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SYNTHESIS AND CHEMISTRY OF NOVEL POLYNITROPOLYCYCLIC CAGE MOLECULES

ALAN P. MARCHAND
Department of Chemistry, North Texas State University NT Station, Box 5068, Denton, TX 76203-5068, U.S.A.

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1. INTRODUCTION

The synthesis and chemistry of novel, strained, saturated polycarbocyclic "cage" molecules has proved to be a source of fascination for organic chemists. Cage hydrocarbons possess rigid, highly compact structures; such molecules frequently display unusual symmetry properties that render them aesthetically pleasing. Concomitant with their compact nature, carbon–carbon bond angles and bond lengths in carbocyclic cage molecules frequently deviate markedly from the "normal" values associated with sp^3 hybridized carbon atoms. When this occurs, such deviations provide a measure of strain energy that is contained within the cage system. Steric strain can also express itself in a cage system through, e.g., increased negative heat of combustion and increased positive heat of formation relative to that of a corresponding unstrained system.[1]

The incorporation of high levels of molecular strain into cage systems confers upon them corresponding levels of thermodynamic instability. Thus, organic chemists who are attracted by the challenge inherent in the synthesis of such highly strained molecules must seek ways to circumvent or otherwise mitigate the deleterious effects of strain in these systems. Partly in response to this need, an important area of organic chemistry, referred to as the synthesis of "non-natural products",[2] has emerged and has resulted in the synthesis and study of a large number of novel, highly strained cage molecules.

In recent years, attention has been focused upon applications of cage molecules that take advantage of their strain energy content and compact structures. Potential military applications are at the forefront in this regard. It is reasonable to suppose that highly compact cage molecules might possess correspondingly high densities. Indeed, this expectation has been confirmed both by experiment and by the results of theoretical density calculations. Thus, the use of cage molecules as, for example, a new class of solid and liquid fuels has been suggested, particularly in volume-limited applications where net volumetric heat of combustion must be maximized (as, for instance, would be required for fuels employed in air breathing missiles).[3] The strain energy content of cage molecules which is released upon combustion is an added bonus that lends further appeal to this potential new class of military fuels.

In addition, the potential usefulness of such high energy, high density compounds has captured

the attention and the imagination of the explosives community. Explosive performance has been shown to depend upon a number of different molecular properties. A simple empirical description that permits calculation of detonation velocity, D (expressed in km/s), Chapman–Jouget (detonation) pressure, P_{CJ} (expressed in kbar), and heat of detonation, Q (expressed in cal/g) has been proposed by Kamlet and Jacobs.[4] The pertinent equations are reproduced below:

$$D = 1.01N^{1/2}M^{1/4}Q^{1/4}(1.00+1.30\rho) \quad (1)$$

$$P_{CJ} = 15.58NM^{1/2}Q^{1/2}\rho^2 \quad (2)$$

$$Q = -\sum_i N_i\Delta H^\circ_{f,i} + \Delta H^\circ_{f,exp} \quad (3)$$

where ρ is the density in g cm^{-3}, N is the number of moles of gaseous products per gram of explosive, M is the average molecular weight of the gaseous products, and $\Delta H^\circ_{f,exp}$ is the heat of formation of the explosive. Inspection of these equations reveals that both D and P_{CJ} depend critically upon density (ρ^2) and somewhat less dramatically upon the heat of formation of the explosive. The relative contribution of the latter quantity is increased by the incorporation of strain energy into the explosive (as is often the case for polycyclic cage molecules). Other methods for estimating the density of organic explosives have been developed.[5,6]

Incorporation of nitro groups into energetic molecules has long been recognized to confer upon these molecules desirable explosive properties. In addition to the increment which NO_2 groups contribute toward increasing overall molecular density, these important substituents also contribute to the "oxidant balance". Kamlet has defined a quantity, OB_{100}, which represents "the number of equivalents of oxidant per hundred grams of explosive above the amount required to burn all hydrogen to water and all carbon to carbon monoxide".[7] For explosives that contain carbon, hydrogen, nitrogen and oxygen, OB_{100} is given by eq. (4):

$$OB_{100} = 100(2n_O - n_H - 2n_C - 2n_{COO})/(\text{molecular weight}). \quad (4)$$

Here, n_O, n_H, and n_C represent the number of oxygen, hydrogen and carbon atoms, respectively, and n_{COO} is the number of carboxyl groups. Kamlet and Adolph have established a meaningful relationship between impact sensitivities of organic explosives and OB_{100} values for a wide variety of polynitro compounds.[7]

In addition to their inherent interest as a potential new class of explosives, polynitropolycyclic cage compounds can serve as precursors to cage amines. The discovery that 1-aminoadamantane and several derivatives of this cage system possess antiviral[8] and antineuroleptic properties[9] has prompted the synthesis and pharmacological evaluation of a number of polycyclic cage amines. Recently, amino derivatives of pentacyclic and hexacyclic cage compounds have been shown to possess pharmacological activity that is similar to that of 1-aminoadamantane.[10] The fact that nitro-substituted cage molecules can be reduced readily to the corresponding amino derivatives lends additional interest to polynitropolycyclic cage systems.

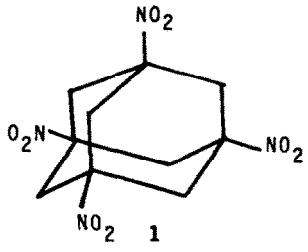
Relatively few polynitropolycyclic compounds have been synthesized. Those whose successful syntheses had been reported in the literature at the time of writing of this Report (Fall, 1987, compounds **1**–**11**) are depicted in Scheme 1. It is instructive to consider the various approaches that were employed in synthesizing these polynitropolycyclic compounds and to explore their generality.

2. SYNTHESES OF POLYNITROPOLYCYCLIC SYSTEMS

A. 1,3,5,7-*Tetranitroadamantane* (**1**)

Adamantane is unique among the types of polycyclic cage molecules shown in Scheme 1 in that an sp^2 hybridized carbon atom is relatively readily accommodated at a bridgehead position in the adamantane system.[11] Hence, generation of a bridgehead adamantyl cation or radical is relatively straightforward, thereby rendering feasible the synthesis of bridgehead-substituted adamantanes via direct functionalization of the parent hydrocarbon.

However, attempts to synthesize polynitroadamantanes via direct nitration of adamantane have met with only limited success. Thus, direct bridgehead nitration of alkyladamantanes with nitrogen dioxide at elevated temperature leads only to the formation of 1-nitro and 1,3-dinitroalkyladamantanes.[12] Photochemical nitration of adamantane with N_2O_5 affords only 1-nitroadamantane.[13]



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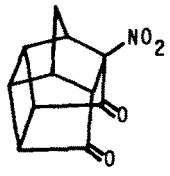

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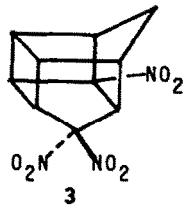

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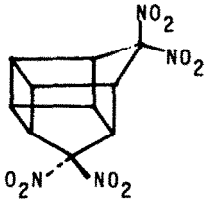

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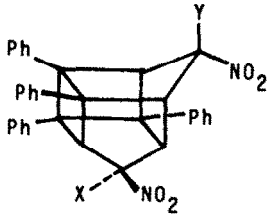
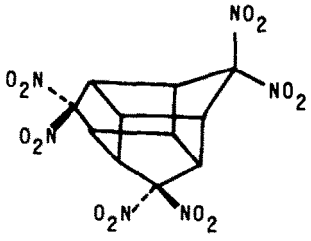


5a: X = Y = H
5b: X = NO_2, Y = H
5c: X = Y = NO_2



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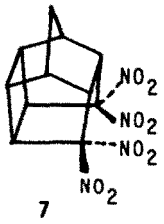

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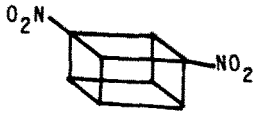

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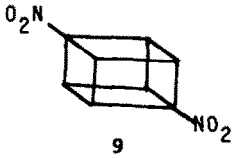

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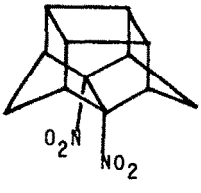

