56-40-6; Boc-Glu(OBzl)ONSu, 32886-40-1; *p*-nitrophenol, 100-02-7; HCl-Gly-Glu(OBzl)-Gly-ONp, 59092-70-5; Boc-Glu(OBzl)-Gly-Gly-ONp, 59092-71-6; Boc-Glu(OMe)-OH, 45214-91-3; glycylglycine, 556-50-3; Boc-Asp(OBzl)-ONSu, 13798-75-9; Boc-Gly-ONSu, 3392-07-2.

References and Notes

(1) (a) This work was supported by research grants from the Ministry of Education, Japanese Government. (b) All optically active amino acid residues are of L configuration.
(2) (a) Department of Polymer Chemistry, Kyoto University; (b) Institute for Protein Research, Osaka University.
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Synthesis of 4-Tetracyclo[5.2.1.$0^{2,6}$.$0^{3,8}$]decene (2,4-Ethenotricyclo[3.3.0.$0^{3,7}$]octane)[1]

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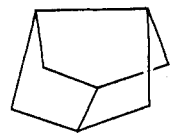
A short first synthesis of the cage olefin 2,4-ethenotricyclo[3.3.0.$0^{3,7}$]octane (**10**) is reported, from dihydrodicyclopentadiene **3** by way of a difunctionalizing and ring-inverting Wagner–Meerwein rearrangement, **4** → **5**, and a transannular carbenic insertion, **7** → **8** → **9**. The intramolecular reactions of the carbenes from *exo*-5,6-trimethylene-7-norbornanone tosylhydrazone (**14**) and the 2,3-olefinic analogue **24** have also been investigated, and are compared with the published reactions of the parent bicyclic carbenes from tosylhydrazones **17** and **26**, respectively.

The synthesis of cage-structured hydrocarbons and their derivatives has been of importance at several levels. The rigid and often symmetrical frameworks of such molecules have furthered understanding of the capabilities and limitations of diverse preparative methods, permitted the determination of new structure–reactivity relationships, and provided test compounds for force-field calculations of molecular energy and geometry. Examples of carbocyclic molecules in this class from which valuable information has been derived in recent years are adamantane,[2] bullvalene,[3] cubane,[4] iceane,[5] and twistane.[2a,c,6] Additional interest has been stimulated lately by the discovery of promising pharmacological properties of certain adamantane[7] and twistane[8] derivatives, apparently due to lipophilic character of the globular hydrocarbon moieties.

Another such spheroidal polycycloalkane, which has received relatively limited attention, is tricyclo[3.3.0.$0^{3,7}$]octane[9] (**1**). We report here a direct synthesis of 2,4-ethenotricyclo[3.3.0.$0^{3,7}$]octane (4-tetracyclo[5.2.1.$0^{2,6}$.$0^{3,8}$]decene) (**10**), the first 2,4-disubstituted derivative of this ring system and an olefin which should be useful for the construction of further new cage compounds. The molecule is the singly bridged relative of diethenotricyclooctane (**2**), recently prepared by Paquette and Wyvratt.[10]



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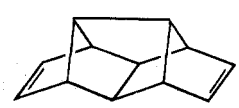
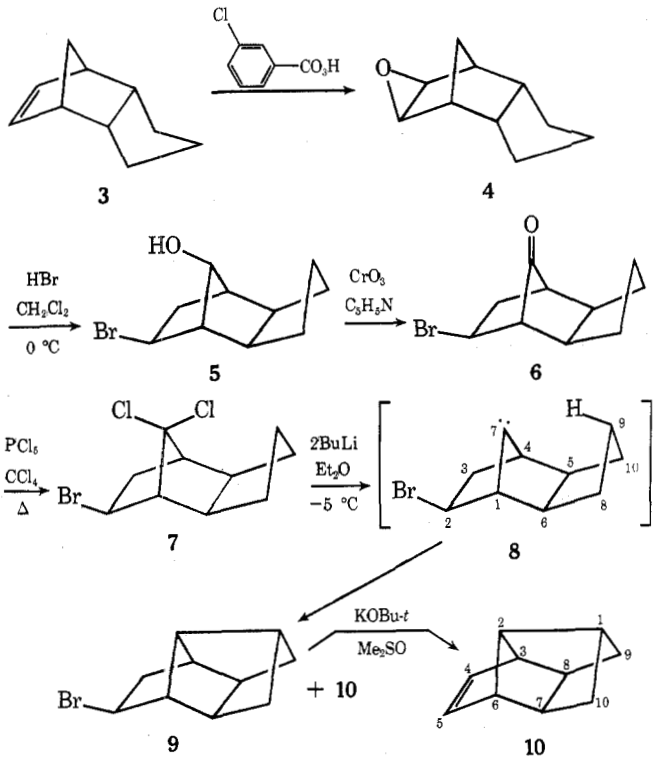


2

The central concepts in the synthesis of **10** were the endo → exo transformation of a 5,6-trimethylenenorborane skeleton by Wagner–Meerwein rearrangement,[11] **4** → **5**, and the transannular C–H insertion,[12] **8** → **9**, of a carbenoid constitutionally constrained against competing olefin formation by hydrogen shift.

