The ρ value for the substituted benzohydroxamic acids is approximately the same as that for the substituted benzoic acids while *N*-methyl benzohydroxamic acids [$XC_6H_4C(O)N(OH)CH_3$] have a much lower ρ value. These results are explained[40] by suggesting that for both the benzoic acids and the benzohydroxamic acids, the acidic proton (if one assumes a NH acid for the hydroxamic acids) is separated from the substituent by two atoms. For the N-substituted hydroxamic acids, the acidic proton must be from the O–H group which is now three atoms removed from the substituent. The lower value of ρ is expected since the effect of the substituent must extend through three atoms as opposed to two atoms.

As described in this report, the ρ value for our substituted N-phenylacetohydroxamic acids is much less than the ρ value for substituted benzoic acids, yet the acidic proton is the same number of atoms removed from the substituent for both series. Our results suggest that there are several important factors which may have more influence on ρ values than distance between the substituent and the acidic site.

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Registry No. $CH_3C(O)N(OH)$-4-C_6H_4I, 67274-49-1; $CH_3C(O)N(OH)$-4-C_6H_4Cl, 1503-91-9; $CH_3C(O)N(OH)$-3-C_6H_4I, 80584-64-1; $CH_3C(O)N(OH)$-4-C_6H_4CN, 80584-65-2; $CH_3C(O)N(OH)$-4-$C_6H_4CH_3$, 27451-21-4; $CH_3C(O)N(OH)$-4-$C_6H_4C(O)CH_3$, 67274-51-5; $CH_3C(O)N(OH)$-3-C_6H_4CN, 80584-66-3; $CH_3C(O)N(OH)C_6H_5$, 1795-83-1; 4-ClC_6H_4NHOH, 823-86-9; 4-CNC_6H_4NHOH, 24171-84-4; 4-$CH_3C_6H_4NHOH$, 623-10-9; 4-$C(O)CH_3C_6H_4NHOH$, 10517-47-2; 3-CNC_6H_4NHOH, 24171-82-2; C_6H_5NHOH, 100-65-2; acetyl chloride, 75-36-5; 4-nitrobenzonitrile, 619-72-7; 3-nitrobenzonitrile, 619-24-9; 4-nitroacetophenone, 100-19-6; 4-nitrotoluene, 99-99-0; 4-chloronitrobenzene, 100-00-5; nitrobenzene, 98-95-3; 4-iodonitrobenzene, 636-98-6.

α-Nitro Ketones. 6.[1] Synthesis and Conformation of 2-Methyl-2-nitro-, *cis*- and *trans*-6-Methyl-2-nitro-, and *cis*- and *trans*-2,6-Dimethyl-2-nitrocyclohexanones

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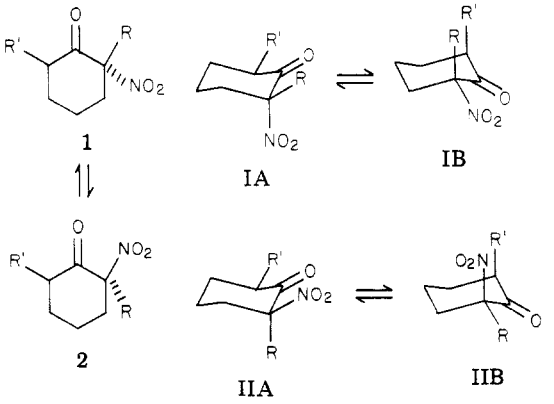
Received September 4, 1981

Nitration of the most substituted (thermodynamically more stable) enol acetate or trimethylsilyl ether of 2-methylcyclohexanone and the phase-transfer methylation of 2-nitrocyclohexanone serve as methods of preparation of 2-methyl-2-nitrocyclohexanone, whereas nitration of the least substituted enol acetate or trimethylsilyl ether of 2-methylcyclohexanone and methylation of the dianion of 2-nitrocyclohexanone lead to *cis*- and *trans*-6-methyl-2-nitrocyclohexanone. Nitration of the enol acetate or trimethylsilyl ether of 2,6-dimethylcyclohexanone and methylation of either 2-methyl-2-nitro- or 6-methyl-2-nitrocyclohexanone are methods of preparation of *cis*- and *trans*-2,6-dimethyl-2-nitrocyclohexanone. ^1H NMR chemical shift and coupling constant data were used to determine the preferred conformations of the cyclohexanones: 2(e)-methyl-2(a)-nitro, *cis*-6(e)-methyl-2(e)-nitro, *trans*-6(e)-methyl-2(a)-nitro, *cis*-2(e),6(e)-dimethyl-2(a)-nitro, *trans*-2(a)-methyl-6(e)-methyl-2(e)-nitro.

In our previous studies[1,3] on the synthesis of α-nitro ketones, the enol acetates that were nitrated were prepared from the ketones and acetic anhydride or isopropenyl acetate. Unsymmetrical ketones led to a mixture of enol acetates which were either separated by GLC and nitrated separately or nitrated as a mixture and the resulting isomeric nitro ketones separated by chromatography or crystallization. We had also demonstrated that the amyl nitrate nitration of potassium enolates generated from unsymmetrical ketones is also nonregioselective.[1] Furthermore, we[3] had observed that the nitration of 2-methyl-4-*tert*-butyl-1-acetoxycyclohexene gave a poor yield of the corresponding 2-nitro ketone and that the isomeric enol acetate 6-methyl-4-*tert*-butyl-1-acetoxycyclohexene could not be directly prepared regioselectively from the corresponding ketone, 2-methyl-4-*tert*-butylcyclohexanone, and isopropenyl acetate or acetic anhydride.[4] Because these preceeding results had a direct bearing on our syntheses of branched-chain sugars, it became important to determine the feasibility of synthesizing α-nitro ketones with a methyl group on the α-carbon as well. We therefore chose to study the synthesis of 2-methyl-, 6-methyl-, and 2,6-dimethyl-2-nitrocyclohexanones via the nitration of ketone derivatives and also to attempt the methylation of α-nitro ketones. In this paper we report the results of such

Scheme I. Configurational and Conformational Equilibria of 2-Nitrocyclohexanones



(1) Part 5: Elfehail, F. E.; Zajac, W. W., Jr. *J. Org. Chem.* **1981**, *46*, 5151.
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0022-3263/82/1947-1176$01.25/0

Table I. ^{1}H NMR Data for 2-Nitrocyclohexanones

2-nitrocyclohexanone	2-H δ	2-H J^3, Hz	2-H W, Hz	δ (2-CH_3)
2-methyl (1a = 2a; R = CH_3, R′ = H)				1.67
cis-6-methyl (2b; R = H, R′ = CH_3)	5.34	11.9, 6.3	18.4	
trans-6-methyl (1b; R = H, R′ = CH_3)	5.08	6.5, 5.0	11.6	
cis-2,6-dimethyl (1c; R = R′ = CH_3)				1.60
trans-2,6-dimethyl (2c; R = R′ = CH_3)				1.86

a study as well as the conformational analysis of the α-nitro ketones synthesized.