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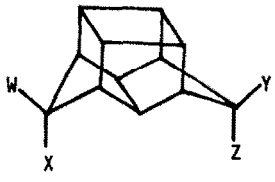
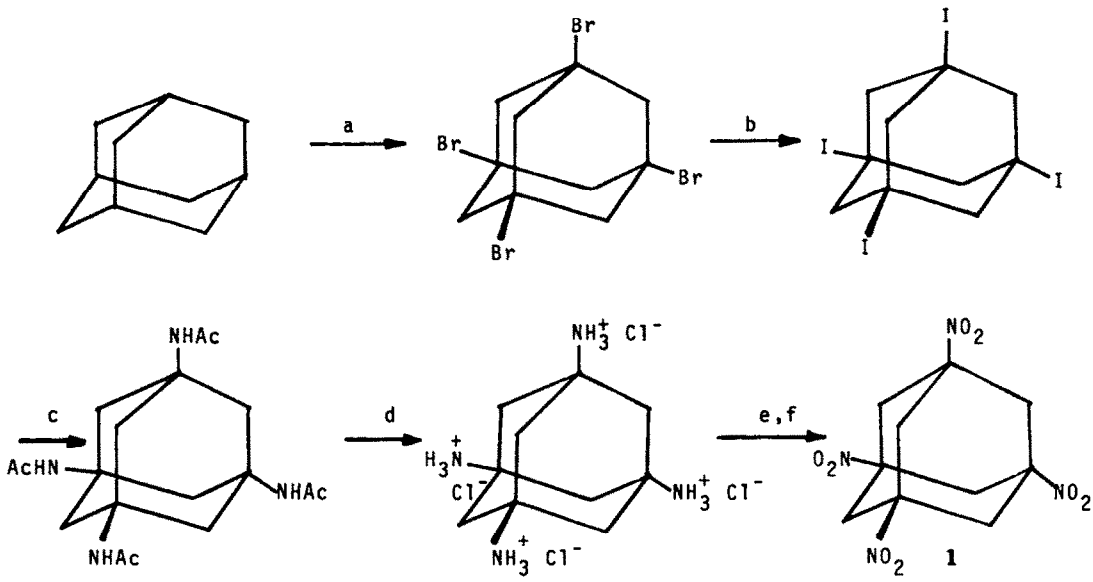


11a: W = Y = H, X = Z = NO_2
11b: W = Z = NO_2, X = Y = H
11c: W = Y = NO_2, X = Z = H
11d: W = X = Y = NO_2, Z = H
11e: W = X = Z = NO_2, Y = H
11f: W = X = Y = Z = NO_2

Scheme 1.

Attempts to introduce NO_2 groups directly into adamantane via irradiation of carbon tetrachloride solutions of adamantane and nitrogen dioxide with an argon-ion laser ($\lambda = 457.9$–514.5 nm) have resulted only in the incorporation of one bridgehead nitro group.[14] Direct nitration of adamantane or of 1-nitroadamantane with nitric acid leads to the formation of nitrate esters of substituted adamantanols.[15]

Nevertheless, Sollott and Gilbert[16] have devised an indirect synthesis of 1,3,5,7-tetranitroadamantane (**1**) which takes advantage of the ease with which adamantane can be directly halogenated at bridgehead positions. Their approach employs bridgehead tetrahalogenation of adamantane; the carbon–halogen bonds are converted subsequently into C—NO_2 groups by the method shown in Scheme 2. A key step in this synthesis is the introduction of four bridgehead acetamido groups via photo-Ritter reaction of 1,3,5,7-tetraiodoadamantane with acetonitrile.[16] Subsequent hydrolysis of the tetraamide followed by oxidation of the resulting tetraaminoadamantane led to the formation of **1**.

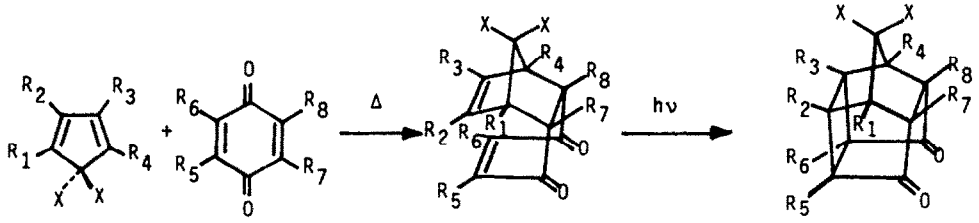


(a) Br_2, $AlCl_3$, 70 °C, 24 h (58%); (b) CH_2I_2, Al foil, 80 °C, 35 min (75%); (c) CH_3CN, H_2O, hν, quartz, 60 °C, 64 h (51%); (d) aqueous HCl, reflux 3 h (79%); (e) aqueous NaOH; (f) $KMnO_4$, acetone, 30 °C, 48 h (e + f, 45%).

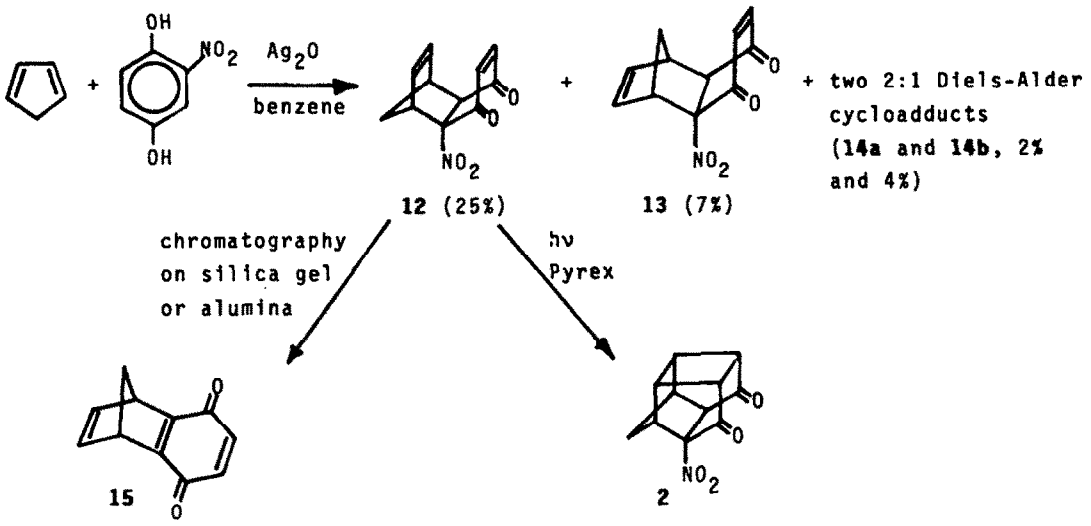
Scheme 2.

B. 9-*Nitropentacyclo*[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]*undecane*-8,11-*dione* (**2**)

A potentially attractive method for introducing NO_2 groups into cage molecules might involve Diels–Alder reactions between appropriately substituted dienes and dienophiles. The pentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (PCUD) system can be accessed via Diels–Alder cycloaddition of substituted cyclopentadienes to substituted *p*-benzoquinones by following the reaction sequence summarized in Scheme 3.[17] Hence, it might be possible to access nitro-substituted PCUDs by utilizing nitro-substituted cyclopentadienes and/or nitro-substituted *p*-benzoquinones in this reaction sequence. In accord with this expectation, cyclopentadiene was found to react with 2-nitro-*p*-benzoquinone to afford a mixture of two 1 : 1 cycloadducts (**12** and **13**) along with two 2 : 1 cycloadducts (**14a** and **14b**, Scheme 4).[18] One of the 1 : 1 cycloadducts, i.e., **12**, in which the cyclohexenedione ring is fused to the *endo* face of the norbornene moiety, could be photocyclized to afford 9-nitropentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**2**). However, this approach suffers from several drawbacks. Nitro-*p*-benzoquinones are unstable and cannot be isolated readily. Rather than rely upon isolation and purification of such unstable species, it is advisable to generate them oxidatively from the corresponding substituted hydroquinone and to trap them subsequently *in situ* with dienophiles.[19] When this procedure was applied to 2-nitrohydroquinone, the desired cycloadduct, **12**, was obtained with poor regioselectivity and only in low yield. Attempted puri-



Scheme 3.



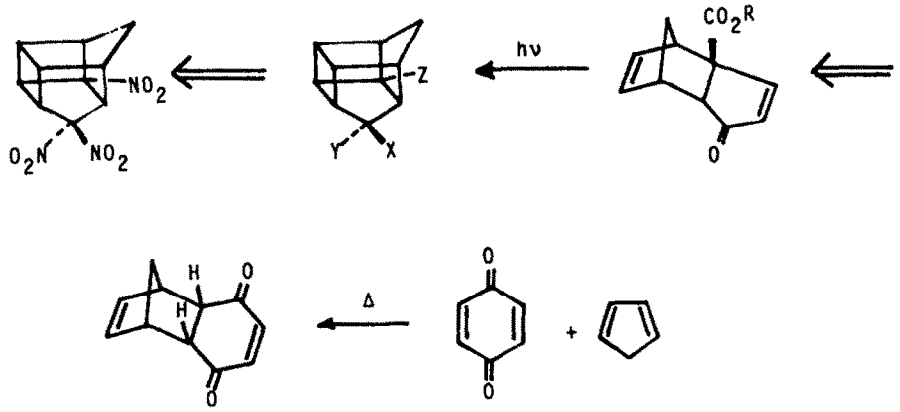
Scheme 4.

fication of **12** via column chromatography resulted in elimination of nitrous acid with concomitant formation of 1,4-dihydro-1,4-methano-5,8-naphthoquinone (**15**, Scheme 4). Accordingly, this approach was not further pursued as a means for synthesizing more highly NO_2-substituted PCUD derivatives.

