The Direction of Base-Catalyzed Aldol Cyclization of 1,5 Diketones

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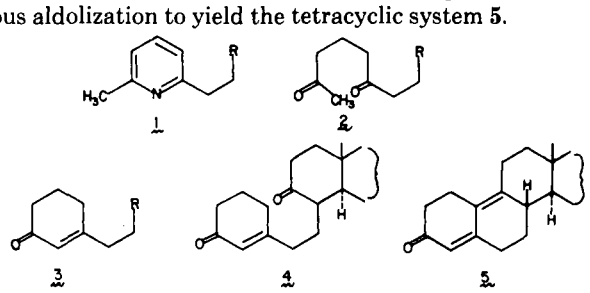
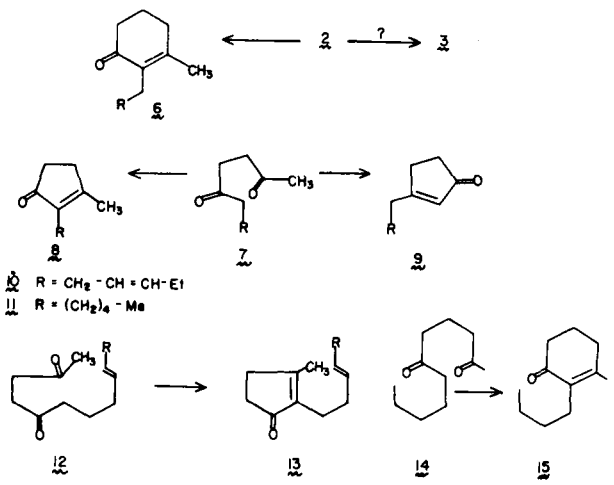
A series of 1,5 diketones of the type $MeC(=O)(CH_2)_3C(=O)CH_2R$ (2) has been prepared. The route involves alkylation of 2,6-lutidine via its lithium salt with RX. The resultant pyridine, of the structure $2\text{-}MeC_5H_3N\text{-}6\text{-}CH_2R$, is converted to the diketone of the type 2 by Birch-type reduction followed by hydrolysis. The base-catalyzed cyclodehydration of systems of the type 2 at room temperature has been examined in detail. The relative amounts of the two isomeric cyclohexenones, $3\text{-}RCH_2$-cyclohex-2-en-1-one (type 3) and 2-R-3-methylcyclohex-2-en-1-one (type 6), were determined by product isolation. In the case of R = methyl the type 3:type 6 ratio is ca. 1:17. When R is straight-chain alkyl, the ratio is close to unity, with a slight preference for the type 3 product. When R is branched alkyl and the branch point is either α or β to the ketone, type 3 product becomes strongly favored. As the branch point is moved γ to the ketone, the ratio veers toward unity. The presence of a dioxolane function in R, δ to the ketone, favors type 6 product. Temperature conditions employed in the base-catalyzed aldol cyclizations are shown to affect the product ratios.

The critical phase in our synthesis of ring A aromatic steroids from 2,6-lutidine involves reduction–hydrolysis of a 6-substituted α-picoline (1) to afford a 7-substituted 2,6-octanedione (2), which suffers aldol cyclization to provide a 3-substituted cyclohexenone (3).[1-4] The R group encompasses the C and D rings of the ultimate steroid. After unmasking the carbonyl group within R, which is α to its center of attachment, the resultant B seco steroid 4, is susceptible to vinylogous aldolization to yield the tetracyclic system 5.



At the time the feasibility of this approach was being studied, there was little decisive information bearing on a key issue, i.e., the aldol cyclization 2 → 3. Clearly there existed, a priori, an alternative aldol cyclization mode, 2 → 6, whose occurrence to any serious extent would have been deleterious to the scheme set forth above.

The precedents involving the formation of cyclopentenones, from the conceptually related cyclization of 1,4 diketones of the type 7, might have been viewed to be discouraging in this connection. An imposing collection of syntheses of *cis*-jasmone (10) and *cis*-dihydrojasmone (11) have involved base-catalyzed cyclization of the type 7 → 8 in which the tetrasubstituted enone is produced to the apparent exclusion of trisubstituted product 9.[5] Furthermore, the well-known synthesis of steroids of the Johnson school involved the base-catalyzed conversion of 12 → 13, with apparent exclusion of interference from the cyclization mode, 7 → 9.[6]



In the case of cyclohexenone formation from 1,5 diketones, we could find only one clearcut example which was relevant[7] to the question of the aldol cyclization course of 2. Stork and Borch had obtained compound 14 by their elegant directed acetylene hydration, and had reported that this compound cyclizes under basic catalysis (KOH/ethanol, reflux) to yield 15, to the apparent exclusion of a product of type 3, R = propyl.[8]

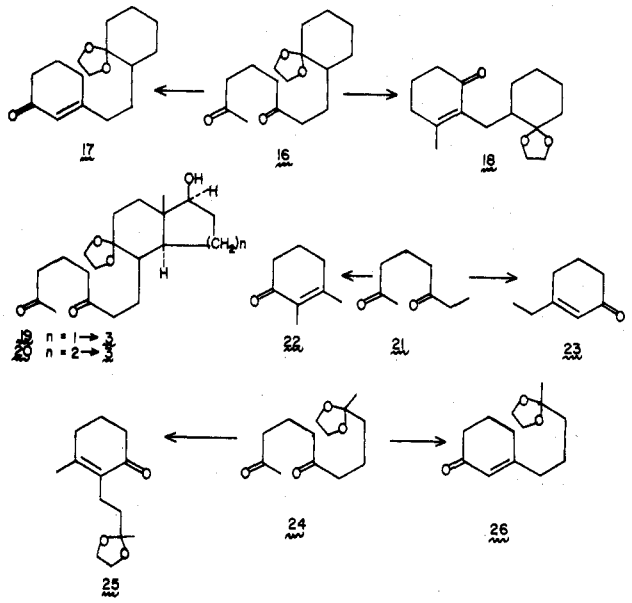
Undeterred by this prior art, we prepared compound 16 by methods which we have previously described and studied its cyclization[2,9] to cyclohexenones under basic conditions. It should be emphasized that for synthetic purposes there is no reason to isolate the intermediate 1,5 diketones since one achieves substantially the same result, in terms of cyclohexenone formation, in much higher yield by directly converting the lutidine system 1 to the product. However, in some cases there are real differences in the ratio of cyclohexenones produced directly from the dihydropyridine and from the 1,5 diketone.[9] Accordingly, all of the reults discussed in this report involve cyclizations of isolated homogeneous 1,5 diketones.