Results and Discussion

Configuration and Conformation of α-Nitro Ketones (See Scheme I). We had previously established the configuration and conformation of α-nitrocyclohexanones by ^{1}H NMR and applied the same method[5] to determine the configuration and conformation of the nitro ketones prepared in this investigation.

In Table I are the ^{1}H NMR parameters used to assign the configurations and to calculate the conformational free energies of the α-nitro ketones.

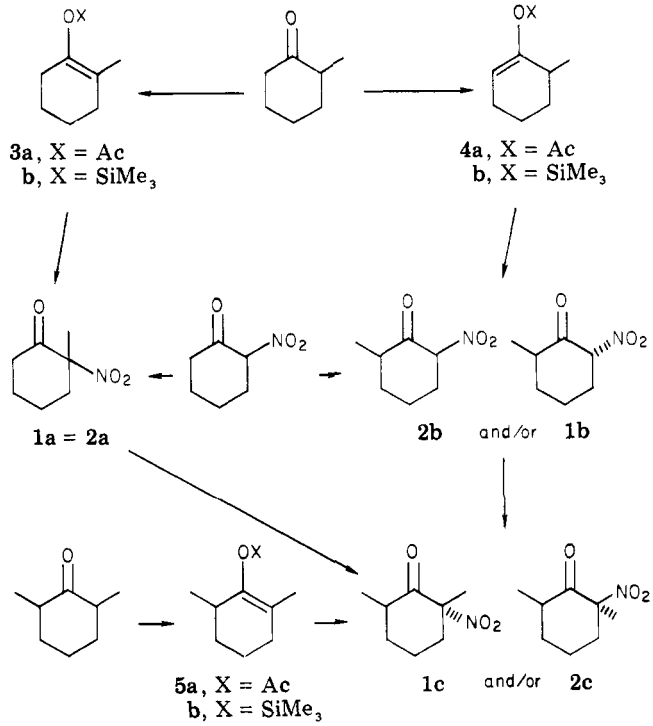
6-Methyl-2-nitrocyclohexanone exists as cis–trans isomers (**2b**, **1b**; R = H, R′ = CH_3). The cis isomer has both substituents in either the diequatorial (IIA; R = H, R′ = CH_3) or diaxial conformation (IIB; R = H, R′ = CH_3) with the former expected to be the exclusive conformation. By use of the ^{1}H NMR chemical shifts, coupling constants, or bandwidths, it was an easy matter to assign the configurations (see Table I). The resonance of the α-proton of the cis isomer (**2b**; R = H, R′ = CH_3) appears at lower field (δ 5.34) than that for the trans isomer **1b** (R = H, R′ = CH_3; δ 5.08), and it appears as a doublet of doublets (W = 18.4 Hz) with J_{aa}^3 = 11.9 and J_{ae}^3 = 6.3 Hz.

For *trans*-6-methyl-2-nitrocyclohexanone (**1b**; R = H, R′ = CH_3) one of the substituents must be axial and the other equatorial, and the system is mobile (W_{av} = 11.6 Hz, J_{av} = 6.5 Hz). For calculation of the ΔG, the more reliable parameters are the bandwidths and coupling constants. Use of the values of 18.4 and 9.6 Hz, respectively, for the bandwidths of the axial and equatorial protons or the J_{aa}^3 = 11.9 Hz and J_{ee}^3 = 4.4 Hz[5] calculation leads to values of 0.63 and 0.55 kcal/mol for the conformational free energy of *trans*-6-methyl-2-nitrocyclohexanone (**1b**; R = H, R′ = CH_3). These values are in modest agreement with the value of 0.43 kcal/mol one calculates using A values of 1.82[6] and 1.39[5] kcal/mol for a 2-methyl and a 2-nitro group in cyclohexanone. Regardless, the more stable conformer (IA; R = H, R′ = CH_3) for the trans compound has the methyl group equatorial and the nitro group axial. Using this conformer (IA; R = H, R′ = CH_3) for the trans isomer and the diequatorial conformer (IIA; R = H, R′ = CH_3) for the cis isomer, one can estimate the cis/trans isomer ratio to be simply the A value of the 2-nitro group, 1.4 kcal/mol (90:10 cis/trans), which is in excellent agreement with the experimentally determined equilibrium ratio.

For determination of the conformational equilibrium of 2-methyl-2-nitrocyclohexanone (**1a**; R = CH_3, R′ = H) and the configuration of the *cis*- and *trans*-2,6-dimethyl-2-nitrocyclohexanones (**1c**, **2c**; R = R′ = CH_3), it was necessary to use the chemical shifts of the methyl groups at C-2. The most stable conformations (IA, IIA; R = R′ = CH_3) of both the *cis*- and *trans*-2,6-dimethyl-2-nitrocyclohexanones (**1c**, **2c**; R = R′ = CH_3) have two substituents equatorial and one axial. The alternate conformations (IB, IIB; R = R′ = CH_3) with two substituents axial and one equatorial would not be expected to contribute at all to the conformational equilibria. In structurally similar types of cyclohexanones it has been observed that the protons of the axial methyl will absorb at lower field than the protons of the equatorial methyl,[7] so it was an easy matter to assign the trans (methyl groups) configuration to the isomer that has the protons of C-2 methyl absorbing at δ 1.86 and the cis configuration to the isomer that has the protons of the methyl group absorbing at δ 1.60. Because the conformations (IA, IIA; R = R′ = CH_3) of the *cis*- and *trans*-2,6-dimethyl-2-nitrocyclohexanones (**1c**, **2c**; R = R′ = CH_3) are biased, they could serve as model compounds to give the chemical shifts of axial and equatorial α-methyl protons in α-nitro ketones, and these in turn could be used to determine the conformation of the flexible 2-methyl-2-nitrocyclohexanone (**1a**; R = CH_3, R′ = H). By use of the preceeding values for the chemical shifts, calculation leads to a K value of 0.36 and a ΔG of –0.63 kcal/mol, favoring the methyl group in the equatorial position. Alternatively, one can estimate the ΔG value to be –0.43 kcal/mol by using the A values of 1.82[6] and 1.39[5] kcal/mol, respectively, for the 2-methyl and 2-nitro groups in a cyclohexanone. Considering that the chemical shift data was not corrected for concentration difference,[8] one observes that the free energies obtained for the conformational equilibrium of 2-methyl-2-nitrocyclohexanone (**1a**; R = CH_3, R′ = H) agree rather well.