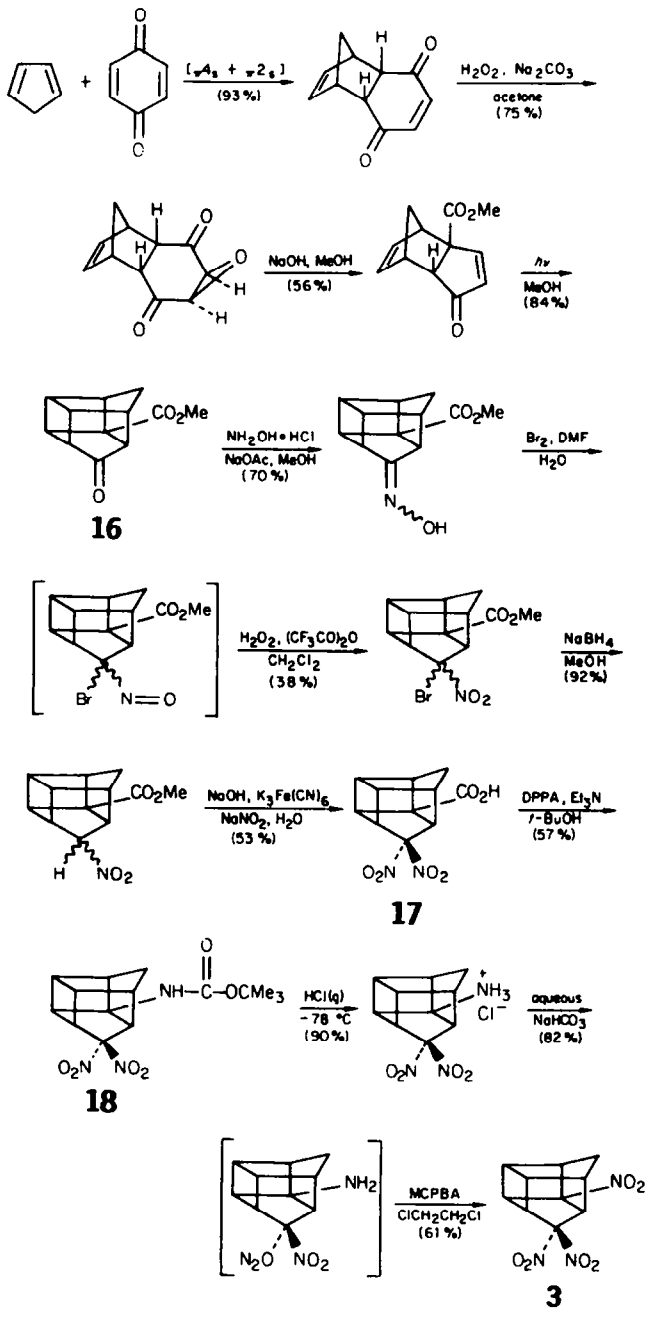
C. *Polynitro*-1,3-*bishomocubanes* (**3–5**)

The philosophy which underlies the synthesis of **3** is presented in the retrosynthetic perspective that appears in Scheme 5.[20] It was recognized that the introduction of the three nitro groups in **3** into the 1,3-bishomocubane system might be performed at an early stage in the synthesis. Alternatively, other substituents (X, Y and Z, Scheme 5) could be introduced and then converted subsequently into NO_2 groups. The latter approach was chosen for the synthesis of **3**; here, X, Y = carbonyl oxygen and Z = CO_2Me. The methods by which these substituents were converted into NO_2 groups are discussed below. Further extension of this same philosophy has led to successful syntheses of additional polynitropolycyclic systems, **4–6**, that are close structural relatives of **3**.

The thirteen-step synthesis of **3** from cyclopentadiene and *p*-benzoquinone is shown in Scheme 6.[20] First, the appropriately substituted cage system, **16**, was constructed by using the method outlined in Scheme 6. The ketone functionality in **16** was first converted into a $CHNO_2$ group,[21,22] and the $CHNO_2$ group was then converted into a dinitromethylene moiety, $C(NO_2)_2$, with concomitant hydrolysis of the ester group elsewhere in the molecule.[23] The carboxylic acid group in product **17** was then converted into the corresponding carbamate (**18**) by using diphenylphosphoryl azide (DPPA).[24] This procedure obviates the need for the potentially explosive intermediate acyl



Scheme 5.



Scheme 6.

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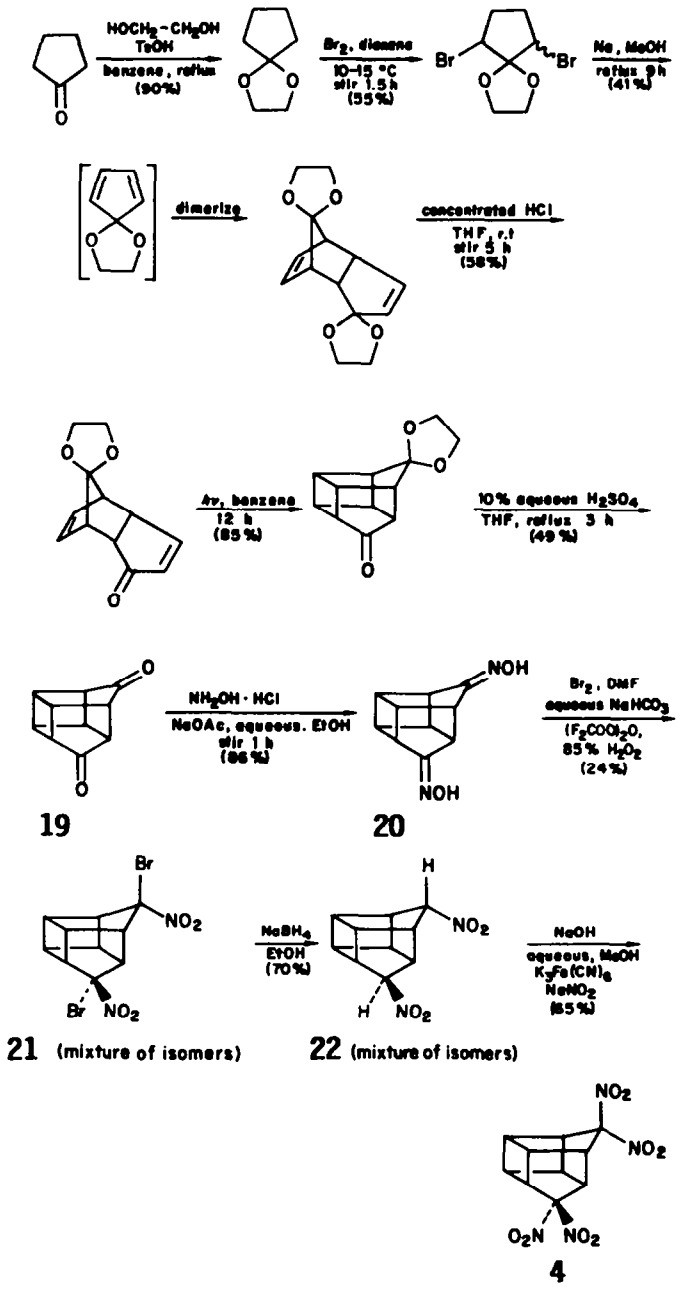
azide that would have been required had a classical Curtius rearrangement been employed instead to convert **17** into **18**.

The same general philosophy has been utilized in a ten-step synthesis of **4** from cyclopentanone (Scheme 7).[24] Here, 1,3-bishomocubanedione **19**[25] was converted into the corresponding bis-oxime (**20**) which was subsequently converted into the corresponding bis-bromonitro cage compound (**21**).[21,22] Reduction of this intermediate to the corresponding dinitro-1,3-bishomocubane (**22**, mixture of isomers) followed by nitration[23] afforded **4** (9.4% overall yield from 1,3-bishomocubanedione). Griffin and coworkers have employed a similar reaction sequence in pursuit of the synthesis of an octabromotetranitro-1,3-bishomocubane (**23**, Scheme 8).[26]

An effort was made to synthesize a tetranitro-1,3-bishomocubane that contains additional substituents which might be converted into NO_2 groups. Phenyl substituents were chosen for this



Scheme 7.

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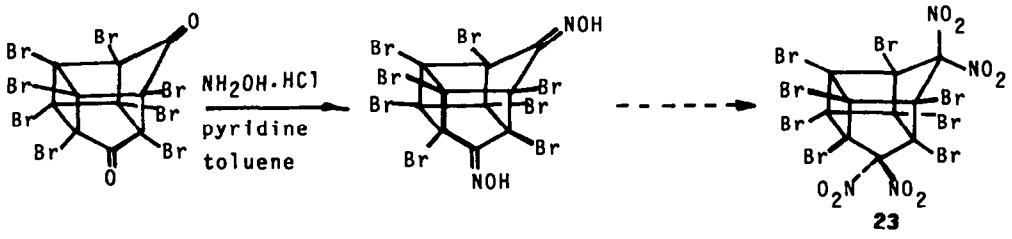
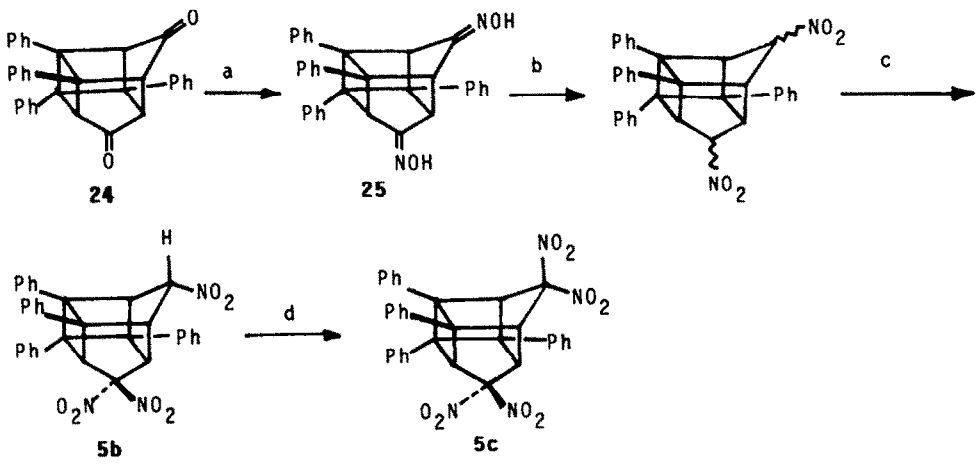


Scheme 8.