Cyclization of 16 in aqueous ethanolic alkali *under reflux* gave a 1:3.4 ratio of 17:18. However, by the simple expedient of conducting the cyclization at room temperature, the ratio of 17:18 was dramatically and favorably reversed to the level of 3.8:1. It was further demonstrated[2] that under these conditions of reflux, 17 is converted to 18 presumably by hydration and retro-aldol followed by aldol cyclization.[10-12]

As we continued to the synthetically crucial substrate 20, the only cyclohexenone obtained was the desired trisubstituted system (3).[2,9] This was the case either at room temperature or under conditions of reflux. Furthermore, the trisubstituted product did not suffer transformation to the tetrasubstituted system (6) even under forcing alkaline conditions.

After the viability of the total synthesis had thus been established, some preliminary studies of the aldol cyclization of simpler 1,5 diketones were reported.[9] Birch-type reduction of 6-ethyl-α-picoline followed by careful hydrolysis gave diketone 21. Alkali-induced cyclodehydration of 21 at room temperature afforded a 19:1 ratio (determined by GLC) of 22:23. This result seemed to be very much in keeping with those expected on the basis of the precedents arising from the cyclization of 1,4 diketones discussed above.[5]

We also prepared the diketone ketal 24 by alkylation of the lithium salt of 2,6-lutidine with the dioxolane of 4-chloro-2-



butanone followed by reduction and hydrolysis. Base-catalyzed cyclization of **24** at room temperature gave a 3:1 ratio of **25:26** (determined by GLC). When this reaction was conducted in refluxing aqueous ethanolic base, the ratio of **25:26** was 10:1.[9]

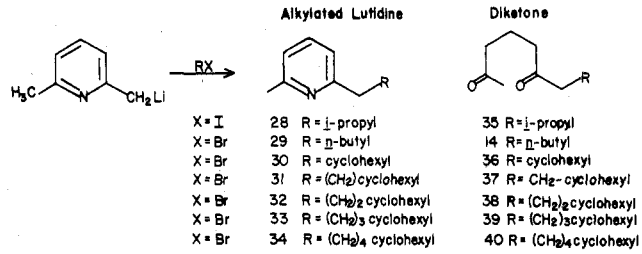
One could thus discern several general effects. Branching in the group R in structure **2** seems to be a factor favoring type **3** (trisubstituted) products. Higher reaction temperatures appear to favor type **6** (tetrasubstituted) products by equilibration. With heavily encumbered R groups such as those found in **19** and **20**, trisubstituted products are favored, exclusively, even at higher temperatures. Whether this reflects an inability to achieve equilibration of the trisubstituted products, or whether in these cases the trisubstituted product is actually thermodynamically more stable, is not known. Since no studies of cyclization of 1,4 diketones similar to **16**, **19**, or **20** had ever been described, there was no reason to suspect any basic differences in the behavior of systems **2** and **7**.

Below we report the results of experiments undertaken to generalize these findings. Except for **21**, the diketones thus far studied under structure **2** were rather special in that the R group contained a ketal. Any specific directive influences of this group could not be readily discerned from our data. Furthermore, it was necessary to define with greater precision the effect of branching on the direction of aldol cyclization and the consequences of varying the distance between the branch point and the ring being produced.

In pursuing this line of study, we have found that there are major differences in the aldol cyclization of 1,5 and 1,4 diketones such as **2** and **7**, respectively. Furthermore, it was found that the ketal does exert a directing effect but the effect favors tetra- rather than trisubstituted products. The findings are summarized below.

Preparation of the 1,5 Diketones. The route which was followed for the preparation of all the 1,5 diketones used in this study involved Birch reduction of 2,6-disubstituted pyridines followed by hydrolytic opening of the dihydropyridines. While the overall yield for the two steps was only in the order of 20–40%, this route was the most convenient for the purposes of this study.

The required pyridines **28** → **34** were prepared by the monoalkylation of 2,6-lutidine via its lithium salt. The latter was generated from the action of the tar base with either phenyl- or butyllithium. The products, obtained in 20–60% yields, were readily separated from the starting material and polyalkylated materials by distillation.



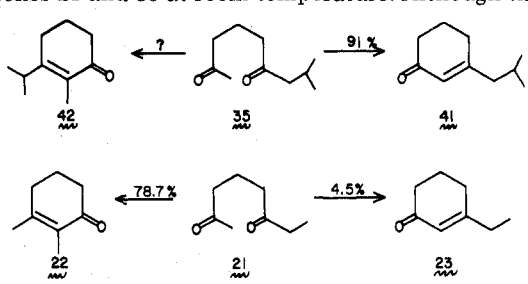
Each pyridine was subjected to Birch-type reduction with sodium in ammonia containing ethanol.[13] After removal of the ammonia, the residue was treated with 10% aqueous sulfuric acid to provide the diketone.[14] Under these conditions, there is no appreciable cyclization to cyclohexenone and the diketone is obtained as the neutral product. This method was of course not feasible for the preparation of diketone ketals **16**, **19**, and **24** since the ketal would have been cleaved.[15] Rapid alkaline hydrolysis of the dihydropyridine intermediate was used to avoid cyclization in these cases.

Starting pyridine compound and overreduction products are easily removed by acidic extraction.

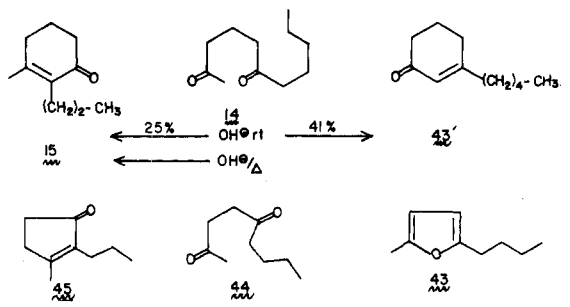
Cyclization of the 1,5 Diketones. The cyclohexenones obtained by base-catalyzed aldol cyclization of the 1,5 diketones were purified by chromatography on silica gel. Elutions were conducted with benzene containing varyingly small amounts of ethyl acetate depending on the ease of the separation. In each case, the tetrasubstituted isomer was eluted first and this was followed by elution of the trisubstituted system. The separations were clean and there seems no reason to doubt that the yield ratio, as determined by isolation, accurately reflects the ratio produced in the reaction.