Having determined the conformations and configurations of the nitro ketones prepared in this investigation, the synthesis of these compounds can now be discussed in detail (see Scheme II).

Scheme II. Synthetic Routes to 2-Nitrocyclohexanones



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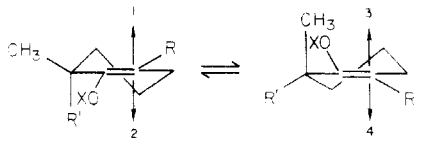
Scheme III. Pathways for Nitration of Enol Acetates or Methylation of Enolates



6a, X = Ac
b, X = But_4N^+
c, X = Li

7a, X = Ac
b, X = But_4N^+
c, X = Li

Nitration of Enol Acetates. The two ketones studied for the purpose of synthesizing the title compounds by nitration were 2-methyl- and 2,6-dimethylcyclohexanone. 2-Methylcyclohexanone can easily be converted to 2-methyl-1-acetoxycyclohexene (**3a**), with only a trace of the Δ^1 isomer, by acetic anhydride.[9] With isopropenyl acetate, however, a 65/35 mixture of the Δ^1 and Δ^6 isomers is obtained which is not separable by GLC.[9] A mixture of *cis*- and *trans*-2,6-dimethylcyclohexanone can be converted to the lone enol acetate **5a** with acetic anhydride.

Nitration of 2-methyl-1-acetoxycyclohexene (**3a**) with nitric acid in acetic anhydride led to only a 21% yield of 2-methyl-2-nitrocyclohexanone (**1a**) and to about 26% of a ring cleavage product, 6-oxoheptanoic acid.[10] From the nitration of a 2/1 mixture of the 2-methyl- and 6-methyl-1-acetoxycyclohexene (**3a**, **4a**) one can observe by NMR the formation of a 15/85 mixture of the *cis*- and *trans*-6-methyl-2-nitrocyclohexanones (**2b**, **1b**). The nitration of the enol acetate of 2,6-dimethylcyclohexanone (**5a**) proceeded somewhat better than with 2-methyl-1-acetoxycyclohexene (**3a**) in that a 54% yield of exclusively *cis*-2,6-dimethyl-2-nitrocyclohexanone (**1c**) was obtained. Nitration of the same enol acetate by using the modification of Bischoff and Schroder[11] gave only a 25% yield of the same nitro ketone.

The isomer distribution of the nitro ketones obtained by the nitration of the enol acetates can be accounted for as we had done previously[3] by an examination of the direction of attack of the electrophile on the two chair conformations of the enol acetates **6a** and **7a** (X = Ac; Scheme III).

If the electrophile attacks the more stable conformer of the enol acetate **6a** via pathway 1, the reaction proceeds through a boat and leads to the 6-methyl and 2-nitro groups being cis and diequatorial. The same arrangement (cis) of the 6-methyl and 2-nitro groups can be obtained via path 3. Although this pathway would proceed through a chair, energetically it is the most demanding of the four pathways because the pseudoaxial methyl of the least stable conformer (**7a**) would interfere with the approach of the electrophile and would cause a severe syn-1,3-destabilizing interaction in the transition state. On the other hand, the most favorable pathway, path 2, also proceeds through a chair, but the electrophile approaches the most stable conformation with no steric interference from the equatorial methyl group, and the 6-methyl and 2-nitro groups end up trans and equatorial and axial, respectively. Path 4 leads to the same trans arrangement of methyl and nitro groups but axial and equatorial, respectively; however, the reaction proceeds through a boat. On the basis of these considerations, one would predict that 6-methyl-1-acetoxycyclohexene (**6a** or **7a**; R = R′ = H) should react predominantly by path 2 and lead to *trans*-6-methyl-2-nitrocyclohexanone (**2b**) as the major product. This is what was observed experimentally. The nitration of 2,6-dimethyl-1-acetoxycyclohexene (**6a** or **7a**; R = CH_3, R′ = H) should also proceed similarly and lead to *cis*-2,6-dimethyl-2-nitrocyclohexanone (**1c**), and this isomer in fact was formed exclusively. The nitration of the remaining enol acetate, 2-methyl-1-acetoxycyclohexene (**3a**), of course, cannot lead to isomers.

Nitration of Enol Silyl Ethers. Because of the limited success in the nitration of 2-methyl-1-acetoxycyclohexene, we turned our attention to the nitration of other enol derivatives. There are a variety of methods for the regioselective generation of enol silyl ethers.[12] It has also been reported that 1-(trimethylsiloxy)cyclohexene can be nitrated with nitronium tetrafluoroborate in acetonitrile at −25 °C to give a 40% yield of 2-nitrocyclohexanone,[13] but nitration with nitryl chloride is reported to give only α-chloro ketones.[14] We choose to study the nitration of the enol silyl ethers of 2-methyl- and 2,6-dimethylcyclohexanone. 2-Methylcyclohexanone was converted regioselectively (99%) into its kinetic enol silyl ether (**4b**, least substituted) with lithium diisopropylamide and trimethylsilyl chloride by the method of Fleming.[15] Nitration of this silyl ether (**4b**) with nitronium tetrafluoroborate led to a 47% yield of a 30/70 mixture of *cis*- and *trans*-6-methyl-2-nitrocyclohexanones (**2b**, **1b**), and depending upon the length of time and manner of workup, the ratio changed and approached the thermodynamic 90:10 cis/trans ratio, determined by pyridine-catalyzed equilibration. 2-Methylcyclohexanone was converted to the thermodynamic enol silyl ether **3b** (most substituted) by means of trimethylsilyl chloride and triethylamine also by the method of Fleming.[15] Nitration of this silyl ether (**3b**) with nitronium tetrafluoroborate led to 2-methyl-2-nitrocyclohexanone (**1a**) in 41% yield. The nitronium tetrafluoroborate nitration of the enol silyl ether of 2,6-dimethylcyclohexanone (**5b**) was disappointing and led to a 15% yield of a mixture of compounds: 7% *cis*-2,6-dimethyl-2-nitrocyclohexanone (**1c**) and the enol nitrate of 2,6-dimethylcyclohexanone (ratio 3:2) and 8% of *trans*-2,6-dimethyl-2-nitrocyclohexanone (**2c**). Because the mechanism of the nitration of the silyl ether is not known, a discussion of the stereochemistry of this nitration reaction is not feasible, and comparison with the stereochemistry of the nitration of enol acetates is not possible.