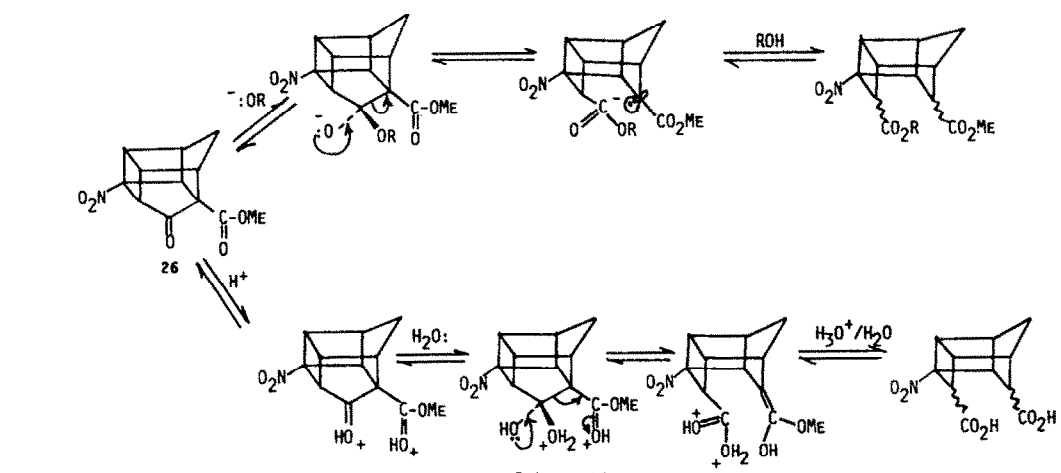


(a) $NH_2OH.HCl$, NaOAc, MeOH, room temperature, 24 h (94%); (b) $(CF_3CO)_2O$, 90% H_2O_2, CH_3CN, $NaHCO_3$, urea, reflux 12 h (77%); this reaction afforded a gross mixture of dinitrotetraphenyl-1,3-bishomocubanes from which pure **5a** could be isolated via fractional recrystallization from methanol; (c) $K_3Fe(CN)_6$, $NaNO_2$, NaOH, MeOH-H_2O, Et_2O, stir at room temperature under nitrogen for 6 h (65%); (d) $K_3Fe(CN)_6$, $NaNO_2$, NaOH, MeOH-H_2O, Et_2O, stir at room temperature under nitrogen for 24 h (50%).

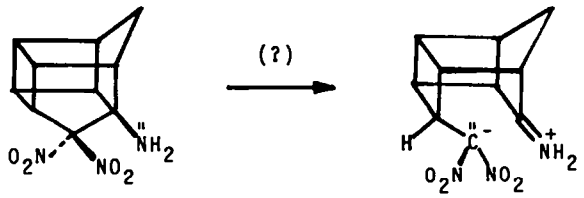
Scheme 9.

purpose. It was hoped that the phenyl groups, once incorporated into the 1,3-bishomocubane ring systems, might be ozonolysed subsequently to carbonyl groups. The CO_2H groups then might be converted to NO_2 groups in the manner described above. To this end, 2,3,4,8-tetraphenylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione (**24**)[27] was synthesized, and the 6,10-carbonyl groups were converted into $C(NO_2)_2$ groups[28] by using a previously published procedure (Scheme 9).[20,24] Unfortunately, attempts to promote ozonolysis of the four phenyl groups in **5c** thus far have met with repeated failure.[29]

In an effort to explore the possibility of synthesizing more highly NO_2-substituted 1,3-bishomocubanes, a model system, **26**, that contains a β-ketoester moiety has been chosen for study. The underlying purpose of such a model study is to address a potentially serious problem, i.e., that which involves competing Haller–Bauer cleavage in cage β-ketoesters. The expected modes of acid- and base-promoted Haller–Bauer cleavage in **26** are illustrated mechanistically in Scheme 10.



Scheme 10.



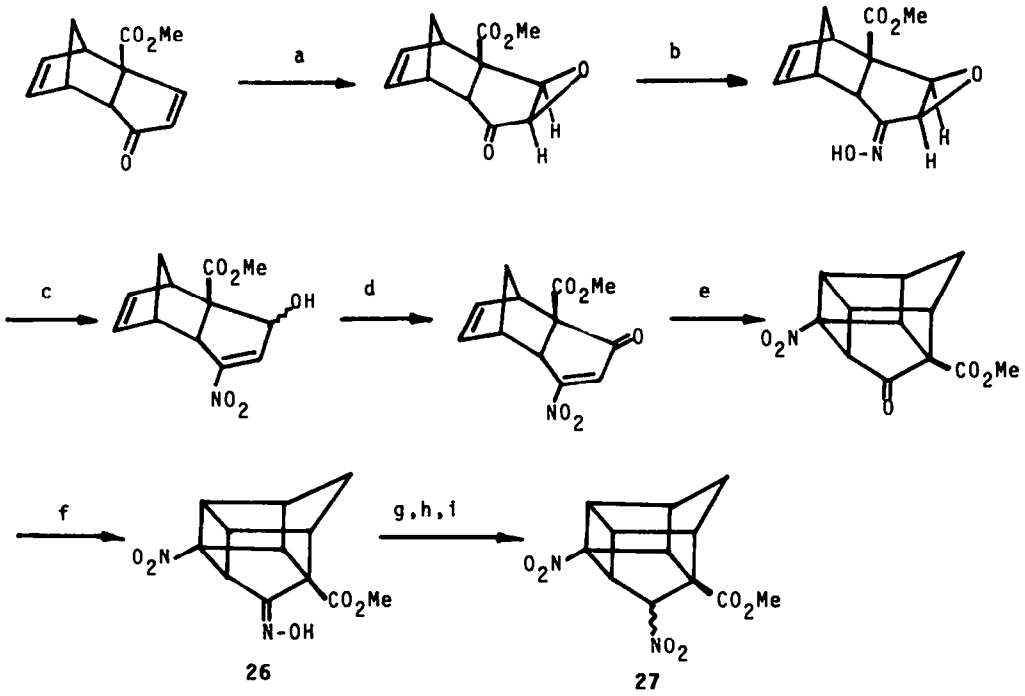
Scheme 11.

An additional potential complication that must be considered involves ring fragmentation in cage molecules that contain vicinal "push–pull" substituents. Such a situation is illustrated in Scheme 11. Here, the "push" is provided by the electron-donating amino group, and the "pull" results from resonance delocalization of negative charge in the carbanion fragment by the geminal NO_2 groups.

Investigations into the potential problems associated with the cage fragmentation reactions discussed above were initiated with the synthesis of model compound **26** (Scheme 12).[30] Conversion of **26** into the corresponding cage dinitroester **27** proved to be straightforward. However, application of Kornblum's procedure[23] to convert the $CHNO_2$ group in **27** to a dinitromethylene group led instead to the formation of a rearranged product (**28**), which was characterized via single crystal X-ray crystallographic analysis.[30] A mechanism which accounts for the formation of **28** from **27** is presented in Scheme 13. Methods by which this novel rearrangement might be utilized to introduce additional NO_2 groups into the 1,3-bishomocubane ring system are currently under active investigation.[29]