Results and Discussion

Reaction of excess cyclopentene with cyclopentadiene according to the procedure of Cristol and co-workers[13] gave rise to a 44% yield of *endo*-5,6-trimethylene-2-norbornene (**3**), which upon reaction with *m*-chloroperbenzoic acid provided the known epoxide[14] **4** in 93.5% yield. Treatment of the epoxide with anhydrous HBr in methylene chloride solution[14c] at 0 °C produced, after recrystallization, a 65% yield of *exo*-2-bromo-*exo*-5,6-trimethylene-*syn*-7-norbornanol (**5**), mp 92.0–93.2 °C, whose ^{1}H NMR spectrum made clear that the desired Wagner–Meerwein rearrangement had occurred.

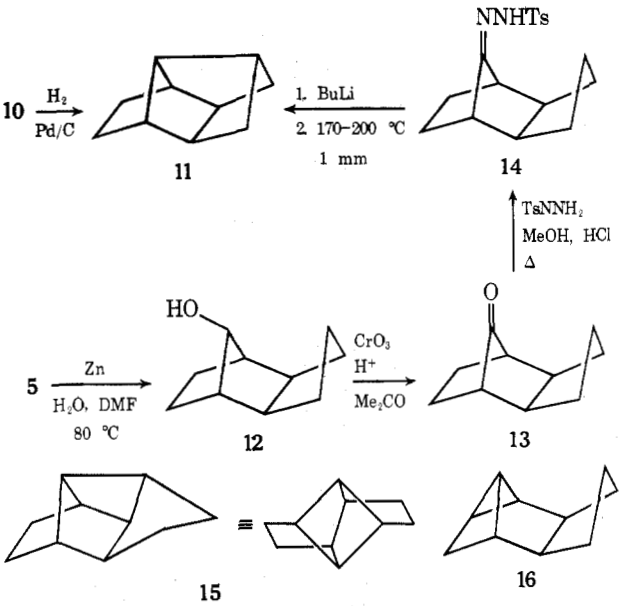


Reaction of bromohydrin **5** with Sarett's reagent[15] at room temperature gave a 79% yield, after short-path distillation, of analytically pure bromo ketone **6**, bp 103–105 °C (1 mm). Reaction of **6** with excess phosphorus pentachloride in boiling CCl_4[16] gave in ca. 75% yield the crystalline *gem*-dichloride **7**, mp 66.0–68.0 °C. From this compound by treatment with 2.0 equiv of *n*-butyllithium in ether[17] at −5 °C was generated the transient carbenoid[18] **8**, which underwent insertion into the proximal C-9 carbon–hydrogen bond to give mainly *exo*-4-bromotetracyclo[5.2.1.0^{2,6}.0^{3,8}]decane (**9**), as well as some of the subsequent elimination product, **10**, in a combined yield of ca. 60%, bp ca. 75 °C (1 mm) (short-path distillation). The conversion of bromide **9** in this mixture to the title olefin, **10**, bp 70–72 °C (13.5 mm), was accomplished in 42% two-step yield from the bromodichloride **7** by reaction with potassium *tert*-butoxide in dimethyl sulfoxide at 40–45 °C.

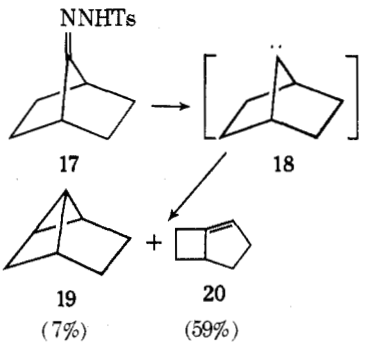
The ^{13}C NMR spectra[19] of **10** were particularly indicative of its structure. The fully proton-decoupled spectrum exhibited six lines of the expected chemical shifts and intensities, while the off-resonance spectrum showed the multiplicities appropriate to the numbers of attached protons.