Methylation of α-Nitro Ketones. An alternate approach to the synthesis of the title compounds would be the introduction of the methyl groups by alkylation of the α-nitro ketones. We had previously reported[3] that the potassium salt of 4-*tert*-butyl-2-nitrocyclohexanone can be methylated by means of methyl iodide in DMF–benzene to give a 23% yield of *trans*-2-methyl-4-*tert*-butyl-2-nitrocyclohexanone and that by phase-transfer methylation we were able to obtain a yield of 31%.[16] We therefore attempted the methylation of the α-nitrocyclohexanones under phase-transfer conditions.

When 2-nitrocyclohexanone was methylated by using 40% aqueous tetrabutylammonium hydroxide in dichloromethane and methyl iodide, 2-methyl-2-nitrocyclohexanone (**1a**) was produced in 54% yield. Methylation of either *cis*- or *trans*- or a mixture of *cis*- and *trans*-6-methyl-2-nitrocyclohexanone (**2b**, **1b**) under the same conditions led to a 36% yield of almost exclusively

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trans-2,6-dimethyl-2-nitrocyclohexanone (5:95 cis/trans). This result can be accounted for by examination of the pathways of the S_N2 attack of the enolate on methyl iodide in a similar manner to account for the stereochemistry of nitration of enol acetates (see Scheme III). Examination of the four pathways of attack on the two conformers of the enolate (**6b**, **7b**; R = NO_2, R′ = H) leads to the conclusion that path 2, which gives the axial methyl group, involves attack by the more stable conformer, proceeds through a chair, and is essentially free of steric hindrance in the transition state, is by far the most favorable energetically.

The methylation of 2-methyl-2-nitrocyclohexanone (**1a**) was carried out by using lithium diisopropylamide in THF/HMPA and gave a mixture of 30% *cis*- and 10% *trans*-2,6-dimethyl-2-nitrocyclohexanone (**1c**, **2c**) and 8% of the enol methyl ether resulting from O-alkylation. The stereochemistry of the methylation products can also be accounted for by examination of the mode of attack of the lithium enolate (**6c** or **7c**; R = H, R′ = NO_2) on methyl iodide. Unlike the methylation of the enolate of 6-methyl-2-nitrocyclohexanone (**6b** or **7b**, R = NO_2, R′ = H), the favorable paths would be 1 and 4 (Scheme III). In this manner steric interaction of a large axial substituent on C-6 and methyl iodide would be avoided even though the reaction would eventually proceed through a boat. Path 1 should be energetically more favorable than path 4 because it involves attack by the more stable conformer of the enolate which has the nitro group axial and not the methyl group. Therefore it is not surprising that *cis*-2,6-dimethyl-2-nitrocyclohexanone (**1c**) is the major product but not the exclusive product of alkylation of 2-methyl-2-nitrocyclohexanone (**1a**) nor that the reaction is energetically demanding.

It is well-known that the dianions of β-dicarbonyl compounds undergo alkylation and acylation at the most basic enolate site.[17] Certain α,α′-dinitrocycloalkanones have been prepared by double nitration of the corresponding cycloalkanones with alkyl nitrates under basic conditions.[18] The introduction of the second nitro group must proceed through an S_N2 attack of the dianion of the α-nitrocycloalkanone on the alkyl nitrate. These preceeding observations suggest that the dianion of α-nitrocyclohexanone should undergo methylation at C-6. We found that treatment of α-nitrocyclohexanone with NaH in THF followed by reaction with lithium diisopropylamide in THF/HMPA and addition of methyl iodide led to a 66% yield of *cis*- and *trans*-6-methyl-2-nitrocyclohexanone (**2b**, **1b**) after aqueous acid workup.

The stereochemistry of the 6-methyl-2-nitrocyclohexanones (**1b**, **2b**) resulting from methylation of the dianion of 2-nitrocyclohexanone is governed by the protonation reaction of the monoanion which results after methylation of the dianion. Protonation of the monoanion takes place on oxygen to give an enol, either the keto nitronic acid or the nitro enol, followed by tautomerization to the α-nitro ketone.[19] The protonation conditions of workup are similar to acid-catalyzed equilibration conditions of α-nitro ketones.[3] It is therefore not surprising that the cis/trans ratio of the 6-methyl-2-nitrocyclohexanones (**2b**, **1b**) obtained from methylation of the dianion of 2-nitrocyclohexanone approached the equilibrium ratio of 90:10.

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In subsequent publications we will report on further application of the use of mono- and dianions of α-nitro ketones in synthesis as well as an improved nitration procedure of 2-substituted 1-acetoxycyclohexenes.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 299 infrared grating spectrometer. ^1H NMR spectra were recorded on a Perkin-Elmer R-32 90-MHz spectrometer, and tetramethylsilane was used as an internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Elemental analyses were carried out by Galbraith Laboratories, Inc.

2,6-Dimethyl-1-acetoxycyclohexene (5a). Procedure A. A mixture of 2,6-dimethylcyclohexanone (2.52 g, 0.02 mol) acetic anhydride (102.4 g, 1.0 mol), and *p*-toluenesulfonic acid (0.3 g) was heated at 110 °C for 37 h. The dark brown solution was then cooled, washed with water (2 × 150 mL), 5% aqueous potassium carbonate (2 × 150 mL), and saturated aqueous sodium chloride (100 mL), and dried over anhydrous magnesium sulfate. The excess acetic anhydride was removed under vacuum distillation, and the remaining liquid was distilled through a 6-in. Vigreaux column to give 2,6-dimethyl-1-acetoxycyclohexene (1.9 g, 56%) as a colorless liquid: bp 50–55 °C (1.0 torr); IR (film) 1755 (C=O), 1698 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 2.11 (s, 3 H, CH_3CO_2), 1.49 (s, 3 H, $=CCH_3$), 0.95 (d, 3 H, J = 6.8 Hz, $CHCH_3$), 2.40 (br m, 1 H, ring proton), 2.20–1.10 (m, 6 H, ring protons). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52. Found: C, 70.47; H, 9.28.