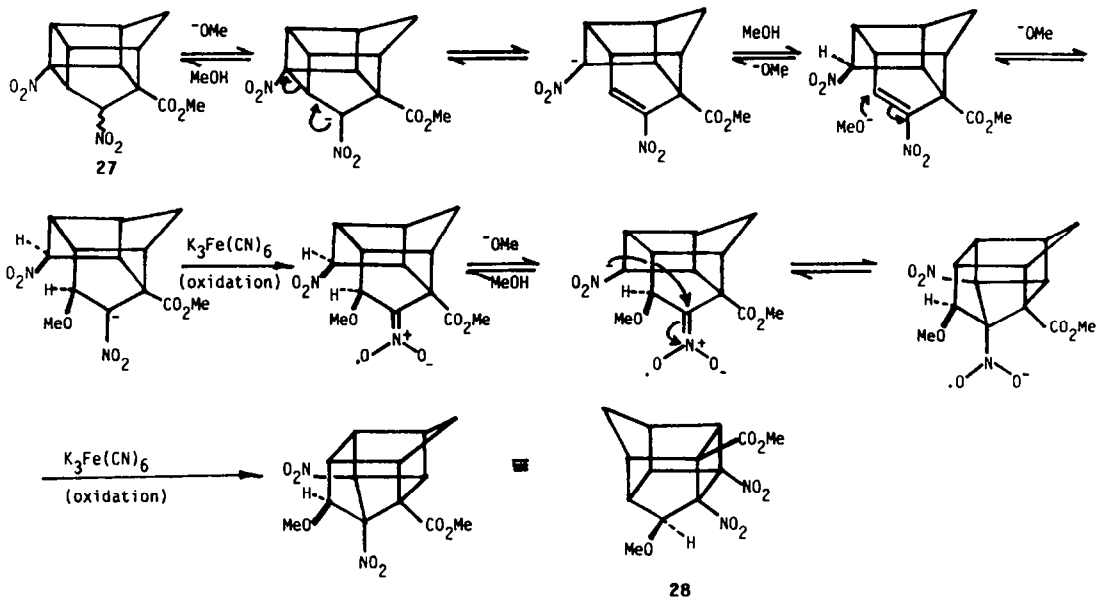
D. 4,4,7,7,11,11-*Hexanitro*[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]*undecane* (*D_3-hexanitrotrishomocubane*, **6**)

The key intermediate in the synthesis of **6**, i.e., D_3-trishomocubanetrione (**29**), has been synthesized by two groups working independently[31,32] (Scheme 14). The straightforward method by



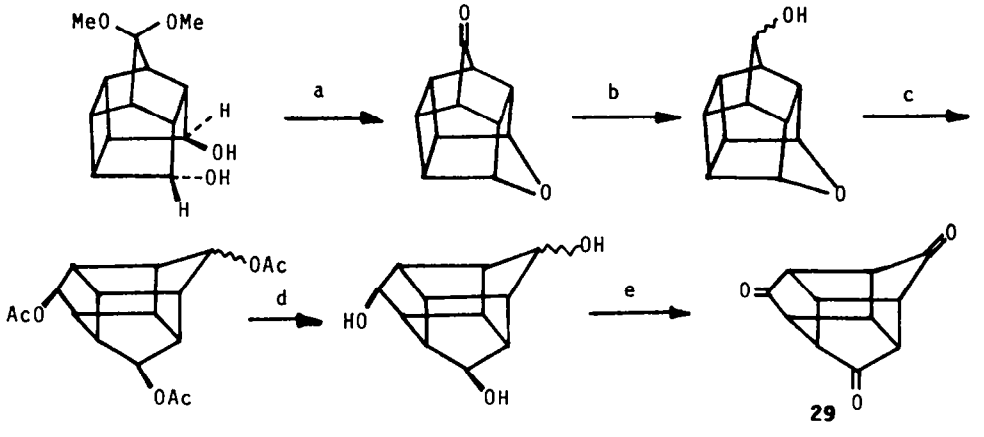
(a) H_2O_2, Na_2CO_3 (83%); (b) $NH_2OH{\cdot}HCl$, NaOAc (82%); (c) H_2O_2, $(CF_3CO)_2O$ (15%); (d) PCC, CH_2Cl_2 (84%); (e) hν, Pyrex, EtOAc (20%); (f) $NH_2OH{\cdot}HCl$, NaOAc (80%); (g) NBS, aqueous dioxane; (h) O_3, CH_2Cl_2, 0 °C; (i) $NaBH_4$, EtOH (g + h + i, 16%).

Scheme 12.

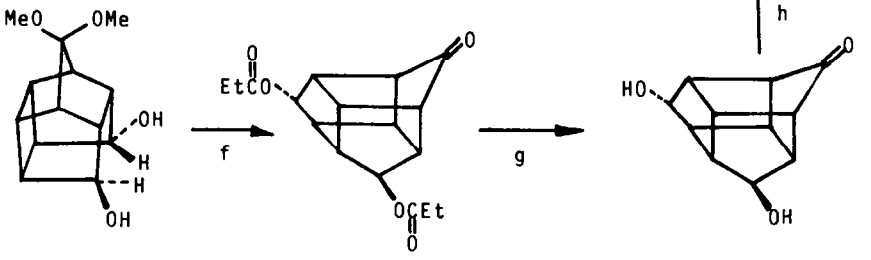


Scheme 13.

Synthesis of **29** reported by Fessner and Prinzbach:[31]

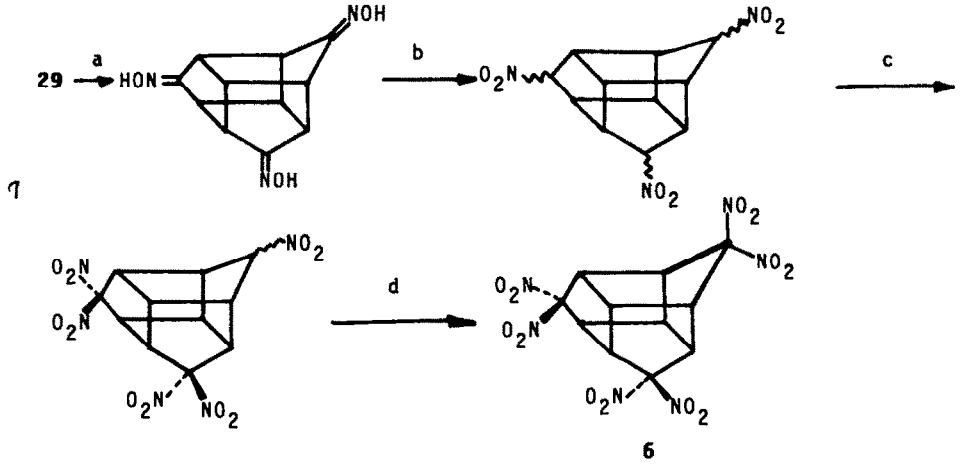


Synthesis of **29** reported by Marchand, et al.:[32]



(a) concentrated H_2SO_4, CH_2Cl_2, room temperature, 24 h (47-59%); (b) $LiAlH_4$, THF, reflux under nitrogen, 1 h (95%); (c) glacial HOAc, concentrated H_2SO_4, reflux 40 h (73%); (d) anhydrous K_2CO_3, anhydrous MeOH, room temperature, 20 h (89-97%); (e) CrO_3, anhydrous acetone, room temperature, 3 h (43-51%); (f) $EtCO_2H$, concentrated H_2SO_4, 150 °C, N_2, 72 h (51%); (g) Na, dry MeOH, room temperature, 1 h (100%); (h) PCC, CH_2Cl_2, room temperature, 2 h (46%).

Scheme 14.



(a) $NH_2OH \cdot HCl$, NaOAc, aqueous MeOH, 0 °C → room temperature, overnight (70%); (b) $(CF_3CO)_2O$, 90% H_2O_2, $NaHCO_3$, urea, CH_3CN, 70–75 °C, overnight (35%); (c) NaOH, aqueous MeOH, 3 h; then $K_3Fe(CN)_6$, aqueous $NaNO_2$, Et_2O, 1 h (65%); (d) NaOH, aqueous MeOH, 24 h; then $K_3Fe(CN)_6$, aqueous $NaNO_2$, Et_2O, 12 h (62%).

Scheme 15.

which **29** was converted into the corresponding D_3-hexanitrotrishomocubane (**6**) is summarized in Scheme 15.[32]

Compound **6** is the most highly NO_2-substituted cage molecule that had been prepared at the time of writing of this review. Although only *ca* 40–50 mg of **6** was available for study, this amount proved sufficient to permit preliminary investigation of its thermal behavior and detonation properties. The following conclusions resulted from his study:[33] (i) when **6** was heated in a differential scanning calorimeter at 10°C min^{-1}, exotherm onset occurred at 272°C, reached a maximum at 308°C, and subsided at 331°C. (ii) A study of the shock sensitivity of **6** revealed that this compound is both less shock sensitive and a substantially more powerful explosive than is 2,4,6-trinitrotoluene(TNT).

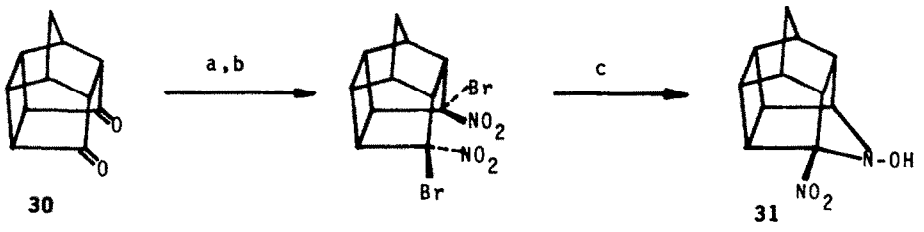
E. 8,8,11,11-*Tetranitropentacyclo*[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]*undecane* (**7**)

The spatial proximity between the 8- and 11-positions in pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane is known to lead to extensive transannular interactions between *endo* substituent groups when present in this system at these two positions.[34,35] Therefore, it might be expected that the existence of non-bonded interactions of this type would complicate attempts to replace each of the ketone carbonyl groups in pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione (**30**)[17a] with $C(NO_2)_2$ groups. In accord with such pessimistic expectations, an initial attempt to synthesize **7** in this manner led unexpectedly to the formation of *N*-hydroxy-3-nitro-4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$] dodecane (**31**, Scheme 16).[36]

Fortunately, a way was found to circumvent such undesired side reactions. The key step in a succesful synthesis of **7**[36a] involved oxidative nitration of the intermediate cage dinitro oxime (**32**) via reaction with 98% red nitric acid followed by treatment of the reaction mixture with 30% aqueous hydrogen peroxide solution.[37] Application of this procedure to compound **32** resulted in direct, one-step conversion of $R_2C{=}NOH$ to $R_2C(NO_2)_2$ (Scheme 17).