The structural assignments of the cyclohexenones follow unambiguously from their NMR spectra. The type **3** (trisubstituted) products all exhibit a broad (long range coupling) 1 H singlet in the region δ 5.8 ppm. The NMR spectra of type **4** (tetrasubstituted) enones, of course, contain no such signal but do contain a 3 H singlet in the region δ 1.9 ppm. The assignments were supported by infrared and mass spectra, though these measurements are not useful for purposes of differentiation.

The effects of branching are dramatically een in the comparison of the results of base-catalyzed aldol cyclization of diketones **21** and **35** at room temperature. Although the cy-



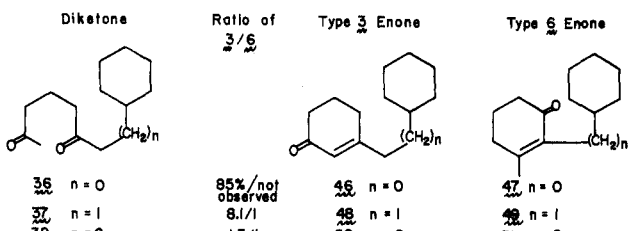
clization of **21** under these conditions had been studied before,[9] this was repeated. The 17:1 ratio of cyclohexenones **22:23** produced in this work, as ascertained by product isolation, compared quite closely with the 19:1 ratio previously reported on the basis of GLC analysis. These results stand in sharp contrast to the virtually exclusive isolation of **41** from cyclization of **35** under identical conditions. TLC analysis leaves open the possibility of the presence of some tetrasubstituted enone **42** but the amount, if any, was too small for isolation. It was now of interest to study the room temperature base-catalyzed aldol cyclization of diketone **14**. As noted above, Stork and Borch[7] had obtained only compound **15** from more forcing alkaline cyclization conditions. *Under our conditions at room temperature, a 1.5:1 ratio of cyclohexenones* **43:15** *was obtained.* When diketone **14** was subjected to the condi-



tions of Stork and Borch, we found, as was reported,[7] that compound **15** was the only isolated product. In a separate experiment it was shown that cyclohexenone **43** could be isomerized to **15** in aqueous ethanolic alkali under reflux.[10,11] This situation is similar to our findings in the case of enone **17** which could be isomerized to **18** under the same conditions.[2] These results leave open the possibility of some difference in the kinetic distribution of cyclohexenones in the room temperature vs. forcing conditions, but the simplest interpretation is that the formation of tetrasubstituted products at elevated temperatures is the consequence of thermodynamic equilibration. In any case, it is seen that in the cyclization of 1,5 diketones of the type **2** where R is straight chain, the kinetic distribution of products is near unity and, in fact, tends to favor type **3** product. Diketone **21** (i.e., **2**, R = H) is actually the exception in that even kinetically (room temperature), the type **6** product is overwhelmingly favored.

We also examined the analogous cyclization of the 1,4 diketone **44**, readily obtained by hydrolysis of 2-methyl-5-*n*-butylfuran. Cyclization of **44** even at room temperature gives cyclopentenone **45** as the only isolated product. *Apparently, there is a major difference in the directionality of base-catalyzed cyclization of 1,5 and 1,4 diketones under identical conditions.* This difference had previously been obscured by our own report of the room temperature cyclization of **21** which gives overwhelmingly **22** product and by the previous report that **14** affords **15** under high temperature conditions. The former case is seen to be the exception at the kinetic level. The later case reflects thermodynamic, rather than kinetic, control.

Analysis of the results of cyclization of diketones **36** → **40**



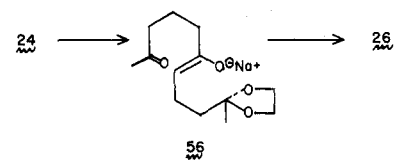
at room temperature indicates the effect of the distance between the carbon branching and the ring to be formed on the distribution of cyclohexenones. It is seen that as the cyclohexyl group is placed further from the C_6 ketone, the ratio of cyclohexenones moves in the direction of unity. In the case of $n = 0$ (**36**), only type **3** product is isolated. This is the analogue of compound **35**. Again it is seen that formation of type **6** product is seriously discouraged where the branched carbon would be adjacent to the ring.

In the cyclohexyl series, the consequence of branching is largely dissipated in passing from compound **37** to compound **38**. In the tetrasubstituted (type **6**) product, this corresponds to changing from a cyclohexylmethyl to a 2-cyclohexylethyl substituent at the α carbon of the β-methylenone system. The stage at which this effect is lost as "n" increases may well vary from system to system.

It will be noted that the case of $n = 1$ is the analogue of **16** which was the model case for the steroid work.[2] The ratio of type **3**/type **6** product obtained from cyclization of **37** at room temperature is 8.1:1 whereas in the case of **16** these products are produced in a ratio of 3.8:1. Thus it appears that in this case the ketal linkage, in fact, exerts a small but distinct directing effect in favor of the type **6** mode of cyclization.

The same tendency is seen in more pronounced form in comparison of the cyclization of **24** [type **6** (**25**)/type **3** (**26**) = 1:4] relative to **14** [type **3** (**43**)/type **6** (**15**) = 1.5:1]. A closer model for the expected result for a carbon branched analogue of **24** would be diketone **39** where the type **3** (**52**)/type **6** (**53**) ratio is 1.3:1. Thus the preponderance of type **6** product (4:1) in the case of **14** is clearly ascribable to the ketal which is exerting a decisive influence in favor of the tetrasubstituted enone at the kinetic level.

While the structural reasons for the effect are not known, it seems possible that the ketal oxygens serve to stabilize that enolate which is the precursor to tetrasubstituted product by bonding to the metal counterion (cf. **56**). The possibility of



56

controlling the course of aldol cyclization of systems such as **2** by the placement of remote groups which might influence the course of enolization is a potential consequence of this work.

The nature of the effect of carbon branching in promoting formation of the tetrasubstituted enone is not known in detail. It may be operative, on steric grounds, by retardation of the formation of the β-aldol precursor of the type **6** product. Alternatively, it may be operative by retardation of the final dehydration step.

In the light of these data, the cyclization of **19** and **20** in the direction of type **3** products, which was critical to the steroid total synthesis, is by no means anomalous. The apparent anomaly arose from an inadequate data base since there is virtually no correlation in the cyclization of systems such as **2** and **7**.