Procedure B. Aqueous perchloric acid (70%, 0.17 mL) was added to a stirred mixture of 2,6-dimethylcyclohexanone (31.5 g, 0.25 mol) and acetic anhydride (115.0 g, 1.125 mol) in carbon tetrachloride (300 mL), and the mixture was stirred at room temperature for 5 h. The resulting dark brown solution was poured into a cold (0–5 °C) mixture of pentane (200 mL) and saturated aqueous sodium bicarbonate (200 mL). Excess solid sodium bicarbonate was added to neutralize the acetic acid formed. The aqueous layer was separated and extracted with pentane (2 × 300 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvents were evaporated in vacuo. The remaining dark brown liquid was distilled through a 6-in. Vigreaux column to obtain 2,6-dimethyl-1-acetoxycyclohexene: 22.0 g (52%); colorless liquid; bp 80 °C (3.5 torr).

2,6-Dimethyl-1-(trimethylsiloxy)cyclohexene (5b). Procedure A. Chlorotrimethylsilane (7.7 mL, 0.06 mol) was added dropwise, at room temperature under nitrogen, to a stirred solution of 2,6-dimethylcyclohexanone (6.3 g, 0.05 mol), triethylamine (17 mL, 0.12 mol), and dry dimethylformamide (20 mL) in a 100-mL round-bottomed flask. The resulting cloudy mixture was refluxed at 110 °C for 120 h, cooled, diluted with ether (100 mL), and washed with saturated aqueous sodium bicarbonate (100 mL). The aqueous phase was separated and extracted with ether (3 × 100 mL). The combined ether fractions were washed rapidly and respectively with 0.5 M hydrochloric acid (100 mL), saturated aqueous sodium bicarbonate (2 × 100 mL), and water (100 mL). The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo to yield a reddish orange liquid which was distilled through a 6-in Vigreaux column to give three fractions of colorless liquids. The first two fractions of boiling points 25–30 and 30–50 °C (1.5 torr) were mixtures of the starting ketone and 2,6-dimethyl-1-(trimethylsiloxy)cyclohexene. The third fraction was pure 2,6-dimethyl-1-(trimethylsiloxy)-cyclohexene: 5.2 g (52%); bp 52–54 °C (1.5 torr); IR (film) 1680 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 2.40–1.23 (2 m, 7 H, ring protons), 1.57 (br s, 3 H, $=CCH_3$), 1.04 (d, 3 H, J = 6.5 Hz, $CHCH_3$), 0.18 (s, 9 H, $Si(CH_3)_3$). Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.67; H, 11.11. Found: C, 66.42; H, 11.09.

Procedure B. *n*-Butyllithium (66 mL of a 1.6 M solution in hexane, 0.106 mol) was added dropwise at −78 °C under nitrogen to a stirred solution of dry diisopropylamine (16.8 mL, 0.12 mol) in dry tetrahydrofuran (240 mL) in a 500-mL round-bottomed flask. 2,6-Dimethylcyclohexanone (12.6 g, 0.10 mol) in dry tetrahydrofuran (10 mL) was added dropwise over 10 min to the lithium diisopropylamide solution at −78 °C, and the solution was stirred for 1 h. Chlorotrimethylsilane (21.5 mL, 0.17 mol) was then added dropwise, and this clear, colorless solution was allowed to warm to room temperature. After the mixture was sitrred

overnight, the solvent was removed in vacuo, and dry pentane (100 mL) was added to precipitate the lithium chloride. The colorless filtrate was concentrated and then distilled through a 6-in. Vigreaux column to give 2,6-dimethyl-1-(trimethylsiloxy)-cyclohexene: 11.1 g (56%); bp 75–76.5 °C (8 torr).

Nitration of 2-Methyl-1-acetoxycyclohexene (3a). Concentrated nitric acid (70%, 12.9 mL, 0.206 mol) was added dropwise over 30 min to a stirred mixture of 2-methyl-1-acetoxycyclohexene[9] (29.7 g, 0.193 mol) and acetic anhydride (70.0 g, 0.686 mol) at 15–22 °C. The yellow solution that formed was allowed to stir at 15–22 °C for 2 h and then distilled in vacuo, keeping the bath temperature between 40 and 45 °C, to remove any residual acetyl nitrate, acetic acid, and excess acetic anhydride. Crystallization attempts on the green, oily liquid failed. Distillation under reduced pressure was performed, and three fractions were collected. The first two fractions were 2-methyl-2-nitrocyclohexanone, and traces of impurities were obtained from the third fraction. However, 2-methyl-2-nitrocyclohexanone could be crystallized from ether at acetone–dry ice temperature to yield a white crystalline solid: 6.3 g (21%); mp 34–35 °C; IR (film) 1730 (C=O), 1546 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 3.00–2.30 (2 m, 3 H, ring protons), 2.24–1.52 (m, 5 H, ring protons), 1.60 (s, 3 H, CCH_3).

The third fraction [7.2 g (26%); bp 135–145 °C (1.8 torr)] was crystallized from ether at acetone–dry ice temperature to give an amorphous solid (4.8 g, 17.3%) which formed colorless platelike crystals after being stored in a refrigerator: mp 35–36 °C; IR (film) 3680–2440 (OH), 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 11.27 (br s, 1 H), 2.61–2.26 (m, 4 H), 2.14 (s, 3 H), 1.80–1.50 (m, 4 H).

This solid was 6-oxoheptanoic acid [lit.[10] bp 158–162 °C (9 torr); mp 33–34 °C], and it was converted into its methyl ester: bp 82–85 °C (1.3 torr); [lit.[10] bp 108–112 °C (13 torr)]; IR (film) 1738, 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.68 (s, 3 H, OCH_3), 2.62–2.21 (m, 4 H, methylene protons), 2.14 (s, 3 H, $COCH_3$), 1.82–1.48 (m, 4 H, methylene protons).