F. 1,3- *and* 1,4-*Dinitrocubanes* (**8** *and* **9**)

1,3-Dinitrocubane (**8**) and 1,4-dinitrocubane (**9**) have been synthesized from the corresponding cubane 1,3-[38] and 1,4-dicarboxylic acids,[39] respectively (Scheme 18). Efforts to prepare polynitrocubanes that contain more than two NO_2 groups have focused upon the synthesis of appro-

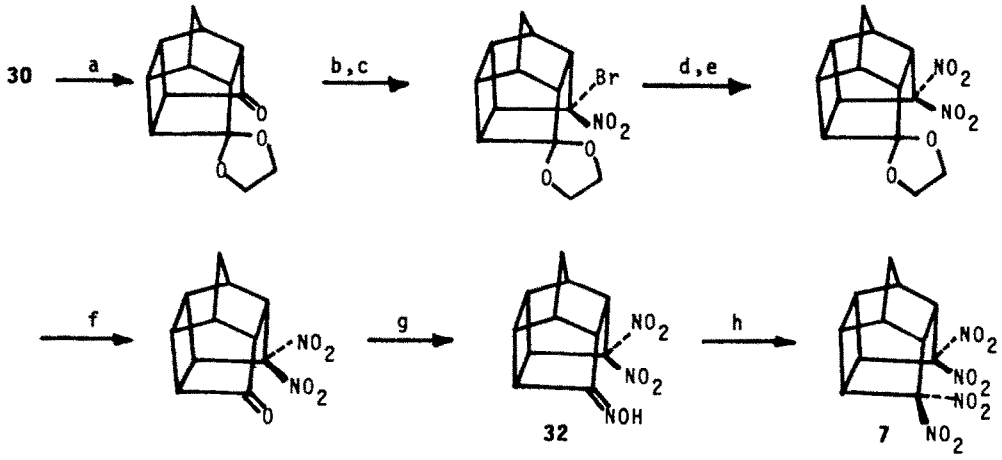


(a) $NH_2OH \cdot HCl$, NaOAc, EtOH (87%); (b) NBS, $NaHCO_3$, dioxane, room temperature, 48 h (49%); (c) $NaBH_4$, 60% aqueous EtOH, room temperature, 45 minutes (28%).

Scheme 16.

priately polyfunctionalized cubanes. Griffin and coworkers have succeeded in synthesizing polyhalogenated cubanes that might serve as precursors to polynitrocubanes.[40] Of particular interest is the fact that base promoted semibenzilic acid rearrangement of the two α-haloketone groups in octabromo-1,3-bishomocubane-5,9-dione (**33**)[41] affords only one of three possible isomeric hexabromocubanedicarboxylic acids (i.e., **34**, Scheme 19).

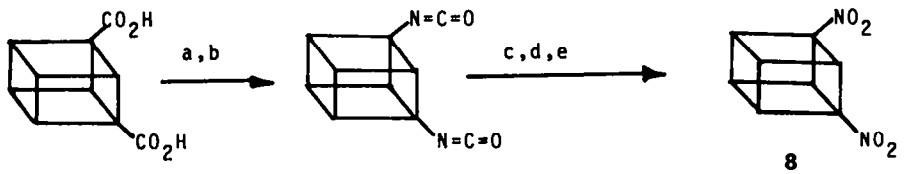
Eaton and coworkers have developed an alternative approach to the synthesis of polyfunctionalized cubanes that relies upon direct metalation of the cubane skeleton. Their approach is based upon earlier demonstrations that functional groups such as tertiary amides,[42] oxazines[43] and oxazolines[44] promote *ortho* lithiation of appropriately substituted aromatic systems. Initial



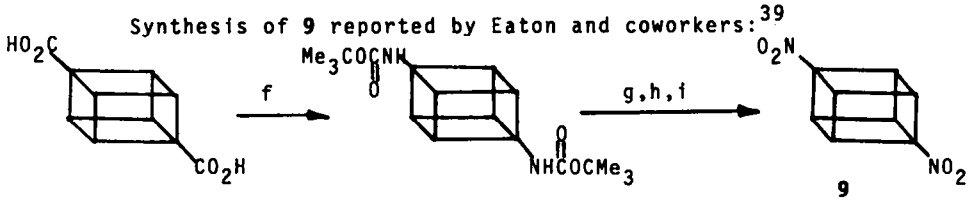
(a) $HOCH_2CH_2OH$, TsOH, benzene, Dean-Stark tube (92%); (b) $NH_2OH \cdot HCl$, NaOAc, EtOH, room temperature, overnight (79%); (c) Br_2, $NaHCO_3$, DMF, 0 °C, then O_3, CH_2Cl_2, 0 °C (80%); (d) $NaBH_4$, 60% aqueous EtOH, room temperature, 0.5 h (97%); (e) $K_3Fe(CN)_6$, $NaNO_2$, aqueous MeOH, NaOH, room temperature, 0.5 h (73%); (f) concentrated H_2SO_4, CH_2Cl_2, room temperature, overnight (73%); (g) $NH_2OH \cdot HCl$, NaOAc, EtOH, room temperature, overnight (89%); (h) 98% red HNO_3, NH_4NO_3, CH_2Cl_2, reflux 1 h, then 30% H_2O_2, reflux 1 h (31%, based on recovered cage dinitroketone).

Scheme 17.

Synthesis of 8 reported by Griffin and coworkers:[38]

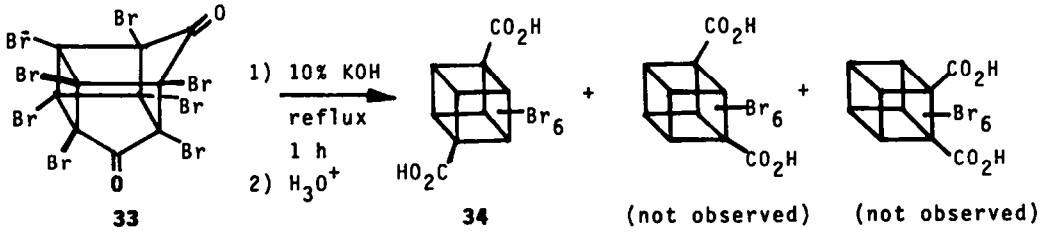


Synthesis of 9 reported by Eaton and coworkers:[39]



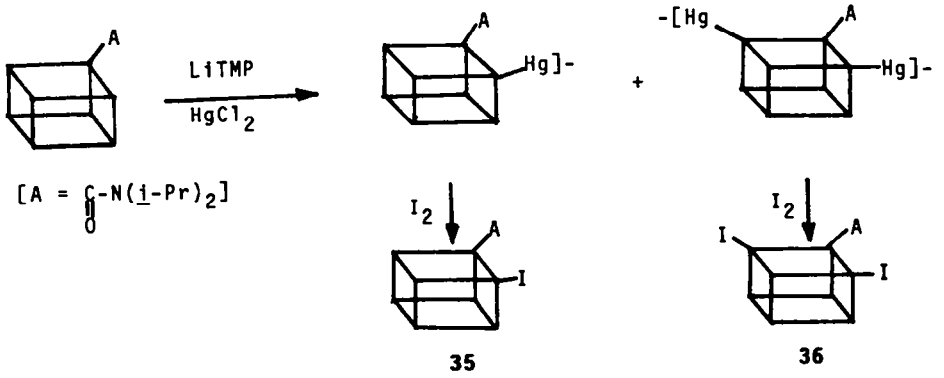
(a) $SOCl_2$, benzene, reflux 1 h (97%); (b) activated NaN_3, H_2O, benzene, reflux 4 h; (c) concentrated aqueous HCl, dioxane, 0 °C, 1 h; (d) aqueous NaOH; (e) MCPBA, $CHCl_3$, reflux 3 h (7%); (f) $(PhO)_2P(O)N_3$, Me_3COH, Et_3N (94%); (g) HCl(g), methanol, -60 °C (67%); (h) aqueous NaOH (71%); (i) MCPBA, $ClCH_2CH_2Cl$, reflux 4 h (40%).

Scheme 18.

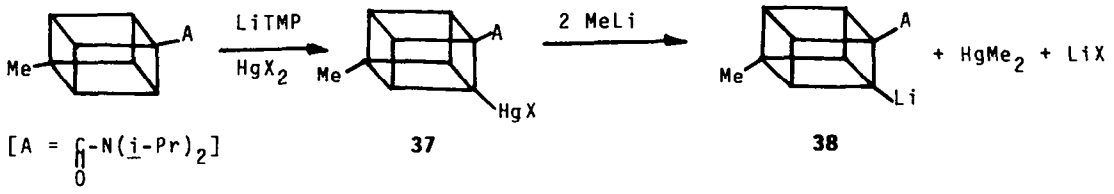


Scheme 19.