Experimental Section

Preparation of 2-Isobutyl-6-methylpyridine (28). To a mixture of 100 ml of anhydrous ether containing 1.4 g (0.2 mol) of lithium metal under a nitrogen atmosphere was added dropwise 15.7 g (0.1 mol) of bromobenzene. The mixture was heated under reflux until the lithium had completely disappeared (approximately 1.5 h). To this mixture was added 9.3 g (0.087 mmol) of 2,6-lutidine. The mixture was stirred under reflux for 30 min. To this mixture was added 6.15 g (0.036 mmol) of isopropyl iodide in an equal volume of anhydrous ether. The mixture was heated under reflux for 30 min. The reaction mixture was then diluted with water and extracted with methylene chloride. The organic layers were dried over anhydrous Na_2SO_4. Evaporation of the volatiles afforded 4.95 g of a brown residue. Distillation of the crude oil at 10 mm yielded 3.21 g (60%)[17] of **28** as a pale yellow liquid, boiling at 70–75 °C; λ_{max} ($CHCl_3$) 1580, 1595 cm^{-1}; δ ($CDCl_3$) 7.28–7.57 (m, 1), 6.77–7.0 (m, 2), 1.88–2.73 (m, 6 containing s ca. 3 at δ 2.52), 0.87, 0.98 (d, 6); *m/e* 149 (P), 107.

Preparation of 8-Methyl-2,6-nonanedione (35). To a solution of 1.00 g (6.7 mmol) of **28**, 1.23 g (26.8 mmol) of absolute ethanol, and 5.0 ml of anhydrous ether in 60 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 354 mg (15.4 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles were evaporated under a stream of nitrogen. To the residue was added 10 ml of aqueous 10% H_2SO_4, and the solution was stirred at room temperature for 15 min. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of methylene chloride. The organic layers were dried over anhydrous Na_2SO_4 and the

solvent was removed to afford a residue (612 mg). This was washed with three 15-ml portions of aqueous 10% HCl to afford 305 mg (27%) of diketone **35** as a yellow oil: λ_{max} ($CHCl_3$) 1718 cm^{-1}; δ ($CDCl_3$) 1.5–2.6 (m, 12 H containing s ca. 3 H at δ 2.12). 0.85, 0.97 (d, 6 H); *m/e* 170 (P), 85.

Anal. Calcd for $C_{10}H_{18}O_2$: *m/e* 170.13068. Found: *m/e* 170.13035.

Neutralization of the combined acidic layers, extraction with chloroform, and drying (Na_2SO_4) afforded 523 mg of basic material.

Room Temperature Cyclization of Diketone 35. Formation of 3-Isobutylcyclohex-2-en-1-one (41). To a solution of 936 mg (5.5 mmol) of diketone **35** in 22 ml of ethanol was added a solution of 550 mg (13.75 mmol) of sodium hydroxide in 11 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was acidified with 10% aqueous HCl and extracted with three 100-ml portions of chloroform. The organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 929 mg of a yellow oil. Chromatography of the oil on 100 g of silica gel using 10:1 benzene–ethyl acetate as eluent yielded 759 mg (91%) of cyclohexenone **41** as an oil: λ_{max} ($CHCl_3$) 1660 cm^{-1}; δ ($CDCl_3$) 0.88, 0.98 (d, 6), 1.93–2.5 (m, 9), 5.88 ppm (s, 1); 2,4-DNP mp 136–138 °C (lit.[18] 135 °C).

Anal. Calcd for $C_{10}H_{16}O$: *m/e* 152.120115. Found: *m/e* 152.120149.

Preparation of 2-Pentyl-6-methylpyridine (29). To a solution of 147 ml of *n*-BuLi (1.6 M in hexane), maintained under a nitrogen atmosphere, was added dropwise 25.0 g (0.234 mol) of 2,6-lutidine in 50 ml of anhydrous ether. The mixture was stirred at reflux for 30 min. To this mixture was added 16.03 g (0.117 mmol) of *n*-butyl bromide in an equal volume of anhydrous ether. The solution was heated under reflux for 30 min. This was followed by dilution with water and extraction with ether. The organic layers were combined and dried over anhydrous Na_2SO_4. Evaporation and solvent removal afforded 18.5 g of a yellow oil. Vacuum distillation of the crude oil yielded 13.2 g (69%)[17] of compound **29:** bp 42–45 °C (22 mm); λ_{max} ($CHCl_3$) 1582, 1597 cm^{-1}; δ ($CDCl_3$) 7.17–7.47 (m, 1), 6.68–6.88 (m, 2), 2.48–2.82 (m, 2), 2.38 (s, 3), 0.77–1.85 ppm (m, 9).

Anal. Calcd for $C_{11}H_{17}N$: *m/e* 163.13609. Found: *m/e* 163.13609.

Preparation of 2,6-Undecanedione (14). To a solution of 1.00 g (6.1 mmol) of **29,** 1.13 g (24.4 mmol) of absolute ethanol and 6 ml of anhydrous ether in 60 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 323 mg (14 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles were evaporated under a stream of nitrogen. To the residue was added 10 ml of aqueous 10% H_2SO_4 and the solution was stirred at room temperature for 15 min. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed to afford 701 mg (62%) of diketone **14** as tan crystals: mp 46–48 °C; λ_{max} ($CDCl_3$) 1712 cm^{-1}; δ ($CDCl_3$) 0.9–2.6 ppm (m, 20 containing s ca. 3 at 2.13).

Anal. Calcd for $C_{11}H_{20}O_2$: *m/e* 184.14633. Found: *m/e* 184.14619.

Neutralization of the acidic layer, extraction with chloroform, and drying (Na_2SO_4) yielded 232 mg of basic material.

Room Temperature Cyclization of Diketone 14. Formation of 2-Butyl-3-methylcyclohex-2-en-1-one (15) and 3-Pentylcyclohex-2-en-1-one (43′). To a solution of 172 mg (0.94 mmol) of diketone **14** in 3.74 ml of ethanol was added a solution prepared from 94 mg (2.35 mmol) of sodium hydroxide and 1.87 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was acidified with 10% aqueous HCl and was extracted with three 250-ml portions of chloroform. The organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 143 mg of a yellow oil. Chromatography of the oil on 30 g of silica gel using 40:1 benzene–ethyl acetate as eluent yielded 39 mg (25%) of **15** as an oil: λ_{max} ($CHCl_3$) 1656 cm^{-1}; δ ($CDCl_3$) 1.8–2.5 (m, 11 containing s ca. 3 at 1.93), 0.83–1.42 ppm (m, 7); 2,4-DNP mp 147–148 °C (lit.[19] 144 °C).

Anal. Calcd for $C_{11}H_{18}O$: *m/e* 166.13577. Found: *m/e* 166.13561.

