Synthesis of Nitro Derivatives of [4]Peristylane Having High-Density Characteristics

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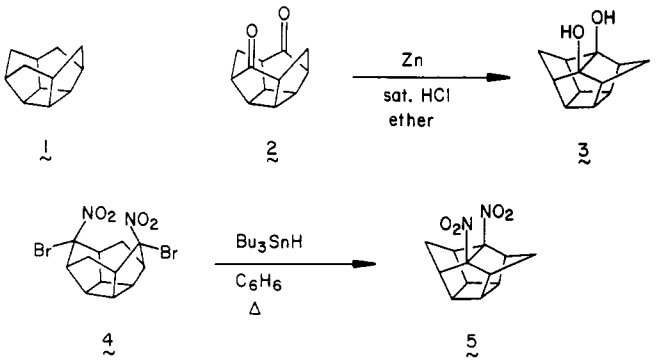
Reduction of the dioxime of [4]peristylane-2,6-dione (8) with sodium cyanoborohydride delivered the bis(hydroxylamine) 9, which was directly condensed with *N*-benzylidenebenzenesulfonamide and benzaldehyde to give the bis(nitrone) 10. Ozonolysis of 10 gave rise to *endo,endo*-2,6-dinitro[4]peristylane (6). In a separate sequence, 8 was oxidized with 100% nitric acid in the presence of ammonium nitrate. The resulting dinitro ketone 11 was oximated and then oxidatively brominated. When sodium borohydride reduction of 14 was uncovered to proceed with transannular CC bond formation, the dinitro oxime 12 was instead oxidized as above. The reaction afforded the targeted 2,2,6,6-tetranitro[4]peristylane (7). Density measurements performed on 6, 7, 11, and 13 indicate that the presence of one geminal pair of nitro groups increases crystal packing efficiency steeply. However, the presence of a second pair of nitro groups transannular to the first has little more impact than positioning of a ketone carbonyl or lactone bridge at that site.

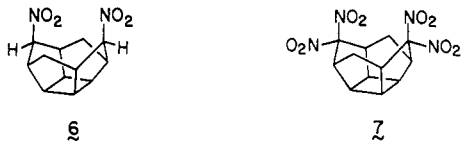
The [4]peristylane ring system (1)[1] is comprised of a cyclobutane base that is "walled in" by four mutually fused cyclopentane rings. A *chemical* consequence of the atomic proximities enforced along the fluted perimeter of 1 is the notable ease with which transannular reactions occur in appropriate derivatives. The efficient closure of the 2,6-dione 2 to diol 3[1] and the ready reductive cyclization of 4 to 5 under free radical conditions[2] are exemplary of this behavior.



1 2 3 4 5

The quite rigid nature of the [4]peristylane framework appears also to impact on the *physical* properties of this class of molecules. Thus, the symmetry and compactness of 2 combine to allow close packing in its unit cell, such that this diketone exhibits a substantive density of 1.42 g/cm^3.[3]

As part of a program designed to prepare energetic compounds endowed with high density and good thermal stability, we[2,4] and several other research groups[5–8] have focused attention on polynitro polycyclic caged systems. The preliminary indicators relative to 1 and 2 suggested to us that properties of the desired type might well be contained in 6 and 7. We describe herein the synthesis of these nitro compounds as well as related molecules, with particular attention given to the manner in which transannular reactions were ultimately circumvented.



6 7

Synthetic Considerations

***endo,endo*-2,6-Dinitro[4]peristylane (6).** The previously described dioxime 8[2] was designated from the outset as the starting material of consequence. From among the relatively few oxidative methods available for transforming oximes directly to nitro compounds, that involving buffered *m*-chloroperbenzoic acid in hot acetonitrile[4] was examined first. However, treatment of 8 under these conditions delivered 5 (95% isolated) with no hint of 6 or any of its epimers. The identical reaction course was followed, albeit with lessened efficiency, when 8 was exposed to sodium dichromate in water or acetic acid[9] or simply to alkaline hydrogen peroxide. When very complex product mixtures resulted from attempted oxidation with potassium permanganate, the decision was made to proceed instead via a multistep sequence (Scheme I).