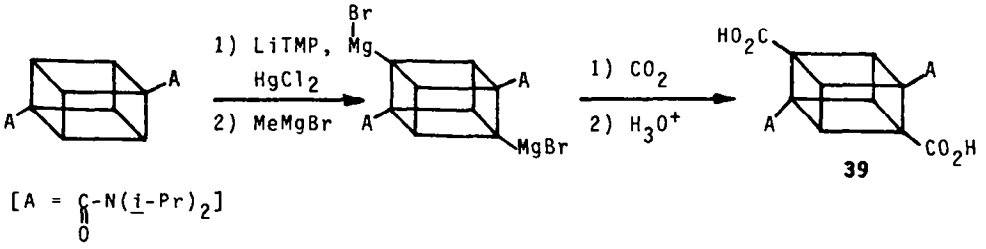
attempts to directly *ortho*-lithiate *N,N*-diisopropylcubanecarboxamide with excess lithium tetramethylpiperidide resulted only in very low conversion to the corresponding lithium derivative (i.e., *ca* 3%).[45] More extensive metalation of the cubane skeleton was made possible by performing equilibrium transmetalation.[46] Thus, treatment of cubane-*N,N*-diisopropylamide with lithium tetramethylpiperidide (LiTMP) in the presence of mercury(II) chloride was found to afford the corresponding mono- and di-"*ortho*"-mercurated products.[45] Subsequent reaction of these organomercury intermediates with elemental iodine afforded the corresponding mono- and diiodinated cubanecarboxamides (**35** and **36**, respectively, Scheme 20).[45] *N,N,N′,N′*-Tetraisobutyl-



Scheme 20.



Scheme 21.



Scheme 22.

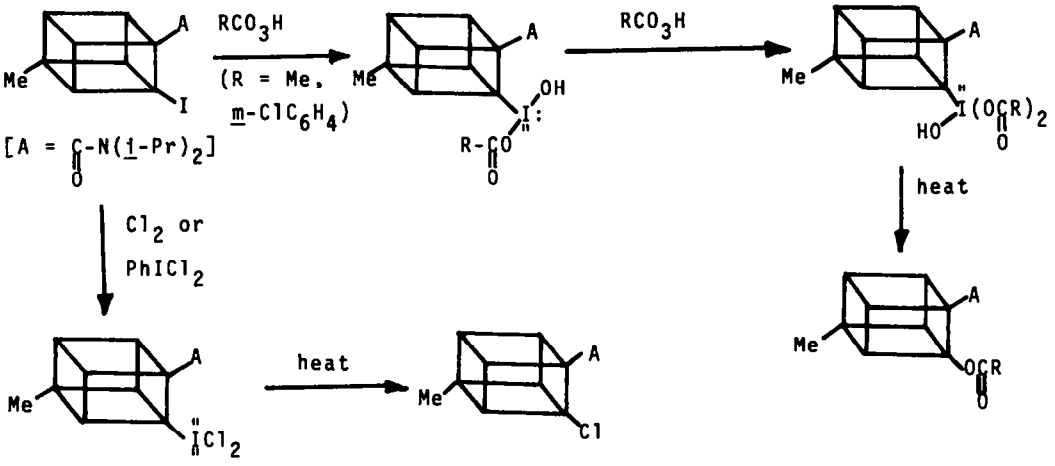
cubane-1,4-dicarboxamide, when reacted with excess LiTMP/$HgCl_2$ followed by treatment with I_2, afforded the corresponding 2,5-diiodo and 2,3,5-triiodo derivatives.[45] Similarly, reaction of *N,N,N′,N′*-tetraisobutylcubane-1,4-dicarboxamide with LiTMP in the presence of anhydrous $ZnCl_2$, $CdCl_2$, Me_3SnCl and Me_3SiCl afforded the corresponding zinc, cadmium, tin and silicon derivatives, respectively.[47]

As noted above, direct *ortho*-lithiation of cubanecarboxamides affords the corresponding lithiated cubane only in very low yield. Increased yields of lithiated cubanes have been achieved via "reverse transmetalation".[48] In this procedure, the organomercury intermediate, e.g., **37**, is treated with methyllithium (2 equivalents); the corresponding cubyllithium (**38**) is formed in high yield via a transmetalation reaction (Scheme 21).[48] Such a transmetalation procedure has been employed in a recent successful synthesis of a tetracarboxyl-substituted cubane (**39**, Scheme 22).

It has been suggested that the carboxamide functionality in the substituted cubane substrate promotes *ortho*-lithiation via a stabilizing interaction between the incoming lithium atom and the amide oxygen atom.[45] The results of *ab initio* self-consistent field molecular orbital calculations (STO-3G level) lend support to this suggestion.[49] Furthermore, these calculational results suggest that the carboxamide functionality inductively stabilizes the anion formed when LiTMP abstracts an "*ortho*" proton in a cubanecarboxamide, thereby selectively enhancing the acidity of "*ortho*" protons in the substrate.[49]

The next problem that must be addressed concerns procedures for introducing NO_2 groups directly onto the cubane skeleton. The method that was utilized successfully for synthesizing 1,3- and 1,4-dinitrocubanes involved sequential conversion of CO_2H groups in the appropriate cubanedicarboxylic acid first to NH_2 and then to NO_2 (Scheme 18).[38,39] In view of the arguments presented earlier (cf. Scheme 11), it seems unlikely that this approach will be useful for synthesizing polynitrocubanes in cases where the precursor cubanepolycarboxylic acid contains two (or more) adjacent CO_2H groups. Accordingly, new methods by which NO_2 substituents can be directly incorporated onto the intact cubane skeleton must be sought.

One such procedure that appears to be particularly promising in this regard has been reported recently by Eaton and Cunkle.[50] Peracid oxidation of iodocubanes has been found to afford relatively stable hypervalent iodine intermediates which can be replaced subsequently by nucleophiles. Similarly, a hypervalent iodine species is formed via reaction of iodocubane with chlorine or with $PhI(Cl)_2$; this species decomposes slowly at room temperature to afford the corresponding chlorocubane (Scheme 23).[50] The reactions shown in Scheme 23 are remarkable in that the net result of this procedure is a formal nucleophilic substitution on iodine in cubyl iodides. Nucleophilic displacement of bridgehead halogen in such a highly strained cage system could not be performed via ordinary S_N1 or S_N2 reactions. The potential usefulness of this oxidative deiodination–substitution route as a method for synthesizing polynitrocubanes remains to be explored.



Scheme 23.

G. 2,3-*Dinitrohexacyclo*[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{4,8}$.$0^{9,12}$]*dodecane* (**10**)

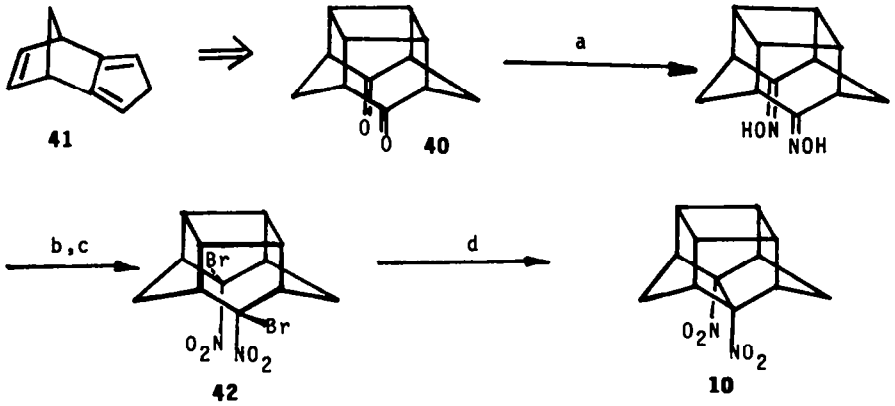
The key intermediate in the synthesis of **10** is [4]peristylane-2,6-dione (**40**). Compound **40** has been synthesized by Paquette and coworkers[51,52] in seven steps starting with tricyclo[5.2.1.$0^{2,6}$] deca-2,5,8-triene (**41**). The method by which **40** was then converted into **10** is summarized in Scheme 24.[53]

An unusual feature of this synthesis is the tri-*n*-butyltin hydride-promoted reductive cyclization of **42**. This reaction involves an unusual 1,5-elimination that occurs smoothly in **42** *without* competing denitration. In this connection, it may be worthwhile to note that a similar 1,5-reductive cyclization that affords the parent 1,3-bishomopentaprismane (**43**) has been reported recently (Scheme 25).[54]

H. *Di-, tri- and tetranitrohexacyclo*[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{4,8}$.$0^{9,12}$]*dodecanes* (**11a–e**)

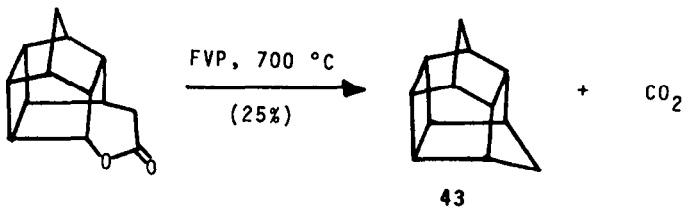
Additional polynitro derivatives of the 1,3-bishomopentaprismane system have been synthesized by Paquette and coworkers.[55] The key intermediate in their syntheses of compounds of the type **11** is the corresponding 1,3-bishomopentaprismane-5,11-dione (**44**). Successful syntheses of **44** have been reported by three different research groups working independently;[56–58] their respective approaches are outlined in Scheme 26.