Continued elution with the same solvent system afforded 64 mg (41%) of cyclohexenone **43′** as an oil: λ_{max} ($CHCl_3$) 1661 cm^{-1}; δ ($CDCl_3$) 0.7–2.5 (m, 17), 5.88 ppm (s, 1); 2,4-DPN mp 125–126 °C.

Anal. Calcd for $C_{11}H_{18}O$: *m/e* 166.13577. Found: *m/e* 166.13546.

Preparation of 2,6-Octanedione (21). To a solution of 1.01 g (8.3 mmol) of 2-methyl-6-ethylpyridine, 1.52 g (0.33 mmol) of absolute ethanol, and 5.0 ml of anhydrous ether in 50 ml of anhydrous ammonia (freshly distilled from sodium) was slowly added 440 mg (20 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles evaporated under a stream of nitrogen. To the residue was added 10 ml of aqueous 10% H_2SO_4 and the solution was stirred at room temperature for 15 min. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were combined and dried over anhydrous Na_2SO_4 and the solvent was evaporated at the water pump to yield 755 mg (64%) of diketone **21** as an oil: λ_{max} ($CHCl_3$) 1712 cm^{-1}; δ $CDCl_3$) 1.67–2.63 (m, 11 containing s ca. 3 at 2.12), 0.92–1.17 ppm (t, 3); *m/e* 142 (P).

Neutralization of the acidic layer, extraction with chloroform, and drying (Na_2SO_4) afforded 200 mg of basic material.

Room Temperature Cyclization of Diketone 21. Formation of 2,3-Dimethylcyclohex-2-en-1-one (22) and 3-Ethylcyclohex-2-en-1-one (23). To a solution of 306 mg (2.2 mmol) of diketone **21** in 8.6 ml of ethanol was added a solution of 215 mg (5.38 mmol) of sodium hydroxide in 4.3 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was acidified with 10% aqueous HCl and then stirred for 15 min at room temperature. The solution was extracted with three 50-ml portions of chloroform and the organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 250 mg of a yellow oil. Chromatography of the oil on 40 g of silica gel using chloroform as eluent yielded 124 mg of pure **22** and 131 mg of a mixture of **22** and **23**. The mixture was rechromatographed on 20 g of silica gel using 95:5 hexane–ether as eluent. This chromatography yielded 86 mg (210 mg total, 78.7%) of the tetrasubstituted isomer **22** as an oil: λ_{max} ($CHCl_3$) 1645 cm^{-1}; δ ($CDCl_3$) 2.17–2.5 (m, 6), 2.0 (s, 3), 1.77 ppm (s, 3); *m/e* 124 (P). 2,4 DNP mp 198–200 °C (lit.[20] 198–199 °C).

Continued elution with chloroform as eluent afforded 12 mg (4.5%) of the isomeric cyclohexenone **23** as an oil: λ_{max} ($CHCl_3$) 1658 cm^{-1}; δ ($CDCl_3$) 6.07 (s, 1), 2.0–2.5 (m, 8), 1.12–1.37 ppm (t, 3); *m/e* 124 (P). 2,4 DNP mp 163–164 °C (lit.[21] 160–161 °C).

Preparation of 2-Cyclohexylmethyl-6-methylpyridine (30). To a solution of 30 ml of *n*-BuLi (1.6 M in hexane), maintained under a nitrogen atmosphere, was slowly added 4.6 g (0.043 mol) of 2,6-lutidine in 5 ml of anhydrous ether. The mixture was stirred at reflux for 1 h. To this mixture was added 7.0 g (0.043 mol) of cyclohexyl bromide in an equal volume of anhydrous ether. Addition required 15 min. The solution was heated under reflux overnight to ensure complete reaction. The solution was hydrolyzed and extracted with three 100-ml portions of ether and the organic layers dried over anhydrous Na_2SO_4. Solvent evaporation yielded 8.12 g of a brown oil. Vacuum distillation of the crude liquid yielded 2.4 g (29%) of **30:** bp 73–75 °C (0.15 mm); λ_{max} ($CHCl_3$) 1577, 1592 cm^{-1}; δ ($CDCl_3$) 7.32–7.57 (m, 1), 6.78–6.98 (m, 2), 2.48–2.70 (m, 5 containing s ca. 3 at δ 2.53), 0.98–1.95 ppm (m, 11); *m/e* 189 (P), 107.

Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.47; H, 10.18; N, 7.31.

Conversion of 30 to 7-Cyclohexyl-2,6-heptanedione (36). To a solution of 997 mg (5.27 mmol) of compound **30** and 970 mg (21 mmol) of absolute ethanol in 5.0 ml of anhydrous ether in 50 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 279 mg (12 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles evaporated under a stream of nitrogen. To the residue was added 10 ml of 10% H_2SO_4 and the solution was stirred at room temperature for 15 min. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated to yield 944 mg of a yellow oil. Chromatography of the oil on 100 g of silica gel using 10:1 benzene–ethyl acetate as eluent afforded 545 mg (49%) of diketone **36:** λ_{max} ($CHCl_3$) 1715 cm^{-1}; δ ($CDCl_3$) 1.0–2.6 ppm (m, 22 containing s ca. 3 at δ 2.13).

Anal. Calcd for $C_{13}H_{22}O_2$: *m/e* 210.16198. Found: *m/e* 210.16173.

Room Temperature Cyclization of Diketone 36. Formation of 3-Cyclohexylmethylcyclohex-2-en-1-one (46). To a solution of 320 mg (1.52 mmol) of diketone **36** in 6.2 ml of ethanol was added a solution of 152 mg (3.8 mmol) of sodium hydroxide in 3.1 ml of water. The solution was stirred under nitrogen at room temperature for 2.5 h. The solution was then acidified with 10% aqueous HCl and extracted with three 50-ml portions of chloroform. The organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded 288 mg of a yellow oil. Chromatography of the oil on 20 g of silica gel using 10:1 benzene–ethyl acetate as eluent afforded 250 mg (85%) of cyclohexenone **46** as an oil: λ_{max} ($CHCl_3$) 1658 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 (m, 19), 5.87 ppm (s, 1); 2,4-DNP mp 150–153 °C.

Anal. Calcd for $C_{13}H_{20}O$: *m/e* 192.15151. Found: *m/e* 192.15060.