To this end, 8 was reduced to bis(hydroxylamine) 9 with sodium cyanoborohydride in methanol (50%)[10] or preferably in acetic acid (85%).[11] The response of 9 to oxidants such as $Na_2Cr_2O_7$ and MCPBA in acetonitrile was similar to that of 8, thereby signaling that conversion to related, if not identical, reactive intermediates was materializing. Accordingly, 9 was treated with *N*-benzylidenebenzenesulfonamide[12] and 2 equiv of benzaldehyde to form the bis(nitrone) 10. Without purification, 10 was directly ozonolyzed in dichloromethane solution at −78 °C,[13] the overall yield of 6 was 40%. Failure to drive

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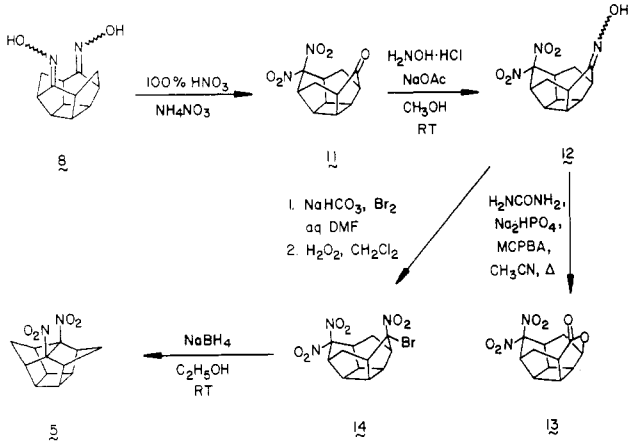
the formation of **10** with excess benzaldehyde led to severely reduced yields (12%).

The endo orientation of the nitro groups in **6** was made evident by the chemical shift and multiplicity of the α-NO_2 protons (δ 4.76, d, J = 7.0 Hz), which compare well with those of the structurally related *endo,endo*-2,6-ditosylate (δ 4.64, d, J = 7.9 Hz).[1] The four-line ^{13}C NMR spectrum of **6** was similarly consistent with its C_{2v} symmetry.

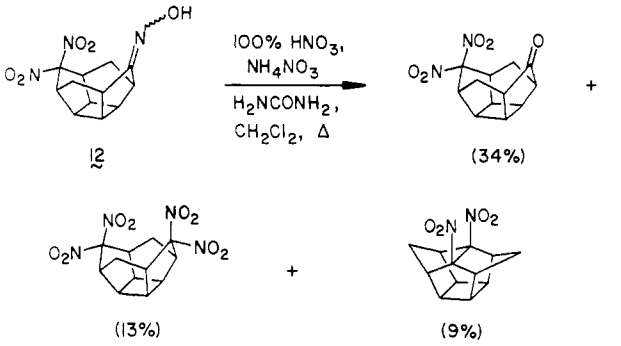
In an attempt to effect epimerization within **6**, the compound was subjected to heating with sodium bicarbonate in 10% aqueous ethanol. No special precautions were taken to exclude oxygen completely. The subsequent isolation of **5** as major product served only to corroborate our prior experience relating to the ease of covalent CC bond formation in that fashion that leads to functionalized 1,3-bis(homopentaprismanes).

2,2,6,6-Tetranitro[4]peristylane (7). Oxidation of **8** with 100% nitric acid in the presence of ammonium nitrate according to Ungnade and Kissinger[14] gave rise to dinitro ketone **11** in 45% yield. It is not known at the experimental level whether one of the oximino functionalities suffers hydrolysis prior to or after elaboration of the geminal pair of nitro groups. Subsequent observations suggest, however, that the latter alternative is the more probable. The carbonyl group in **11** is reactive toward hydroxylamine, as evidenced by essentially quantitative conversion to oxime **12** at room temperature. Since buffered MCPBA acts on **12** to provide the dinitro lactone **13**, the proximal nitro groups in these molecules evidently exert an inductive effect that renders the transannular trigonal carbon atom rather hyperreactive to nucleophilic attack. In this particular instance, **12** seemingly experiences hydrolysis to **11** prior to Baeyer–Villiger ring expansion.



Bromination of **12** in aqueous dimethylformamide containing sodium bicarbonate[15] proceeded with anticipated exo delivery of the halogen to give a bromonitroso product that was directly oxidized to **14** with hydrogen peroxide. Of interest was the subsequent finding that sodium borohydride[16] acts on **14** to generate at best a trace of trinitro[4]peristylane. Since the principal end product of this reduction is once again **5**, nitro groups can seemingly be ejected from these systems with relative ease.