Nitration of a Mixture of 2-Methyl-1-acetoxy- and 6-Methyl-1-acetoxycyclohexenes (3a and 4a). In a 25-mL flask equipped with a condenser was placed a 65/35 mixture[9] of 2-methyl-1-acetoxy- and 6-methyl-1-acetoxycyclohexenes (2 mmol, 0.308 g), $CHCl_3$ (2 mL), ammonium nitrate (2 mmol, 0.16 g), and trifluoroacetic anhydride (1.5 mL). After the mixture was stirred for 1 h at room temperature, the resulting yellow solution was diluted with dichloromethane (20 mL) and then poured into ice–water (15 mL). The aqueous layer was separated and extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed rapidly with cold 1% sodium bicarbonate (20 mL), water (20 mL), and saturated aqueous sodium chloride (20 mL) and dried over anhydrous magnesium sulfate. The solvents were then evaporated to give a crude mixture of 2-methyl-2-nitrocyclohexanone and 6-methyl-2-nitrocyclohexanone (15:85 cis/trans) as a clear, light yellow liquid, 0.314 g (100%).

Nitration of 2,6-Dimethyl-1-acetoxycyclohexene (5a). Concentrated nitric acid (70%, 5.1 mL, 0.082 mol) was added dropwise over 20 min to a stirred mixture of 2,6-dimethyl-1-acetoxycyclohexene (12.6 g, 0.075 mol) and acetic anhydride (30.6 g, 0.300 mol) at 15–20 °C. The yellow solution that formed was allowed to stir at 15–20 °C for 4 h and then distilled in vacuo, keeping the bath temperature below 50 °C, to remove residual acetyl nitrate, acetic acid, and excess acetic anhydride. The remaining green, viscous liquid was crystallized from ether at acetone–dry ice temperature to give *cis*-2,6-dimethyl-2-nitrocyclohexanone as a white crystalline solid, mp 24.0–24.5 °C. The mother liquor was concentrated and distilled to give *cis*-2,6-dimethyl-2-nitrocyclohexanone: bp 83–88 °C (1.9 torr); total yield 6.9 g (54%): IR (film); 1729 (C=O), 1545 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 3.02–2.50 (m, 2 H, ring protons), 2.35–1.20 (m, 5 H, ring protons), 1.60 (s, 3 H, CCH_3), 1.09 (d, 3 H, J = 6.5 Hz, $CHCH_3$). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.12; H, 7.69; N, 8.18.

Nitration of 2-Methyl-1-(trimethylsiloxy)cyclohexene (3b). 2-Methyl-1-(trimethylsiloxy)cyclohexene[15] (5.0 g, 0.027 mol) was added dropwise over 20 min to a stirred mixture of nitronium tetrafluoroborate (4.3 g, 0.032 mol) in dry acetonitrile (60 mL) at −25 °C under nitrogen. After being stirred at this temperature for 1 h, the mixture was warmed to room temperature and further stirred for 3 h. The solvent was evaporated in vacuo at low temperature, and the resulting viscous liquid was diluted with ether (300 mL), washed several times with water until neutral to pH paper, dried over anhydrous magnesium sulfate, and concentrated to give a crude, reddish orange liquid (1.75 g). The crude mixture was then distilled under reduced pressure, and two fractions were collected at 69–73 (1.3 torr) and 77 °C (1.3 torr) (0.49 g, 12%). ^1H NMR of both fractions showed that it was mostly 2-methyl-2-nitrocyclohexanone. However, traces of 2-methylcyclohexenyl 1-nitrate could also be seen: IR (film) 1733 (C=O), 1638 (NO_2 stretching vibration of nitrate ester), 1552 (NO_2 stretching vibration of aliphatic nitro group), 850 cm^{-1} (N—O stretching vibration of nitrate ester); ^1H NMR ($CDCl_3$) δ 3.04–2.38 (2 m, 6 H, ring protons), 2.18–1.70 (m, 10 H, ring protons), 1.67 (s, 3 H CCH_3), 1.54 (s, 3 H, $=CCH_3$).

Nitration of 6-Methyl-1-(trimethylsiloxy)cyclohexene (4b). 6-Methyl-1-(trimethylsiloxy)cyclohexene[15] (18.4 g, 0.10 mol) was added dropwise over 20 min to a stirred mixture of nitronium tetrafluoroborate (15.92 g, 0.12 mol) in dry acetonitrile (250 mL) at −25 °C under nitrogen. After being stirred at this temperature for 1 h, the mixture was warmed to room temperature and further stirred for 45 min. The solvent was evaporated in vacuo at room temperature, and the resulting orange, viscous liquid was diluted with ether (300 mL), washed several times with water to pH ~6, dried over anhydrous magnesium sulfate, and concentrated to give a crude oil (11.5 g). ^1H NMR of this crude product showed that both the cis and trans isomers were present in approximately a 1:1 ratio. The mixture was then distilled to yield a light yellow liquid [bp 104–115 °C (1.3 torr)] of *cis*- and *trans*-6-methyl-2-nitrocyclohexanones (7.3 g, 47%) in a ratio of 2:5 by NMR: ^1H NMR ($CDCl_3$) δ 5.34 (dd, 1 H, J = 11.9, 6.3 Hz, $CHNO_2$, cis isomer), 5.08 (dd, 1 H, J = 6.5, 5.0 Hz, $CHNO_2$, trans isomer), 2.94–1.30 (2 m, 14 H, ring protons), 1.19 (d, 3 H, J = 7 Hz, $CHCH_3$, trans isomer), 1.08 (d, 3 H, J = 7 Hz, $CHCH_3$, cis isomer).

However, the cis isomer could be isolated from the mixture by crystallization from ethanol at acetone–dry ice temperature as a white crystalline solid: mp 40.5–42.0 °C; IR (cis isomer, $CHCl_3$) 1735 (C=O), 1560 cm^{-1} (NO_2). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.01; N, 8.92. Found: C, 53.25; H, 7.07; N, 8.85.