Preparation of 2-(2-Cyclohexyl)ethyl-6-methylpyridine (31). To a solution of 30 ml of *n*-BuLi (1.6 M in hexane), maintained under a nitrogen atmosphere, was slowly added 4.6 g (0.043 mol) of 2,6-lutidine in 5 ml of anhydrous ether. The mixture was stirred at reflux for 1 h. To this mixture was added 7.0 g (0.040 mol) of cyclohexylmethyl bromide in an equal volume of anhydrous ether. The solution was heated under reflux for 5 h. The solution was diluted with water and extracted with ether. The organic extracts were combined and

dried over anhydrous Na_2SO_4 and the solvent removed to afford 9.96 g of a yellow oil. Vacuum distillation of the crude oil afforded 4.14 g (52%) of **31**: bp 92–93 °C (0.29 mm); λ_{max} ($CHCl_3$) 1582, 1592 cm^{-1}; δ ($CDCl_3$) 7.33–7.58 (m, 1), 6.87–6.98 (m, 2), 2.65–2.93 (m, 2), 2.53 (s, 3), 1.0–1.95 ppm (m, 13); *m/e* 203 (P).

Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.66; H, 10.40; N, 6.87.

Conversion of 31 to 8-Cyclohexyl-2,6-octanedione (37). To a solution of 1.01 g (4.9 mmol) of compound **31**, 902 mg (19.6 mmol) of absolute ethanol, and 5.0 ml of anhydrous ether in 50 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 260 mg (11.3 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles evaporated under a stream of nitrogen. To the residue was added 10 ml of 10% H_2SO_4 and the solution was stirred at room temperature for 15 min. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were combined and dried over anhydrous Na_2SO_4 and the solvent removed to yield 220 mg (20%) of crystalline diketone **37**: mp 52–54 °C; λ_{max} ($CHCl_3$) 1712 cm^{-1}; δ ($CDCl_3$) 1.0–2.6 (m, 24 containing s ca. 3 at δ 2.13); *m/e* 244, 128 (P).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.80; H, 10.76.

Neutralization of the acidic layer, extraction with chloroform, and drying (Na_2SO_4) yielded 431 mg of unreacted **31** (42%).

Room Temperature Cyclization of Diketone 37. Formation of 3-(2-Cyclohexyl)ethylcyclohex-2-en-1-one (48) and 3-Cyclohexylmethyl-3-methylcyclohex-2-en-1-one (49). To a solution of 202 mg (0.91 mmol) of diketone **37** in 3.6 ml of ethanol was added a solution prepared from 91 mg (2.3 mmol) of sodium hydroxide in 1.8 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was acidified with 10% aqueous HCl and extracted with three 50-ml portions of chloroform, and the organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 170 mg of a yellow oil. Chromatography of the oil on 17 g of silica gel using 10:1 benzene–ethyl acetate as eluent yielded 11 mg (6.1%) of **49** as an oil: λ_{max} ($CHCl_3$) 1658 cm^{-1}; δ ($CDCl_3$) 0.8–2.5 ppm (m, containing s ca. 3 at δ 1.93).

Anal. Calcd for $C_{14}H_{22}O$: *m/e* 206.16706. Found: *m/e* 206.16711.

Continued elution with the same solvent system gave **48** (92 mg, 50%) as an oil: λ_{max} ($CHCl_3$) 1658 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 (m, 21), 5.87 ppm (s, 1); 2,4-DNP mp 149–151 °C.

Anal. Calcd for $C_{14}H_{22}O$: *m/e* 206.16706. Found: *m/e* 206.16650.

Preparation of 2-(3-Cyclohexyl)propyl-6-methylpyridine (32). To a solution of 15 ml of *n*-BuLi (1.6 M in hexane), maintained under a nitrogen atmosphere, was slowly added 2.3 g (0.021 mol) of 2,6-lutidine in 2.5 ml of anhydrous ether. The mixture was stirred under reflux for 1 h. To this mixture was added 3.8 g (0.020 mol) of 2-cyclohexylethyl bromide in an equal volume of anhydrous ether. The solution was heated under reflux for 5 h. The solution was diluted with water and extracted with ether. The organic layers were dried over anhydrous Na_2SO_4. Solvent removal afforded 5.11 g of a yellow oil. Vacuum distillation of the crude oil yielded 2.55 g (59%) of **32**: bp 101–103 °C (0.17 mm); λ_{max} ($CHCl_3$) 1582, 1600 cm^{-1}; δ ($CDCl_3$) 7.4–7.6 (m. 1), 6.9–7.0 (m, 2), 2.62–2.88 (m, 2), 2.53 (s, 3), 0.83–1.92 ppm (m, 15); *m/e* 217 (P).

Anal. Calcd for $C_{15}H_{23}N$; C, 82.89; H, 10.67; N, 6.44. Found: C, 82.70; H, 10.66; N, 6.59.

Conversion of 32 to 9-Cyclohexyl-2,6-nonanedione (38). To a solution of 1.02 g (4.7 mmol) of compound **32**, 865 mg (18.8 mmol) of absolute ethanol, and 5.0 ml anhydrous ether in 50 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 249 mg (10.8 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles were evaporated under a stream of nitrogen. To the residue was added 10 ml of 10% H_2SO_4 and the solution was stirred for 15 min at room temperature. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated to yield 469 mg of a yellow oil. Chromatography of the oil on 50 g of silica gel using 10:1 benzene–ethyl acetate as eluent afforded 382 mg (34%) of diketone **38**: λ_{max} ($CHCl_3$) 1715 cm^{-1}; δ ($CDCl_3$) 1.0–2.6 ppm (m, cntaining s ca. 3 at δ 2.13).

Anal. Calcd for $C_{15}H_{26}O_2$: *m/e* 238.19328. Found: *m/e* 238.19320.

Neutralization of the acidic layer, extraction with chloroform, and drying (Na_2SO_4) afforded 660 mg of basic material.

Room Temperature Cyclization of Diketone 38. Formation of 3-(3-Cyclohexyl)propylcyclohex-2-en-1-one (50) and 2-(2-Cyclohexyl)methyl-3-methylcyclohex-2-en-1-one (51). To a solution of 251 mg (1.06 mmol) of diketone **38** in 4.2 ml of ethanol was added a solution of 106 mg (2.7 mmol) of sodium hydroxide in 2.1 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was acidified with 10% aqueous HCl and stirred at room temperature for 15 min. The solution was extracted with three 50-ml portions of chloroform and the organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 224 mg of a yellow oil. Chromatography of the oil on 25 g of silica gel using 10:1 benzene–ethyl acetate as eluent yielded 84 mg (36.4%) of **51** as an oil: λ_{max} ($CHCl_3$) 1656 cm^{-1}; δ ($CDCl_3$) 0.9–2.5 ppm (m, containing s ca. 3 at δ 1.93); 2,4-DNP mp 146–148 °C.