In view of the success encountered in the **8** → **11** conversion, **12** was in turn subjected to analogous oxidative nitration. In this instance, reconversion to ketone **11** via hydrolysis was observed to be competitive (34% isolated). The desired tetranitro derivative **7** was produced concurrently (13%), as was the ubiquitous **5** (9%). Following chromatographic purification, **7** was shown by ^1H and ^{13}C NMR analyses to have the spectral properties demanded by its C_{2v} symmetry.



At the present time, the three-step conversion of dioxime **8** to **7** outlined above represents the uniquely successful access route to this strained polynitro compound.

Crystal Density Measurements

Initial attention was given to dinitro ketone **11** and the derived lactone **13**. Their denisities, determined by the solvent neutral buoyancy method in aqueous cesium chloride solution,[4] were shown to be 1.67 and 1.69 g/cm^3, respectively.[17] A relevant implication of these results is that replacement of a carbonyl group in **2** by a *gem*-dinitro array increases density substantially. On the other hand, the ketone-to-lactone modification involved in the progression from **11** to **13** makes no significant additional impact.

The densities of **6** and **7**, obtained by the same flotation procedure, was found to be 1.54 and 1.70 g/cm^3, respectively. As expected, the values are intimately linked to the number of nitro groups present. However, the close similarity of the values for **7**, **11**, and **13** was sufficient cause to obtain independent density predictions for the nitro compounds. As a result of his interest in these phenomena,[18] Professor Herman Ammon agreed to perform density calculations on **6** and **7**. Through application of a $P\bar{1}$ space group search procedure, he has realized the values of 1.533 and 1.663 g/cm^3, in good agreement with the experimental values. Thus, the presence on the [4]peristylane perimeter of one geminal pair of nitro groups increases crystal packing efficiency steeply. Installation of a second pair of nitro groups transannular to the first is not significantly more beneficial.

It now remains to determine whether additional nitro groups on the perimeter of **7** or along its cyclobutane base will increase density beyond the 1.7 g/cm^3 "barrier". Studies in pursuit of these objectives are currently in progress.

Experimental Section

Buffered Peracid Oxidation of 8. Into a nitrogen-blanketed, flame-dried flask was introduced urea (20 mg), disodium hydrogen phosphate (0.8 g), and dioxime **8** (109 mg, 0.50 mmol). Anhydrous acetonitrile (5 mL) was next added, and the mixture was heated at the reflux temperature for 10 min. *m*-Chloroperbenzoic acid (344 mg of 80% purity, 4 equiv) was introduced in small lots during 1 h, and reflux was continued for an additional 2.5 h. The cooled reaction mixture was freed of solvent in vacuo, and the residue was extracted with dichloromethane (3 × 20 mL). The combined extracts were washed with saturated sodium bicarbonate solution (4 × 15 mL), water (4 × 15 mL), and brine (4 × 15 mL)

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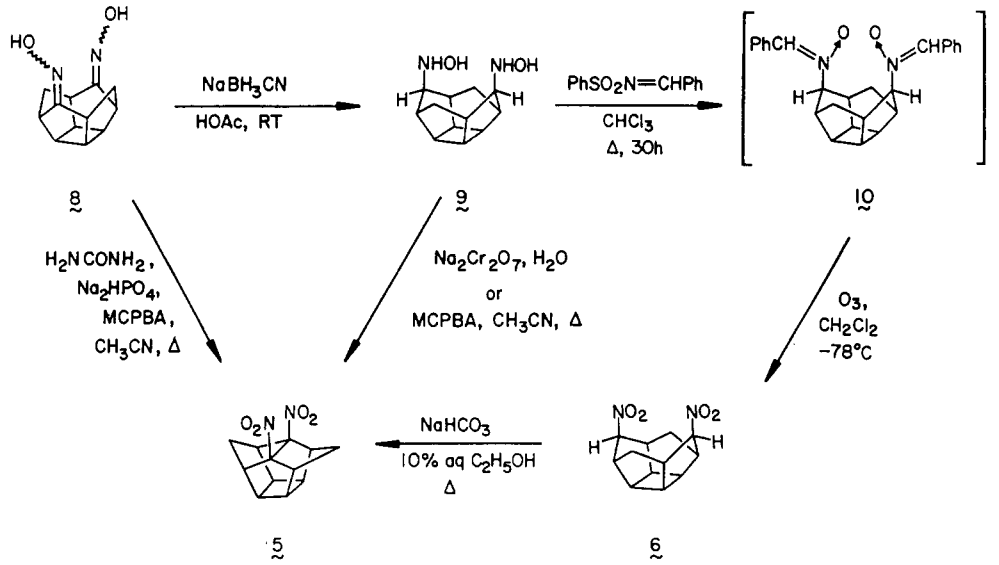
Scheme I



prior to drying. Solvent evaporation left 120 mg (95%) of **5** as a colorless solid, mp >300 °C. The spectra of **5** were identical with those previously recorded.[2]