Elaboration of cage diketone **44** into the corresponding dinitro-1,3-dishomopentaprismanes was performed via conversion of **44** into dioxime **45** followed by oxidation of **45** with buffered *m*-



(a) $NH_2OH \cdot HCl$, NaOAc, MeOH, 20 °C (89%); (b) Br_2, $NaHCO_3$, DMF, H_2O; (c) CF_3CO_3H, CH_2Cl_2 (b + c, 8%); (d) (n-Bu)$_3$SnH, benzene, heat (50%).

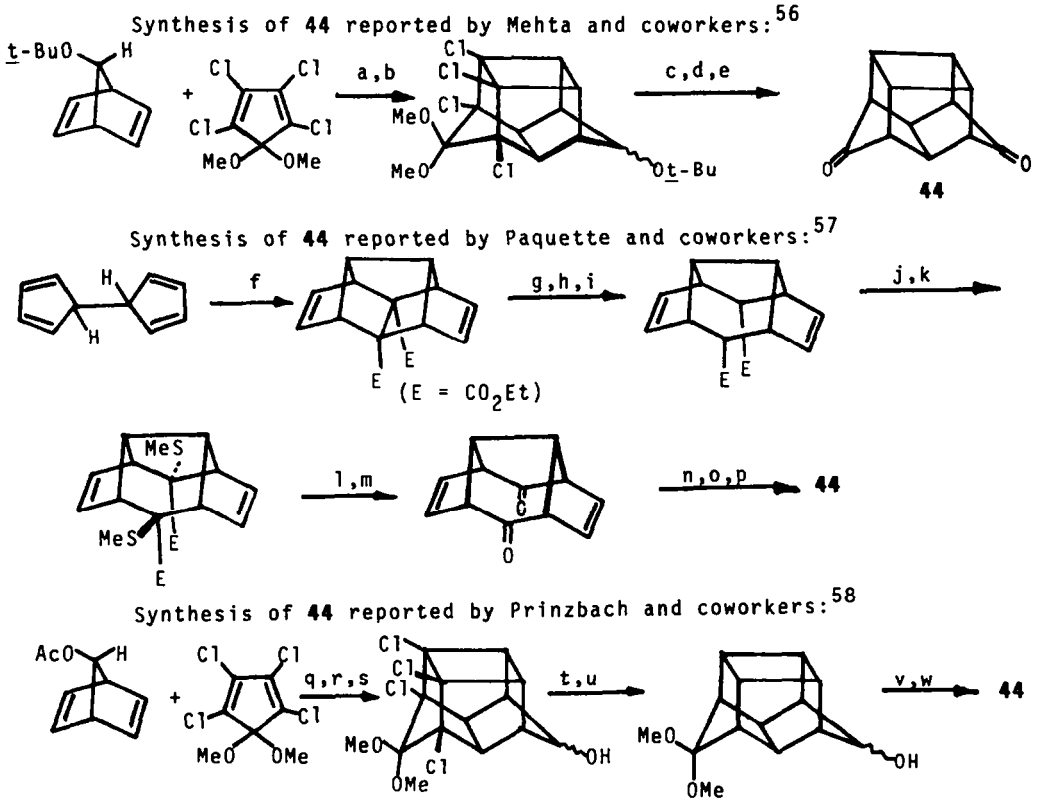
Scheme 24.



Scheme 25.

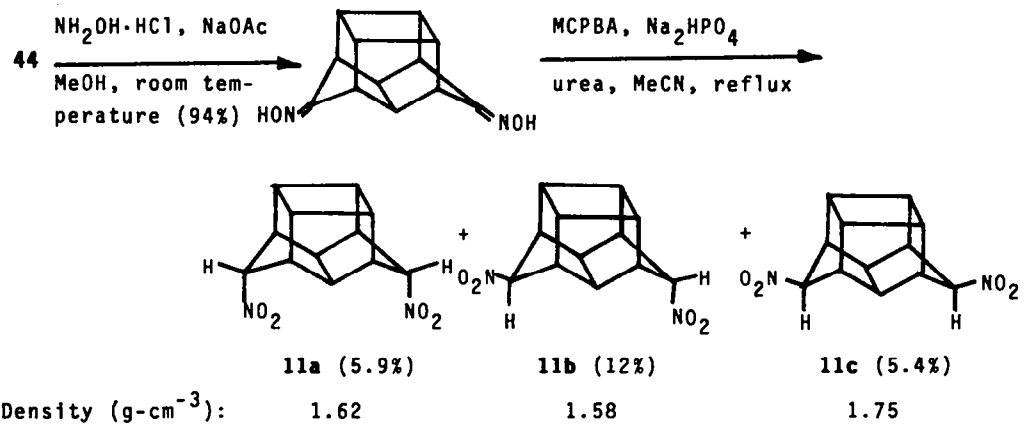
chloroperbenzoic acid (MCPBA) in refluxing acetonitrile. Application of this reaction sequence afforded all of the three possible dinitro-1,3-bishomopentaprismanes (**11a–c**, Scheme 27).[55]

Interestingly, the densities of **11a–c** (measured by the flotation method) differ significantly from one another (see density values given in Scheme 27). This result indicates a clear dependence of density upon C—NO_2 bond configuration; the most dense of these three isomeric dinitro-1,4-

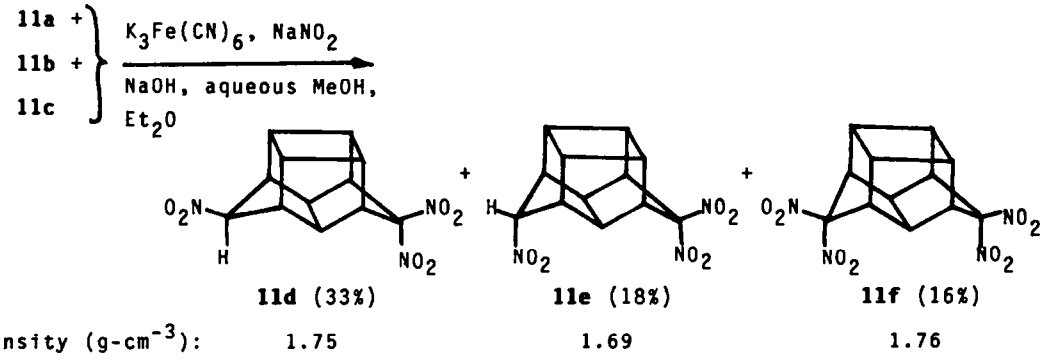


(a) Heat (2 isomers, 60%); (b) hν, $Me_2C{=}O$ (95%); (c) Li, t-BuOH, THF (85%); (d) 4 N HCl, dioxane (80%); (e) PCC, CH_2Cl_2 (80%); (f) DMAD; (g) Na, toluene; (h) Me_3SiCl; (i) aqueous MeOH (g + h + i, 95%); (j) LDA, MeS-SMe (61%; 90-94%, based on recovered starting material); (k) aqueous NaOH, followed by H_3O^+ (100%); (l) NCS, $NaHCO_3$, MeOH; (m) H_3O^+ (l + m, 55%); (n) $HOCH_2CH_2OH$, TsOH (92%); (o) hν, $Me_2C{=}O$ (98%); (p) 2 N HCl, THF, 0 °C (95%); (q) heat (2 isomers, 59%); (r) hν, 9:1 ethyl acetate-acetone, Pyrex (97%); (s) $LiAlH_4$, Et_2O (96%); (t) Na, liquid NH_3; (u) NH_4Cl (t + u, 95%); (v) PCC, CH_2Cl_2, room temperature, 48 h (79%); (w) 10% aqueous H_2SO_4, CH_2Cl_2, stir vigorously, room temperature, 10 h (95%).

Scheme 26.



Scheme 27.



Scheme 28.

bishomopentaprismanes, i.e., **11c**, is the one in which both NO_2 groups occupy quasi-equatorial positions.

Additional NO_2 substituents could be introduced into **11a–c** via application of the nitration procedure described by Kornblum *et al.*[23] In this manner, trinitro-1,3-bishomopentaprismanes **11d** and **11e** and a tetranitro-1,3-bishomopentaprismane (**11f**) could be synthesized (Scheme 28).[55] It is interesting to note that the density of **11c** (i.e., 1.75 g cm^{-3}) is virtually identical to that of **11f**, thereby demonstrating the importance of stereochemical factors in determining overall molecular density. Thus, it is possible to increase the density of a cage molecule either by increasing the degree of nitro substitution or by "judicious stereodisposition of fewer nitro groups".[55] Clearly, the latter alternative merits closer experimental scrutiny.

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