Catalytic hydrogenation of a sample of olefin **10** yielded the tetracyclodecane **11**.[33] The saturated product, bp 71–72 °C (15 mm), was also prepared from bromohydrin **5** by reductive debromination with zinc dust in aqueous *N,N*-dimethylformamide, oxidation of the resultant alcohol, **12**, to ketone **13**, and vacuum pyrolysis of the lithium salt[20] of the derived *p*-toluenesulfonylhydrazone, **14**. The proton-decoupled ^{13}C NMR spectrum of **11** permitted a clear distinction between it and the two other possible insertion products, **15** and **16**. Like olefin **10**, **11** showed an appropriate six-line spectrum. Compound **15** has C_2 symmetry, dictating a five-line ^{13}C spectrum, as observed in fact for the perchloro derivative;[21] **15** is itself a known compound,[21] possessing a ^1H NMR spectrum markedly different from that of **11**. Isomer **16** lacks symmetry and should have a ten-line ^{13}C spectrum. The off-resonance ^{13}C spectrum of **11** exhibits the expected two triplets and four doublets.

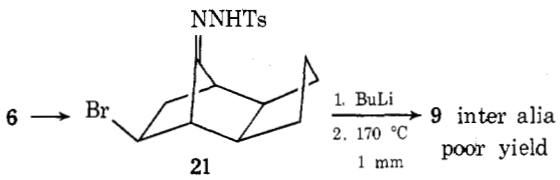
The clean conversion of tosylhydrazone **14** into hydrocarbon **11** is noteworthy in comparison with the corresponding chemistry of 7-norbornanone tosylhydrazone (**17**) studied by



Moss and co-workers.[22] 7-Norbornylidene (**18**) from this source gives rise to 7% of the strained insertion product **19** plus 59% of the rearrangement product 1-bicyclo[3.2.0]heptene (**20**). The proximity of the C-9 methylene group in **8**, then, provides an insertion pathway more favorable than both reactions characteristic of the parent carbene, **18**. It is thus apparent that the formation of **20** from the lithium salt of tosylhydrazone **17** proceeds via the carbene intermediate, **18**, rather than by an alternative concerted decomposition.



Attempted preparation of bromide **9** by analogous pyrolysis of the lithium salt of tosylhydrazone **21** was unsuccessful,



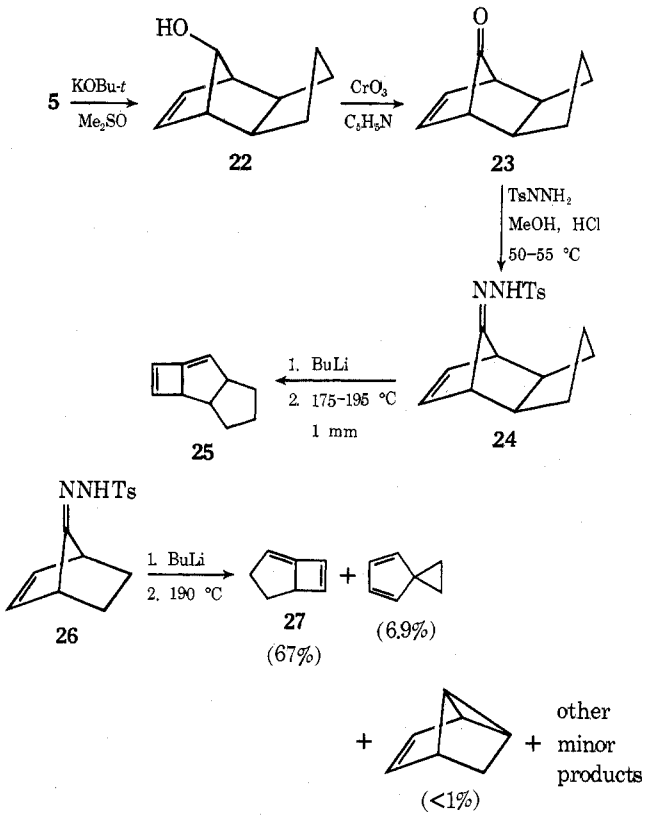
producing only a meager yield of **9** as part of a complex product mixture. The unfavorable results in this reaction are probably a consequence of the heterolytic instability of the bromide substituent at elevated temperatures.

An investigation was also conducted of the thermal decomposition of the lithium salt of the unsaturated tosylhydrazone, **24**. This reaction was of interest as a possible alternative route to the objective olefin, **10**, and also for purposes of comparison with corresponding results from the simple norbornenyl reactant **26**, as reported by Moss et al.[23] and Murahashi et al.[24]

Treatment of bromohydrin **5** with potassium *tert*-butoxide in dimethyl sulfoxide at room temperature gave *exo*-5,6-trimethylene-2-norbornen-*syn*-7-ol (**22**) in 66% yield after short-path distillation, mp 43.0–44.0 °C. Sarett oxidation produced the enone, **23**, in 75% yield, bp ca. 49 °C (1 mm), a

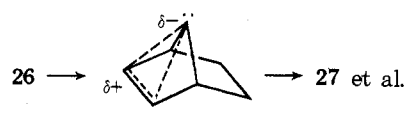
labile substance which becomes yellow over several days at room temperature and decomposed on attampted gas chromatography. Conversion of **23** to the tosylhydrazone, **24**, by reaction with *p*-toluenesulfonylhydrazine in methanol required catalysis by concentrated hydrochloric acid at a temperature of 50–55 °C; the yield was 63%.