***endo,endo*-2,6-Bis(hydroxylamino)[4]peristylane (9).** To an ice-cold solution of **8** (218 mg, 1.0 mmol in glacial acetic acid under argon was added 189 mg (3 mmol) of sodium cyanoborohydride with stirring. After a 4-h reaction period at 20 °C, water (5 mL) was added, powdered sodium hydroxide was introduced at 0 °C until pH 11 was attained, and the product was extracted into ethyl acetate (5 × 25 mL). The combined organic phases were washed with brine, dried, and evaporated to leave 193 mg (85%) of crude **9** as a colorless solid, mp 193 °C. This material was not further purified: IR (KBr, cm^{-1}) 3390, 3250, 2950, 1760, 1650, 1490, 1450, 1100, 1050, 890, 700; MS, m/z (M^+) calcd 222.1368, obsd 222.1373.

***endo,endo*-2,6-Dinitro[4]peristylane (6).** A solution of **9** (244 mg, 1.1 mmol), *N*-benzylidenebenzenesulfonamide (270 mg, 1.1 mmol), and benzaldehyde (450 mg, ca. 2 equiv) in 25 mL of chloroform was heated at reflux under argon for 30 h. The cloudy, yellow reaction mixture was cooled to room temperature, filtered through anhydrous magnesium sulfate, and concentrated to leave impure **10** as a semisolid residue, which was immediately taken up in dichloromethane (50 mL), cooled to −78 °C, and ozonolyzed. Reductive workup of this mixture with aqueous sodium bisulfite after warming to 20 °C and washing with brine gave a colorless organic phase. Drying and solvent evaporation left a residue, which was purified by MPLC (silica gel, elution with 27% ethyl acetate in petroleum ether). There was isolated 110 mg (40%) of **6** as a colorless solid, mp 156–157 °C (from ethyl acetate–petroleum ether): IR (KBr, cm^{-1}), 2995, 1530, 1460, 1385, 1330, 785, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 4.76 (t, J = 7.0 Hz, 2 H), 3.26–3.16 (m, 8 H), 2.31 (dd, J = 7.0, 4.2 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 91.88, 46.68, 44.29, 32.34; MS, m/z (M^+) calcd 250.0953, obsd 250.0954. Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.58; H, 5.64. Found: C, 57.68; H, 5.69.

Dichromate Oxidation of 9. A solution of **9** (22 mg) and sodium dichromate (110 mg) in water (5.5 mL) was stirred at room temperature overnight. The product was extracted into ethyl acetate, and the combined organic phases were washed with sodium becarbonate solution and brine prior to drying. Solvent evaporation yielded 11 mg of **5**.

Attempted Epimerization of 6. A mixture of **6** (12 mg) and sodium bicarbonate (8 mg) in 10% aqueous ethanol (3 mL) was heated at the reflux temperature overnight. Following removal of the ethanol in vacuo, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic solution was dried and concentrated to give a white solid containing bluish flecks (8 mg). The ^1H NMR spectrum of this material was identical with that of authentic **5**.

6,6-Dinitro[4]peristylan-2-one (11). A solution of ammonium nitrate (400 mg, 5.0 mmol) in 100% nitric acid (0.25 mL, freshly distilled from concentrated sulfuric acid) was stirred for 30 min. Bis(oxime) **8** (109 mg, 0.5 mmol) was introduced in several lots, and the resulting mixture was stirred for an additional 2.5 h, poured over ice and water, stirred for 5 min, and filtered. The white solid so obtained was washed with cold water until free of acid. There was obtained 84 mg (63%) of **11** as a colorless solid: mp 202 °C (from ethyl acetate–petroleum ether); IR (CH_2Cl_2, cm^{-1}) 1730, 1560, 1370, 1320, 1265, 1180; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60–3.57 (br s, 4 H), 3.44 (br s, 2 H), 2.77 (m, 2 H), 2.65 (m, 2 H), 2.47 (d, J = 16 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 225.01, 132.63, 54.09, 53.36, 47.50, 41.46, 39.72; MS, m/z (M^+) calcd 264.0746, obsd 264.0746. Anal. Calcd for $C_{12}H_{12}H_2O_5$: C, 54.53; H, 4.58. Found: C, 54.78; H, 4.67.