Anal. Calcd for $C_{15}H_{24}O$: *m/e* 220.18271. Found: *m/e* 220.18240.

Continued elution with the same solvent system gave cyclohexenone **50** (111 mg, 48.3%) as an oil: λ_{max} ($CHCl_3$) 1664 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 (m, 23), 5.78 (s, 1); 2,4-DNP mp 140–141 °C.

Anal. Calcd for $C_{15}H_{24}O$: *m/e* 220.18271. Found: *m/e* 220.18239.

Preparation of 2-(Cyclohexyl)butyl-6-methylpyridine (33). To a solution of 15 ml of *n*-BuLi (1.6 M in hexane), maintained under a nitrogen atmosphere, was slowly added 2.3 g (0.0215 mol) of 2,6-lutidine in 2.5 ml of anhydrous ether. The mixture was stirred at reflux for 1 h. To this mixture was added 4.1 g (0.020 mmol) of 3-cyclohexylpropyl bromide in an equal volume of anhydrous ether. The solution was heated under reflux overnight. The solution was diluted with water and extracted with three 50-ml portions of ether. The organic layers were dried over anhydrous Na_2SO_4. Solvent removal afforded 5.77 g of a crude liquid. Vacuum distillation of the recovered liquid yielded 2.86 g (62%) of **33**: bp 107–108 °C (0.17 mm); λ_{max} ($CHCl_3$) 1580, 1597 cm^{-1}; δ ($CDCl_3$) 7.35–7.6 (m, 1), 6.87–7.0 (m, 2), 2.65–2.9 (m, 2), 2.52 (s, 3), 0.98–1.88 (m, 17).

Anal. Calcd for $C_{16}H_{25}N$: *m/e* 231.19869. Found: *m/e* 231.19814.

Conversion of 33 to 10-Cyclohexyl-2,6-decanedione (39). To a solution of 516 mg (2.2 mmol) of compound **33**, 405 mg (8.8 mmol) of absolute ethanol, and 3.0 ml of anhydrous ether in 30 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 116 mg (5.04 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles were evaporated under a stream of nitrogen. To the residue was added 10 ml of 10% H_2SO_4 and the solution was stirred for 15 min at room temperature. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were combined and dried over anhydrous Na_2SO_4. Solvent removal afforded 360 mg of crude diketone **39**. Chromatography of the oil on 30 g of silica gel using 10:1 benzene–ethyl acetate as eluent yielded 202 mg (36%) of crystalline diketone **39**: mp 43.0–44.5 °C; λ_{max} ($CHCl_3$) 1698 cm^{-1}; δ ($CDCl_3$) 1.0–2.6 ppm (m, containing s ca. 3 at δ 2.13).

Anal. Calcd for $C_{16}H_{28}O_2$: *m/e* 252.20893. Found: *m/e* 252.20908.

Neutralization of the acidic layer, extraction with chloroform, and drying (Na_2SO_4) afforded 190 mg of basic material.

Room Temperature Cyclization of Diketone 39. Formation of 3-(4-Cyclohexyl)butylcyclohex-2-en-1-one (52) and 2-(3-Cyclohexyl)propyl-3-methylcyclohex-2-en-1-one (53). To a solution of 115 mg (0.46 mmol) of diketone **39** in 1.8 ml of ethanol was added a solution prepared from 46 mg (1.15 mmol) of sodium hydroxide in 0.92 ml of water. The solution was stirred under nitrogen at room temperature for 2.5 h. The solution was then acidified with 10% aqueous HCl and extracted with chloroform. The organic layers were dried over anhydrous Na_2SO_4. Solvent evaporation yielded 108 mg of a yellow oil. Chromatography of the oil on 6 g of silicic acid using 30:1 benzene–ethyl acetate as eluent afforded 41.8 mg (40%) of **53** as an oil: λ_{max} ($CHCl_3$) 1664 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 ppm (m, containing s ca. 3 at δ 1.93). 2,4 DNP mp 171–173 °C.

Anal. Calcd for $C_{16}H_{26}O$: *m/e* 234.19837. Found: *m/e* 234.19818.

Continued elution with the same solvent system gave cyclohexenone **52** (57.2 mg, 54%) as an oil: λ_{max} ($CHCl_3$) 1664 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 (m, 25), 5.83 (s, 1). 2,4 DNP mp 118–121 °C.

Anal. Calcd for $C_{16}H_{26}O$: *m/e* 234.19837. Found: *m/e* 234.19819.

Preparation of 2-(5-Cyclohexyl)pentyl-6-methylpyridine (34). To a solution of 38 ml of *n*-BuLi (1.42 M in hexane), maintained under a nitrogen atmosphere, was slowly added 4.6 g (0.043 mol) of 2,6-lutidine in 5 ml of anhydrous ether. The mixture was stirred at reflux for 1 h. To this mixture was added over a 15-min period 9.4 g (0.043 mol) of cyclohexylbutyl bromide in an equal volume of anhydrous ether. The solution was refluxed overnight. The solution was diluted with water and extracted with three 100-ml portions of ether. The organic layers were combined and dried over anhydrous Na_2SO_4. Solvent evaporation yielded 15.17 g of a yellow oil. Vacuum distillation of the crude oil afforded 4.4 g of **34**: bp 120–123 °C (0.20 mm); 42% yield; λ_{max} ($CHCl_3$) 1583, 1596 cm^{-1}; δ ($CDCl_3$) 7.34–7.6 (m, 1), 6.87–7.0 (m, 2), 2.63–2.89 (m, 2), 2.53 (s, 3), 0.98–1.95 ppm (m, 19).

Anal. Calcd for $C_{17}H_{27}N$: *m/e* 245.21434. Found: *m/e* 245.21434.

Conversion of 34 to 11-Cyclohexyl-2,6-undecanedione (40). To a solution of 1.18 g (4.8 mmol) of compound **34**, 883 mg (19.2 mmol) of absolute ethanol, and 5.0 ml of anhydrous ether in 50 ml of anhy-

drous liquid ammonia (freshly distilled from sodium) was slowly added 254 mg (11 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles were evaporated under a stream of nitrogen. To the residue was added 10 ml of 10% H_2SO_4 and the solution was stirred for 15 min at room temperature. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were combined and dried over anhydrous Na_2SO_4. Solvent removal yielded 615 mg of a yellow oil. Chromatography of the oil on 60 g of silica gel using 10:1 benzene–ethyl acetate as eluent afforded 565 mg (44%) of diketone **40**: λ_{max} ($CHCl_3$) 1704 cm^{-1}; δ ($CDCl_3$) 1.0–2.6 ppm (m, containing s ca. 3 at δ 2.12); *m/e* 266 (P).