Vacuum pyrolysis of the lithium salt of **24** gave in 60% yield a compound identified as 2,4-tricyclo[5.3.0.0^{3,6}]decadiene (**25**). This structure was suggested by that of the main product, **27**, from the parent unsaturated tosylhydrazone,[25] **26**. Diene **25**



polymerizes in a matter of minutes in air at room temperature, and over several hours under nitrogen. Its structure was effectively established, however, on the basis of its ^{1}H and ^{13}C NMR spectral features. Taking the extra cyclopentane ring of **25** into account, the chemical shifts and multiplicities of its olefinic protons are virtually identical with those of **27**.

Moss[23] and later Murahashi[24] have interpreted their results from **26** in terms of a bridged nonclassical singlet carbene intermediate **28**, stabilized by interaction of the π-bond electrons with what would otherwise be a vacant p orbital at the carbene center. This stabilization was predicted theoretically by Gleiter and Hoffman,[26] representing an early stage of carbene addition to a carbon–carbon double bond, whose consummation in this case is constitutionally precluded. The concept has been supported by several experimental studies.[27] Thus, the double bond in tosylhydrazone **26** acts in the derived



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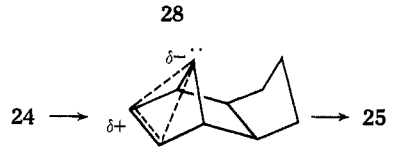

29

carbene to preempt the 7% of C–H insertion found in the saturated system, **17** → **18** → **19**.

The results with tosylhydrazone **24** constitute strengthened evidence for carbene–double bond interaction, **29**, as the olefinic function here diverts reaction entirely from the otherwise especially facile transannular C–H insertion, **14** → **11**.

Efforts to utilize the new olefin **10** in the synthesis of further novel bridged carbopolycyclic compounds are in progress.

Experimental Section

General. Melting points (uncorrected) were obtained in capillary tubes using a Thomas-Hoover melting point apparatus. Boiling points are uncorrected.

Infrared (ir) spectra were obtained on a Beckman Model IR-10 spectrophotometer using sodium chloride optics, as either ca. 2% solutions in CCl_4 (0.5-mm cells), neat thin films, or Nujol mulls.

^{1}H NMR spectra were obtained at 100 MHz using a Varian HA-100 spectrometer operating in the Fourier transform mode. Solvents used were either carbon tetrachloride or deuteriochloroform, containing tetramethylsilane as internal standard. Chemical shifts (δ values) are reported in parts per million downfield from Me_4Si.

^{13}C NMR spectra were obtained at 25.16 MHz using a Varian XL-100-15 spectrometer operated in the Fourier transform mode. All spectra were recorded using $CDCl_3$ as solvent, which also provided the heteronuclear lock. The chemical shifts (δ values) are reported in parts per million downfield from internal Me_4Si.

Mass spectra were obtained using either a Varian M-66 mass spectrometer or a Du Pont Model 21-490B GC-MS system equipped with a 21-094 MS data system.[28]

Analytical gas chromatography (GC) was performed on either a Wilkens Aerograph Hy-Fi Model 600-C or 600-D gas chromatograph equipped with a flame-ionization detector. The following columns were used throughout most of this work, using nitrogen as the carrier gas: (A) 5 ft × 0.125 in. 2% SE-30 on 60–80 mesh Chromosorb G (acid washed, DMCS treated); (B) 5 ft × 0.125 in. 10% SE-30 on 60–80 mesh Chromosorb W (AW, DMCS); (C) 10 ft × 0.125 in. 20% SE-30 on 60–80 mesh Chromosorb W (AW); (D) 10 ft × 0.125 in. 10% Apiezon M on 45–60 mesh Chromosorb W (AW, DMCS); (E) 6 ft × 0.125 in. 10% Carbowax 20M on 50–60 mesh Anakrom ABS.

Preparative-scale GC was conducted with a Barber-Colman Model 5340 thermal-conductivity gas chromatograph using column F, 5 ft × 0.25 in. 10% Apiezon M on 45–60 mesh Chromosorb W (AW, DMCS), with helium as the carrier gas.

Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

***endo*-5,6-Trimethylene-2-norbornene (3).** The procedure used was similar to that described by Cristol and co-workers.[13] In a 250-ml stainless-steel bomb (in other preparations thick-walled glass tubes were used) were placed 140 g (2.06 mol) of cyclopentene, 55 g (0.835 mol) of cyclopentadiene,[29] and several milligrams of 2,6-di-*tert*-butyl-*p*-cresol as a radical inhibitor. The sealed bomb was heated at 190–195 °C overnight, then cooled and opened, and the contents were transferred to a round-bottomed flask fitted with a 6-in. Vigreux column. The excess cyclopentene (97.5 g) was distilled off at atmospheric pressure and combined in the bomb with 50 g of cyclopentadiene and a small amount of radical inhibitor. After heating again overnight, the contents were combined with the residue from the previous run, and the excess cyclopentene was distilled off at atmospheric pressure. The product was then distilled at reduced pressure to give 94.6 g (44% based on cyclopentadiene) of a colorless liquid: bp 69–72 °C (22 mm) [lit. bp 92–94 °C (40 mm),[11a] 173–175 °C (764 mm),[11a] 29.5–33 °C (0.45–0.55 mm)[13]]; ^{1}H NMR (CCl_4) δ 0.97 (m), 1.50 (m), 2.70 (m), 6.06 (s, –CH=CH–). Analysis by GC using column C at 80 °C showed the presence of two minor impurities (relative area ca. 2% each), presumably dicyclopentadiene and the *exo*-trimethylenenorbornene isomer. The separation of dicyclopentadiene conducted by Cristol et al.[13] was not utilized here because of the low indicated impurity levels and the prospect for further purification in subsequent steps.

***endo*-5,6-Trimethylene-2-norbornene Oxide (4).** In a 1000-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer, addition funnel, and thermometer were placed 32.0 g (0.157 mol) of 85% *m*-chloroperbenzoic acid (Aldrich) and 350 ml of reagent-grade methylene chloride. To this stirred solution, cooled to ca. 10 °C, was added dropwise over 25 min 20.0 g (0.149 mol) of olefin **3** in 20 ml of CH_2Cl_2. The reaction mixture was allowed to warm gradually to room temperature and stirred overnight. From the reaction mixture cooled to 0 °C was suction filtered the *m*-chlorobenzoic acid, which was washed well with CH_2Cl_2. The filtrate was then transferred to a separatory funnel and washed once with water, three

times with 10% NaOH solution, and once again with water. After drying ($MgSO_4$), rotary evaporation of the solvent gave 22.4 g of a slightly yellow semisolid. Distillation of the crude product at 1 mm through a short neck into an ice bath cooled receiver gave 22.0 g of a colorless, glassy solid (98.5%), whose purity was indicated by GC (column B at 115 °C) to be ca. 95%. Vacuum sublimation of a small sample gave a colorless, crystalline center fraction: mp 117–118 °C (lit. mp 118–119,[14a] 118 °C[14b]); ^{1}H NMR ($CDCl_3$) δ 0.76, 0.85, 1.37 (broad singlets), 1.56 (broad s, 1.49, 1.63 sh), 2.39 (broad s), 3.04 (s, oxirane).

***exo*-2-Bromo-*exo*-5,6-trimethylene-*syn*-7-norbornanol (5).** In a 500-ml, three-necked, round-bottomed flask fitted with a reflux condenser with drying tube, a gas-inlet tube, and a magnetic stirrer were placed 20.7 g of the distilled epoxide **4** and 200 ml of reagent-grade CH_2Cl_2 (stored over 4A molecular seives). The flask and its contents were tared and then cooled in an ice bath, and gaseous anhydrous HBr was introduced into the magnetically stirred solution at a moderate rate from a tared lecture bottle via the gas-inlet tube. When the weight of the lecture bottle indicated that the approximate amount of HBr had been consumed, the flask and contents were weighed. Approximately 13 g (0.16 mol, ca. 16% excess) of HBr was absorbed. After stirring in the ice bath for 1.5 h and at room temperature for 2 h, 100 ml of a saturated sodium bicarbonate solution was slowly added via the addition funnel to the vigorously stirred reaction mixture. After 15 min, the resulting two-phase mixture was transferred to a separatory funnel, and after shaking the layers were separated. The organic layer was washed with two additional portions of saturated $NaHCO_3$ solution and then with one portion of brine, and was dried over anhydrous $MgSO_4$. The dried extract was treated with charcoal and the solvents removed by rotary evaporation to give a solvent-wet white solid, which was immediately recrystallized at 0 °C from ca. 200 ml of hot hexane. After drying in vacuo, there was obtained 20.0 g (65%) of a white solid, mp 90–92 °C. An analytical sample was obtained by a second recrystallization from light petroleum: mp 92.0–93.2 °C; ir (CCl_4) 905, 1092, 1171, 1230, 1453, 2880, 2960, 3580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80–2.70 (complex m), 3.87 (d of q, CHBr), 4.10 (s, >CHO–). The absorption positions and patterns for the protons at C-2 and C-7 are markedly characteristic of exo-2- and -7-monosubstituted norbornanes[30] and establish that Wagner–Meerwein rearrangement accompanied the epoxide ring opening.