6,6-Dinitro[4]peristylan-2-one Oxime (12). A mixture of **11** (1.29 g, 4.88 mmol), hydroxylamine hydrochloride (3.39 g, 48.8 mmol), and sodium acetate (8.00 g, 97.5 mmol) in 135 mL of methanol was stirred at room temperature for 3 days. After removal of the volatiles in vacuo, water was added and 1.29 g (95%) of an off-white solid was collected. Recrystallization from 95% ethanol gave **12** as colorless crystals: mp 205 °C dec; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (s, 1 H), 3.8–3.2 (m, 8 H), 2.7–2.3 (m, 4 H); MS, m/z (M^+) calcd 279.0856, obsd 279.0861.

Attempted Oxidation of 12. To a magnetically stirred suspension of **12** (21 mg, 0.075 mmol), urea (8 mg), and disodium hydrogen phosphate (50 mg) in refluxing anhydrous acetonitrile (5 mL) was added *m*-chloroperbenzoic acid (80 mg, 7.5 equiv) in small lots during 1 h. The reaction mixture was heated for an additional 2 h and freed of solvent in vacuo. The residue was taken up in dichloromethane (4 × 20 mL), and the combined organic phases were washed with sodium bisulfite and sodium bicarbonate solutions, water, and brine (3 × 20 mL each). Drying and solvent evaporation left a residue, recrystallization of which from dichloromethane–hexanes gave **13** (11 mg, 52%) as a colorless solid: mp 217–218 °C; IR (KBr, cm^{-1}) 1730, 1560, 1470, 1380, 1320, 1195, 1050, 1025, 820, 790; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (m, 1 H), 3.80–2.95 (series of m, 9 H), 2.43 (ddd, J = 4, 6, 18 Hz, 1 H), 2.30 (td, J = 5, 18 Hz, 1 H); ^{13}C NMR (75 MHz, CD_2Cl_2, ppm) 171.68, 132.49, 85.58, 52.66, 50.95, 48,51, 45,89, 43.71, 40.94, 37.94, 37.30, 3299; MS m/z (M^+) calcd 280.0695, obsd 280.0738. Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.41; H, 4.32. Found: C, 51.57; H, 4.47.

***exo*-2-Bromo-2,6,6-trinitro[4]peristylane (14).** To a mixture of **12** (280 mg, 1.0 mmol), sodium bicarbonate (180 mg, 2.1 mmol), dimethylformamide (4 mL), and water (6 mL) was added a solution of bromine (170 mg, 1.1 mmol) in 2 mL of dimethylformamide at 0 °C. The resulting yellow-green mixture was stirred at 0 °C for 3 h. The solid was separated by filtration, and the filtrate was extracted repeatedly with dichloromethane. The combined organic phases were washed with sodium bisulfite solution and water and subsequently stirred with 30% hydrogen peroxide (5 mL) for 1 h. The dichloromethane layer was washed

with water and brine, dried, and concentrated. After silica gel chromatography with 4:1 petroleum ether–ethyl acetate as eluent and recrystallization from 95% ethanol, there was obtained 45 mg (12%) of **14** as white crystals, mp 223.5–225 °C; IR (KBr, cm^{-1}) 3010, 2895, 1545, 1465, 1370, 1355, 1330; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68 (m, 4 H), 3.59–3.44 (m, 4 H), 2.64 (m, 2 H), 2.15 (td, J = 2.8, 18 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 135.70, 102.59, 57.62, 52.83, 44.58, 44.49, 35.73; MS, m/z ($M^+ - 2NO_2$) calcd 281.0052, obsd 218.0083.

Reduction of 14. A solution of **14** (20 mg) in 60% aqueous ethanol (5 mL) was stirred for 1 h at room temperature with sodium borohydride (40 mg). Careful acidification with acetic acid was followed by ethanol removal in vacuo. The residue was extracted with dichloromethane (3 × 20 mL), and the combined organic layers were dried and evaporated. Trituration of the residue with ethyl acetate–petroleum ether afforded 5 mg (30%) of **5**.