Nitration of 2,6-Dimethyl-1-(trimethylsiloxy)cyclohexene (5b). 2,6-Dimethyl-1-(trimethylsiloxy)cyclohexene (1.98 g, 0.010 mol) was added dropwise over 10 min to a stirred mixture of nitronium tetrafluoroborate (1.6 g, 0.012 mol) in dry acetonitrile (20 mL) at −25 °C under nitrogen. After being stirred at this temperature for 1 h, the mixture was warmed to room temperature and stirred for 2 h. The solvent was evaporated in vacuo at room temperature, and the resulting viscous oil was diluted with ether (100 mL), washed several times with water until neutral to pH paper, dried over anhydrous magnesium sulfate, and concentrated to give a crude, yellow liquid (0.61 g). The crude mixture was separated by silica gel preparative layer chromatography (ether/petroleum ether, 1:2, as an eluent), and two major bands were collected. The first band (R_f 0.86) was a mixture of two components (0.125 g, 7.3%), approximately in a ratio of 3:2. The major one was *cis*-2,6-dimethyl-2-nitrocyclohexanone, and the other was 2,6-dimethylcyclohexenyl 1-nitrate. IR (film) 1730 (C=O), 1632 (NO_2 stretching vibration of nitrate ester), 1545 (NO_2 stretching vibration of aliphatic nitro group), 860 cm^{-1} (N—O stretching vibration of nitrate ester); ^1H NMR ($CDCl_3$) δ 3.02–1.20 (3 m, 14 H, ring protons), 1.61 (s, 3 H, CCH_3), 1.53 (s, 3 H, $=CCH_3$), 1.09 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.04 (d, 3 H, J = 7 Hz, $CHCH_3$).

The second band (R_f 0.46) was *trans*-2,6-dimethyl-2-nitrocyclohexanone, 0.146 g (8.5%). It could be crystallized from an ether and petroleum ether mixture at acetone–dry ice temperature to give a white solid: mp 45.0–46.0 °C; IR (film) 1725 (C=O), 1545 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 3.05–2.40 (m, 2 H, ring protons), 2.40–1.25 (m, 5 H, ring protons), 1.86 (s, 3 H, CCH_3), 1.10 (d, 3 H, J = 6.5 Hz, $CHCH_3$).

Methylation of the Monoanion of 2-Nitrocyclohexanone. 2-Nitrocyclohexanone (10.01 g, 0.07 mol) in dichloromethane (70 mL) was added in one portion to a stirred solution of tetrabutylammonium hydroxide (45.5 g of a 40% solution, 0.07 mol) in water (70 mL). After the mixture was stirred for 10 min, methyl iodide (49.7 g, 0.35 mol) was added all at once at room temperature. The mixture was stirred vigorously for 36 h, and then the organic layer was separated and washed once with water (100 mL). The aqueous layers were extracted with dichloromethane (150

mL), and the combined organic fractions were dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and dry ether (300 mL) was added to precipitate the tetrabutylammonium iodide. The filtrate was evaporated to yield a viscous, red liquid (10.94 g). ^{1}H NMR on this crude oil showed the presence of 2-methyl-2-nitrocyclohexanone and a ring cleavage product, methyl 6-nitrohexanoate. The mixture was distilled, and a light yellow liquid (6.9 g) was collected; bp 80–110 °C (1.1 torr). The NMR of this distillate again indicated a mixture of both components, approximately in a ratio of 6:1: ^{1}H NMR ($CDCl_3$) δ 4.35 (t, 2 H, J = 6.8 Hz, CH_2NO_2), 3.61 (s, 3 H, OCH_3), 3.03–2.43 (2 m, 3 H, ring protons), 2.29 (t, 2 H, J = 7 Hz, CH_2CO_2), 2.17–1.57 (m, 11 H, methylene protons), 1.61 (s, 3 H, CCH_3).

However, 2-methyl-2-nitrocyclohexanone, the major component, could be isolated from the mixture by crystallization from either ether or ethanol at acetone–dry ice temperature as colorless crystals: 4.5 g (41%); mp 35.5–36.5 °C; bp 88–90 °C (1.5 torr); IR (film) 1730 (C=O), 1548 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 3.05–2.43 (2 m, 3 H, ring protons), 2.19–1.57 (m, 5 H, ring protons), 1.64 (s, 3 H, CCH_3). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.01; N, 8.92. Found: C, 53.44; H, 7.17; N, 8.80.

If the reaction was carried by using 2 equiv of tetrabutylammonium hydroxide and 3 equiv of methyl iodide, the main product was methyl 6-nitroheptanoate: ^{1}H NMR ($CDCl_3$) δ 4.55 (sextet, 1 H, J = 6.8 Hz, $CHNO_2$), 3.65 (s, 3 H, OCH_3), 2.30 (t, 2 H, J = 6.8 Hz, CH_2CO_2), 2.20–1.12 (m, 6 H, $(CH_2)_3$), 1.50 (d, 3 H, J = 6.8 Hz, $CHCH_3$).

Methylation of 6-Methyl-2-nitrocyclohexanone. 6-Methyl-2-nitrocyclohexanone (1.57 g, 0.01 mol) in dichloromethane (10 mL) was added in one portion to a stirred solution of tetrabutylammonium hydroxide (6.5 g of a 40% solution, 0.01 mol) in water (10 mL). After the mixture was stirred for 10 min, methyl iodide (7.05 g, 0.05 mol) was added all at once at room temperature. The mixture was stirred vigorously for 20 h, and then the organic layer was separated and washed once with water (10 mL). The aqueous layers were extracted with dichloromethane (20 mL), and the combined organic fractions were dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and dry ether was added to precipitate the tetrabutylammonium iodide. The filtrate was evaporated under reduced pressure to yield a reddish liquid (1.64 g). ^{1}H NMR on the crude product indicated the presence of both cis and trans isomers and slight traces of a ring cleavage product, methyl 2-methyl-6-nitrohexanoate. The crude mixture was distilled, and three fractions were collected. The first fraction was *cis*-2,6-dimethyl-2-nitrocyclohexanone: 50 mg; bp 83–95 °C (1.4 torr); ^{1}H NMR ($CDCl_3$) δ 3.03–2.64 (m, 2 H, ring protons), 2.22–1.24 (m, 5 H, ring protons), 1.63 (s, 3 H, CCH_3), 1.11 (d, 3 H, J = 7 Hz, $CHCH_3$).