Anal. Calcd for $C_{10}H_{15}BrO$: C, 51.96; H, 6.55. Found: C, 51.77; H, 6.95.

***exo*-2-Bromo-*exo*-5,6-trimethylene-7-norbornanone (6).** In a 2-l., three-necked, round-bottomed flask equipped with a reflux condenser with attached nitrogen inlet, mechanical stirrer, and addition funnel was placed 550 ml of dry pyridine (stored over 4A molecular sieves). To the stirred solvent, cooled in a 10 °C water bath, was slowly added in small portions, under a positive nitrogen pressure, 52 g (0.52 mol) of technical chromium trioxide flakes.[15] The resulting orange suspension was stirred at 10–15 °C for 15 min, then at room temperature for an additional 20 min. To this vigorously stirred, room-temperature reagent was added dropwise from the addition funnel over 20 min 20 g (86.6 mmol) of the once recrystallized bromohydrin **5** dissolved in 125 ml of pyridine. After stirring at room temperature for 40 h, an aliquot was withdrawn, and the reaction was shown by thin layer chromatography (TLC) (Eastman silica gel, 5% ether in hexane) to be essentially complete. The reaction mixture was then poured into 1500 ml of ice–water and extracted with four portions of ether. The combined ether layer was then washed three times with water, five times with a total of 1500 ml of 10% $CuSO_4$ solution, once with water, and once with brine, and then dried over $MgSO_4$. Rotary evaporation of the ether gave 18.5 g of a crude yellow liquid, which upon short-path distillation afforded 15.6 g (79%) of a colorless, analytically pure liquid: bp 103–105 °C (1 mm); ir (neat) 668, 720, 846, 890, 942, 988, 1120, 1210, 1231, 1450, 1470, 1770, 1820, 2870, 2950 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.0–2.6 (complex m), 4.06 (d of q, CHBr). This material showed only one spot on TLC, and fully solidified upon standing in the freezer at −22 °C.

Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.41; H, 5.73. Found: C, 52.28; H, 5.79.

***exo*-2-Bromo-*exo*-5,6-trimethylene-7,7-dichloronorbornane (7).** In a 500-ml, three-necked, round-bottomed flask fitted with a reflux condenser with attached nitrogen inlet, magnetic stirrer, and addition funnel were placed 120 ml of dry (stored over 4A molecular sieves) reagent-grade carbon tetrachloride and 22.8 g (0.109 mol) of phosphorus pentachloride.[16] To this stirred room-temperature suspension, under a static nitrogen atmosphere, was added in one portion from the addition funnel 10.0 g (43.6 mmol) of the pure bromo ketone **6** dissolved in 65 ml of CCl_4. After stirring at room temperature for 5 min, the reaction mixture was brought to a gentle boil under reflux and stirred for 42 h. The colorless reaction mixture was allowed to cool to room temperature and was then poured over 300 ml of crushed ice. The resulting two-phase mixture was transferred to a separatory funnel and shaken, and the layers were separated. The aqueous phase was extracted once with CCl_4, and the combined organic solution was washed once with water, three times with saturated $NaHCO_3$ solution, and once with brine, then dried over $MgSO_4$. Rotary evaporation of the solvent gave 13.0 g of a crude, colorless oil, which crystallized at −30 °C and remained solid at room temperature. The crude product was recrystallized from ca. 50 ml of hot petroleum ether (bp 30–60 °C) at −22 °C to give 9.25 g (32.6 mmol, 74.7%) of a white, crystalline powder after drying in vacuo, mp 60–63.5 °C. An analytical sample was obtained from a second recrystallization (0 °C) of a small amount of the above material: mp 66.0–68.0 °C; ir (CCl_4) 974, 1145, 1160, 1203, 1212, 1251, 1282, 1292, 1300, 1318, 1455, 2878, 2896, 2935, 2960, 2990 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.0–2.9 (complex m), 3.87 (complex d of d, CHBr). TLC showed only one component.

Anal. Calcd for $C_{10}H_{13}BrCl_2$: C, 42.28; H, 4.62. Found: C, 42.21; H, 4.60.