2,2,6,6-Tetranitro[4]peristylane (7). To a refluxing suspension of **12** (160 mg, 0.575 mol) in dichloromethane (10 mL) was added under argon a solution of 100% nitric acid (2.0 mL), ammonium nitrate (15 mg, 0.19 mmol), and urea (15 mg, 0.25 mmol) in 5 mL of the same solvent. The solid dissolved immediately, and the solution turned orange. After 1 h at the reflux temperature, the reaction mixture was cooled and washed with ice water and brine. Following drying and solvent removal, the residue was subjected to MPLC on silica gel with dichloromethane as eluant. The first fraction afforded 25.2 mg (13%) of **7**: colorless crystals; mp 219–220 °C dec (from dichloromethane–hexanes); IR (KBr, cm^{-1}) 3010, 2885, 1575, 1565, 1465, 1375, 1330, 1300, 1205, 1120, 855, 835, 800, 790; ^1H NMR (300 MHz, acetone-d_6) δ 3.81 (m, 4 H), 3.58 (m, 4 H), 3.04 (dt, J = 17, 12 Hz, 2 H), 2.36 (dt, J = 17, 2.1 Hz, 2 H); ^{13}C NMR (75 MHz, CD_3COCD_3, ppm) 133.28, 53.64, 45.95, 35.97. Anal. Calcd for $C_{12}H_{12}N_4O_8$: C, 42.36; H, 3.55. Found: C, 42.42; H, 3.74.

Continued elution afforded a second fraction consisting of **5** (13.2 mg, 9.3%), the ^1H and ^{13}C NMR spectra of which were identical with those previously reported.

Finally, a last fraction contained 51.7 mg (34%) of **11**.

Acknowledgment. This research was made possible by the financial support of the U.S. Army Research and Development Command.

Cleavage of Carbon–Carbon Bonds with High Stereochemical Control. 4. Base-Induced Cleavage of Optically Active Nonenolizable Benzylic Ketones[1]

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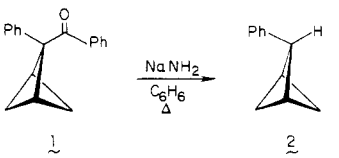
Treatment of the optically active tertiary α-phenyl ketones **9a** and **9b** with amide ion in anhydrous benzene, or with *tert*-butoxide ion in benzene or *tert*-butyl alcohol, results in C–C bond cleavage at the stereogenic center and protonation of the respective benzylic carbanions. These reactions proceed with 44–86% retention of configuration, maximal stereoselectivity materializing when *tert*-butoxide ion was employed. These observations signal that the reactive carbanion intermediates are efficiently captured from the front side as benzoyl is replaced by hydrogen. Use of *t*-BuOD leads to essentially complete d_1 incorporation. The stereoselectivity is reversed when recourse is made to $KOCH_2CH_2OH$ in ethylene glycol solution. Thus, retention is obtained in nonpolar media and inversion is observed in very polar protic media. The factors that underlie this dichotomy are discussed.

The Haller–Bauer reaction, that base-promoted process which results in C–C bond cleavage of nonenolizable ketones,[2] has not yet gained proper consideration as one of the more important degradative reactions in organic chemistry. The simplicity of the process is not at issue, since merely warming the substrate with an amide base[2] or with potassium *tert*-butoxide[3] delivers the product. Rather, the historical evolution of this transformation seems to have clouded its remarkable potential for highly stereocontrolled electrophilic capture. Originally, the Haller–Bauer reaction was designed to serve as a method for the synthesis of aryl amides.[2] More recently, the process has been expanded to constitute a tool for effecting the replacement of a benzoyl group by hydrogen as in the conversion of **1** to **2**.[4]



1 2

During the early development of this transformation, it was noted that C–C bond cleavage understandably holds particular effectiveness when the incipient carbanion is stabilized, e.g., in benzylic[4,5] and cyclopropyl examples.[1c,3b,6] Particularly relevant in this connection is Walborsky's elegant demonstration that anionic centers in three-membered rings generated by the Haller–Bauer method are protonated with retention of configuration.[6a–d] The *inherent mechanistic* significance of these studies was substantively lessened when independent studies revealed that

(1) (a) Paper 3 in this series: Paquette, L. A.; Gilday, J. P.; Ra, C. S.; Hoppe, M. *J. Org. Chem.* **1988**, *53*, 704. (b) Paper 2 in this series: Paquette, L. A.; Gilday, J. P.; Ra, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6858. (c) Paper 1 in this series: Paquette, L. A.; Uchida, T.; Gallucci, J. C. *Ibid.* **1984**, *106*, 335.

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