The second fraction [390 mg; bp 95–110 °C (1.4 torr)] was a mixture of cis and trans isomers which could be separated by fractional crystallization. The third fraction [180 mg; bp 110–115 °C (1.4 torr)] was pure *trans*-2,6-dimethyl-2-nitrocyclohexanone. The total yield of alkylation products was 0.63 g (36%). The light yellow liquid trans isomer could be crystallized from an ether and petroleum ether mixture at acetone–dry ice temperature to yield white crystals: mp 45.5–46.5 °C; IR (film) 1728 (C=O), 1550 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 3.00–2.50 (m, 2 H, ring protons), 2.38–1.25 (m, 5 H, ring protons); 1.86 (s, 3 H, CCH_3), 1.08 (d, 3 H, J = 6.5 Hz, $CHCH_3$). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.35; H, 7.52; N, 8.19.

Instead of being distilled, the crude mixture could also be separated by silica gel preparative layer chromatography by using dichloromethane as an eluting solvent. The first band was cis isomer, and the second one was trans isomer.

Methylation of 2-Methyl-2-nitrocyclohexanone. *n*-Butyllithium (3.3 mL of a 1.6 M solution in hexane, 5.3 mmol) was added to a stirred solution of dry diisopropylamine (1.03 mL, 7.4 mmol) in dry tetrahydrofuran (6 mL) at 0 °C under nitrogen. After being stirred for 15 min, the solution was cooled to −78 °C. Hexamethylphosphoric triamide (1.01 mL, 5.8 mmol) was added, and the mixture was stirred for 30 min. 2-Methyl-2-nitrocyclohexanone (0.785 g, 5 mmol) in dry tetrahydrofuran (2 mL) was then added dropwise over 5 min, and the orange solution that formed was allowed to stir for another 30 min. Methyl iodide (2.84 g, 20 mmol) was added all at once at −78 °C. The resulting mixture was stirred at the same temperature for 30 min and then stirred at 0–10 °C for 3 h. Water was added to dissolve the precipitate that had formed, and the aqueous layer was separated and extracted with ether (2 × 30 mL). The combined ether fractions were washed with saturated aqueous ammonium chloride (2 × 30 mL), dried over anhydrous magnesium sulfate, and then evaporated in vacuo to yield a yellow liquid (0.594 g). ^{1}H NMR on the crude liquid showed the presence of both cis and trans isomers, O-alkylation product, and the starting nitro ketone. The crude mixture was separated by silica gel preparative layer chromatography, and a mixture of ether and petroleum ether (1:3) was used as an eluent. Three major bands were collected. The first band (R_f 0.73; 0.325 g, 38%) was a mixture of *cis*-2,6-dimethyl-2-nitrocyclohexanone and 1-methoxy-6-methyl-6-nitrocyclohexene, in a ratio of 4:1: IR (film) 1730 (C=O), 1668 (C=C), 1549 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 4.98 (t, 1 H, J = 4.5 Hz, $=CHCH_2$), 3.54 (s, 3 H, OCH_3), 3.00–1.21 (3 m, 13 H, ring protons), 1.70 (s, 3 H, CCH_3), 1.60 (s, 3 H, CCH_3), 1.09 (d, 3 H, J = 6.8 Hz, $CHCH_3$).

The second band (R_f 0.51) was the starting nitroketone.

The third band (R_f 0.31; 0.079 g, 9.2%) was pure *trans*-2,6-dimethyl-2-nitrocyclohexanone: ^{1}H NMR ($CDCl_3$) δ 3.00–2.40 (m, 2 H, ring protons), 2.39–1.26 (m, 5 H, ring protons), 1.84 (s, 3 H, CCH_3), 1.09 (d, 3 H, J = 6.5 Hz, $CHCH_3$).

Methylation of the Dianion of 2-Nitrocyclohexanone. *n*-Butyllithium (3.3 mL of a 1.6 M solution in hexane, 5.3 mmol) was added to a stirred solution of dry diisopropylamine (1.03 mL, 7.4 mmol) in dry tetrahydrofuran (8 mL) at −78 °C under nitrogen, and the mixture was stirred for 45 min. Hexamethylphosphoric triamide (1.01 mL, 5.8 mmol), was then added, and the mixture was stirred for another 45 min. Meanwhile, the monoanion of 2-nitrocyclohexanone was generated as follows. Sodium hydride (0.23 g of 57% oil dispersion, 5.5 mmol) was placed in a 150-mL round-bottomed flask fitted with a gas-inlet tube, a rubber septum, and an addition funnel. The oil dispersion was washed out with dry pentane under nitrogen, and dry tetrahydrofuran (30 mL) was added. After the sodium hydride was suspended in tetrahydrofuran for 15 min, 2-nitrocyclohexanone (0.715 g, 5 mmol) in dry tetrahydrofuran (6 mL) was added dropwise over a period of 15 min at room temperature. The mixture was stirred for another 1 h and then cooled to −78 °C, and the clear colorless LDA/HMPA solution was added. After the mixture was stirred for 3 h, methyl iodide (7.1 g, 50 mmol) was added all at once at −78 °C. The reaction mixture was stirred for 30 min, warmed to room temperature, and stirred for an additional 3 h. Water (50 mL) was added to dissolve the salt that formed, and the organic layer was separated and washed once with water (20 mL). The combined aqueous fractions were acidified with 0.4 M hydrochloric acid and then extracted with ether (3 × 50 mL). The combined ether extracts were washed once with water (20 mL), dried over anhydrous magnesium sulfate, and then evaporated to yield a yellow liquid (0.635 g). ^{1}H NMR on the crude product showed the presence of 6-methyl-2-nitrocyclohexanone and starting nitro ketone, approximately in a ratio of 78:22.

Registry No. 1a/2a, 80594-87-2; **1b**, 80594-88-3; **1c**, 80594-89-4; **2b**, 80594-90-7; **2c**, 80594-91-8; **3a**, 1196-73-2; **3b**, 19980-35-9; **4a**, 1541-29-3; **4b**, 19980-33-7; **5a**, 6203-89-0; **5b**, 63547-53-5; 2,6-dimethylcyclohexanone, 2816-57-1; 6-oxoheptanoic acid, 3128-07-2; methyl 6-oxoheptanoate, 2046-21-1; 2-methylcyclohexenyl 1-nitrate, 80594-92-9; 2,6-dimethylcyclohexenyl 1-nitrate, 80594-93-0; 2-nitrocyclohexanone, 4883-67-4; methyl 6-nitroheptanoate, 80594-94-1; 1-methoxy-6-methyl-6-nitrocyclohexene, 80594-95-2.