Room Temperature Cyclization of Diketone 40. Formation of 3-(5-Cyclohexyl)pentylcyclohex-2-en-1-one (54) and 2-(4-Cyclohexyl)butyl-3-methylcyclohex-2-en-1-one (55). To a solution of 90 mg (0.34 mmol) of diketone **40** in 1.4 ml of ethanol was added a solution of 33.8 mg (0.85 mmol) of sodium hydroxide in 0.71 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was then acidified with 10% aqueous HCl and extracted with three 30-ml portions of chloroform. The organic layers were dried over anhydrous Na_2SO_4. Solvent evaporation afforded 80 mg of a yellow oil. Chromatography of the oil on 19 g of silica gel using 30:1 benzene–ethyl acetate as eluent afforded 37.7 mg (45%) of cyclohexenone **55** as an oil: λ_{max} ($CHCl_3$) 1664 cm^{-1}; δ ($CDCl_3$) 0.9–2.5 ppm (m, containing s ca. 3 at δ 1.93); 2,4-DNP mp 136–137 °C.

Anal. Calcd for $C_{17}H_{28}O$: *m/e* 248.21402. Found: *m/e* 248.21145.

Continued elution with the same solvent system gave **54** (42.2 mg, 51%) as an oil: λ_{max} ($CHCl_3$) 1667 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 (m, 27), 5.87 ppm (s, 1); 2,4-DNP mp 131–133 °C.

Anal. Calcd for $C_{17}H_{28}O$: *m/e* 248.21402. Found: *m/e* 248.21400.

Preparation of 2-Methyl-5-*n*-butylfuran (43).[22] To 59 ml of 1.6 M *n*-BuLi (0.095 mmol) cooled to −20 °C and under a nitrogen atmosphere was slowly added a solution of 7.7 g (0.094 mmol) of 2-methylfuran dissolved in 10 ml of THF. The mixture was stirred at −20 °C for 1.5 h. To this was added slowly a solution of 13.1 g (0.096 mmol) of *n*-butyl bromide in 10 ml of THF. Stirring was continued at −20 °C for 1 h and the solution was warmed to room temperature and allowed to stir overnight. The reaction mixture was poured over ice and thoroughly extracted with chloroform. The organic layers were combined and dried over anhydrous Na_2SO_4 and the solvent removed to afford 6 g (47%) of a crude **43** which was used as such in the next experiment without further purification: λ_{max} ($CHCl_3$) 2895, 1575, 1462 cm^{-1}; δ ($CDCl_3$) 5.77 (s, 2), 2.7–2.43 (t, 2), 2.23 (s, 3), 1.7–0.9 (m, 7).

Preparation of 2,5-Nonanedione (44). Glacial acetic acid (3 ml), water (1 ml), 20% H_2SO_4 (4 drops), and 2.1 g (15.2 mmol) of crude 2-methyl-5-*n*-butylfuran were combined and heated under reflux for 4 h. The resulting solution was poured into water and extracted with chloroform. The organic layers were combined and dried over Na_2SO_4. Solvent evaporation afforded 2 g of a crude product which was distilled to yield 1.5 g (63%) of the desired diketone **44**: bp 110–115 °C (15 mm); λ_{max} ($CHCl_3$) 2941, 1725, 1488 cm^{-1}; δ ($CDCl_3$) 2.75 (s, 4), 2.6–2.3 (t, 2), 2.2 (s, 3), 1.7–0.9 (m, 7).

Room Temperature Cyclization of Diketone 44.[22] **Formation of 2-Propyl-3-methylcyclopent-2-en-1-one (45).** To 200 mg (1.28 mmol) of diketone **44** was added 2.56 ml of 5% NaOH (3.2 mmol) and 5.1 ml of EtOH. The solution was stirred at room temperature under nitrogen for 20 h. After neutralization with 10% HCl the solution was extracted with three 20-ml portions of $CHCl_3$. The combined organic layers were dried over Na_2SO_4. Solvent removal afforded 150 mg (85%) of a product whose NMR revealed the presence of cyclopentenone **45**:[22] λ_{max} ($CHCl_3$) 1692, 1645, 2743 cm^{-1}; δ ($CDCl_3$) 2.6–2.1 (m, containing s ca. 3 at δ 2.1), 1.7–0.9 ppm (m, 5).

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Registry No.—**14,** 39557-21-6; **15,** 13679-29-3; **21,** 38275-04-6; **22,** 1122-20-9; **23,** 17299-34-2; **28,** 60439-17-0; **29,** 5394-28-5; **30,** 60439-18-1; **31,** 60439-19-2; **32,** 60439-20-5; **33,** 60439-21-6; **34,** 60439-22-7; **35,** 30963-76-9; **36,** 60439-23-8; **37,** 60439-24-9; **38,** 60439-25-0; **39,** 60439-26-1; **40,** 60439-27-2; **41,** 6301-50-4; **43′,** 60439-28-3; **43′** 2,4-DNP, 60439-29-4; **43,** 3857-27-0; **44,** 25234-82-6; **45,** 50397-91-6; **46,** 60439-30-7; **46** 2,4-DNP, 60439-01-2; **48,** 60439-02-3; **48** 2,4-DNP, 60439-03-4; **49,** 60439-04-5; **50,** 60439-05-6; **50** 2,4-DNP, 60439-06-7; **51,** 60439-07-8; **51** 2,4-DNP, 60439-08-9; **52,** 60439-09-0; **52** 2,4-DNP, 60439-10-3; **53,** 60439-11-4; **53** 2,4-DNP, 60439-12-5; **54,** 60439-13-6; **54** 2,4-DNP, 60439-14-7; **55,** 60439-15-8; **55** 2,4-DNP, 60464-14-4; 2,6-lutidine, 108-48-5; isopropyl iodide, 75-30-9; butyl bromide, 109-65-9; 2-methyl-6-ethylpyridine, 1122-69-6; cyclohexyl bromide, 108-85-0; cyclohexylmethyl bromide, 2550-36-9; 2-cyclohexylethyl bromide, 1647-26-3; 3-cyclohexylpropyl bromide, 34094-21-8; cyclohexylbutyl bromide, 60439-16-9; 2-methylfuran, 534-22-5.

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