish, *J. Pharm. Sci.*, **68**, 1047 (1979).
(7) The NMR spectrum of chlorindione, 2-(4-chlorophenyl)-1,3-indandione, varied greatly when run in $CDCl_3$ compared to acetone-d_6 and dimethyl-d_6-sulfoxide. Solutions in chloroform were also achromatic while acetone and dimethyl sulfoxide solutions were an intense orange. These observations were consistent with formation of the tautomeric enol isomer in the presence of the basic aprotic solvents.
(8) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattin, *J. Am. Chem. Soc.*, **71**, 1068 (1949).
(9) L. J. Bellamy and L. Beecher, *J. Chem. Soc.*, 4487 (1954).
(10) L. J. Bellamy and R. F. Branch, *J. Chem. Soc.*, 4491 (1954).
(11) J. L. Burdett and M. T. Rogers, *J. Am. Chem. Soc.*, **86**, 2106 (1964).
(12) R. D. Campbell and H. M. Gilow, *J. Am. Chem. Soc.*, **82**, 5426 (1960).
(13) R. D. Campbell and H. M. Gilow, *J. Am. Chem. Soc.*, **84**, 1440 (1962).
(14) Ya. Lindaberg, O. Neiland, A. Veiss, and G. Vanag, *Dokl. Akad. Nauk SSSR*, **154**, 1385 (1964).
(15) H. Hart, *Chem. Rev.*, **79**, 515 (1979).
(16) A. I. Kol'tsov and E. M. Kheifets, *Russ. Chem. Rev.* (*Engl. Transl.*), **40**, 773 (1971).

0002-7863/82/1504-6672$01.25/0