***exo*-4-Bromotetracyclo[5.2.1.0^{2,6}.0^{3,8}]decane (9).** In a 250-ml round-bottomed flask fitted with a serum stopper and syringe needle connected to a nitrogen by-pass line were placed 6.0 g (21.2 mmol) of the once recrystallized *gem*-dichloride **7** and 150 ml of anhydrous ether (freshly distilled from $LiAlH_4$). The resulting magnetically stirred, colorless solution was cooled to ca. −5 °C with an ice–salt bath, and 18.5 ml (44.5 mmol) of a 2.4 M solution of *n*-butyllithium in hexane was slowly injected from a syringe over ca. 10 min. (Preliminary small-scale experiments demonstrated a necessity for 2 equiv of butyllithium). The reaction was somewhat exothermic as evidenced by a rise in the bath temperature to ca. −2 °C during the addition. Also, during the addition a white precipitate (presumably LiCl) formed and the solution turned slightly yellow. After the addition was complete, the reaction was stirred at −5 to 0 °C for 1.5 h and then poured into 200 ml of ice–water with stirring. After separation of the layers, the aqueous phase was extracted with two additional small portions of ether, and the combined organic layer (light yellow) was washed once with brine and dried over $MgSO_4$. Rotary evaporation of the ether gave 5.03 g of an orange-yellow liquid, which was shown by GC (column B at 145–190 °C), TLC (silica gel G, hexane), and ^{1}H NMR to contain considerable amounts of olefin **10** as well as lesser amounts of other impurities. The crude liquid was short-path distilled to give two colorless fractions: (1) 2.36 g, bp 65–75 °C (1 mm), and (2) 250 mg, bp 75–90 °C (1 mm). GC analysis showed fraction 1 to be mainly bromide **9** and olefin **10** contaminated with several unidentified impurities, and fraction 2 to consist of ≥95% of bromide **9**. The mass spectrum (Du Pont 21-490 B), as anticipated for an *exo*-norbornyl bromide,[31] showed no molecular-ion peak (*m/e* 213) but a base peak corresponding to the M − Br ion[31] (*m/e* 133). The ^{1}H NMR spectrum (CCl_4) showed, in addition to a complex multiplet at δ 0.8–2.8 for the protons on unsubstituted carbon, a doublet of doublets at δ 4.26 indicative of the endo proton on an exo-2-substituted norbornane;[30] ir (neat) 754, 934, 1184, 1221, 1297, 1446, 2870, 2896, 2975 cm^{-1}.

The bromide **9** decomposed upon attempted preparative GC, and an analytical sample was not obtained.

The synthetic conditions described are considered less than optimal. Preliminary small-scale experiments indicated that improved yield and purity of **9** would have been achieved if the larger scale reaction temperature had been maintained at −30 to −20 °C, with slow addition of the butyllithium.

4-Tetracyclo[5.2.1.0^{2,6}.0^{3,8}]decene (10). In a 50-ml, three-necked, round-bottomed flask fitted with a reflux condenser with attached nitrogen inlet and an addition funnel were placed 1.51 g (13.5 mmol) of potassium *tert*-butoxide (Aldrich) and 15 ml of dry Me_2SO (distilled from CaH_2 and stored over 4A molecular sieves). To this magnetically stirred, room-temperature solution was added via the dropping funnel ca. 2.3 g of fraction 1 from the previous reaction (mainly bromide **9**) dissolved in 15 ml of dry Me_2SO. The reaction mixture was stirred at room temperature for 0.5 h and in a 40–45 °C oil bath for 20 h. The cooled, dark-brown solution was then poured into 150 ml of cold water and extracted with three portions of pentane. The combined pentane extract was washed twice with water and twice with brine, and then dried over $MgSO_4$. Rotary evaporation of the pentane gave 1.5 g of a crude, light-yellow liquid, which was indicated by GC (column B at 90–190 °C) to be ca. 95% of one volatile component. Short-path distillation gave 1.05 g (ca. 73%) of a colorless liquid, ≥95% pure as determined by GC and NMR: bp 70–72 °C (13.5 mm); ir (neat) 705, 726, 799, 827, 1284, 1347, 1591, 2895, 2978, 3060 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.4–2.1 (m), 2.58 (narrow m), 5.70 (t, J = 2.0 Hz, –CH=CH–); ^{13}C NMR, off-resonance decoupled, δ 35.8 (d, >CH–),

40.8 (d, >CH–), 48.3 (t, $-CH_2-$), 59.0 (d, >CH–), 130.3 (d, –CH=CH–); the mass spectrum showed a molecular-ion peak (base peak) at *m/e* 132 (Du Pont 21-490 B). Attempted purification of this material by preparative GC at 115 °C resulted in significant decomposition. The ^1H NMR spectrum of the collected material showed the major presence of **10** but indicated also complex vinylic- and allylic-proton absorptions, suggesting substantial transformation by a retro-Diels–Alder reaction. (Lowering the injector temperature did not remedy the situation.) An analytical sample of **10** was thus not obtained.

Hydrogenation of 10. In a 10-ml, two-necked, pear-shaped flask fitted with a serum stopper and a gas inlet from a hydrogen-filled buret were placed several milligrams of 5% palladium on charcoal and ca. 2 ml of Spectrograde CCl_4. A hydrogen atmosphere was established over the magnetically stirred suspension and maintained for 1 h to partially reduce the catalyst. Then 10 μl of the distilled olefin **10** was injected from a syringe. The reaction mixture was stirred under a hydrogen atmosphere for 2 h, and then suction filtered through a small pad of anhydrous $MgSO_4$ into a 10-ml pear-shaped flask. The CCl_4 solution was concentrated somewhat on the rotary evaporator, and the residue was examined by Fourier-transform ^1H NMR. With the exception of several weak absorptions due to a small amount of unreacted olefin, the spectrum was identical with that of the independently prepared saturated hydrocarbon, **11** (see below).

***exo*-5,6-Trimethylene-*anti*-7-norbornanol (12).** To a magnetically stirred suspension of 10.0 g of zinc dust in 100 ml of aqueous *N,N*-dimethylformamide (DMF) (5% water, 95% DMF, v/v) was added dropwise from an addition funnel 10.0 g (43.4 mmol) of once recrystallized bromohydrin **5** dissolved in 40 ml of the aqueous DMF solution. After stirring at room temperature for several minutes, the reaction mixture was brought to 80 °C with an oil bath and stirred for 12 h. Upon cooling to room temperature, the excess zinc and salts were filtered under suction through a bed of Celite and washed well with pentane. The filtrate was then poured into 500 ml of water and extracted with three portions of pentane. The combined organic extract was washed three times with water and once with brine, then dried over anhydrous $MgSO_4$. Rotary evaporation of the pentane gave 5 g of a crude white solid. Vacuum sublimation (60 °C at 0.5 mm) of the crude product gave 4.25 g (64.5%) of analytically pure, colorless crystals, found to be homogeneous by GC on column B at 120 °C and column E at 150 °C: mp 69.0–70.0 °C; ir (CCl_4) 1018, 1045, 1089, 1155, 1238, 1458, 2982, 2960, 3350–3500, 3635 cm^{-1}; ^1H NMR (CCl_4) δ 0.86 (s), 1.08 (m), 1.79 (m), 3.97 (broad s, >CHO–); ^{13}C NMR, fully decoupled, δ 26.0, 27.2, 32.2, 44.9, 46.5, 76.1 (>CHOH), six lines as required by the symmetry of **12**.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.88; H, 10.61. Found: C, 78.80; H, 10.54.

***exo*-5,6-Trimethylene-7-norbornanone (13).** To a mechanically stirred, cooled (0–5 °C) solution of 4.85 g (31.9 mmol) of crude alcohol **12** in 160 ml of reagent-grade acetone was slowly added from a dropping funnel 43 ml (64.5 mequiv) of Jones reagent (1.5 N)[32] over 20 min. The reaction mixture was stirred at 0–5 °C for 1 h and at room temperature for 1.75 h, then was poured into 300 ml of ice water, and the excess Cr^{VI} was destroyed by the addition of solid sodium bisulfite. The aqueous layer was then extracted four times with ether, and the combined organic layer was washed once with water, twice with saturated $NaHCO_3$ solution, and once again with water, and then dried over $MgSO_4$. Rotary evaporation of the solvent gave 4.0 g of a crude yellow liquid, which contained a trace of unreacted alcohol as evidenced by GC on column E at 135 °C. Short-path distillation afforded 2.04 g (43.5%) of a clear, colorless liquid which was homogeneous by GC (column E at 135 °C): bp 73–75 °C (0.5 mm); ir (neat) 707, 1125, 1451, 1762, 2866, 2880, 2955 cm^{-1}; ^1H NMR (CCl_4) δ 0.9–2.60 (complex m). The distilled product fully solidified in the freezer at −22 °C.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.94; H, 9.41. Found: C, 80.10; H, 9.73.

***exo*-5,6-Trimethylene-7-norbornanone Tosylhydrazone (14).** In a 25-ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser were placed 1.0 g (6.67 mmol) of pure ketone **13**, 1.37 g (7.33 mmol) of tosylhydrazine (Aldrich), and 8 ml of methanol. To this stirred solution was added 3 drops of concentrated HCl, and the reaction was brought to a gentle boil under reflux. After 46 h the reaction mixture was cooled to room temperature and placed in the refrigerator at ca. 0 °C. Suction filtration afforded 1.67 g (78%) of a white, crystalline powder, after drying in vacuo. An analytical sample was obtained by recrystallizing a small amount of the crude material from methanol at 0 °C: mp 178.0–179.0 °C; ir (Nujol) 758, 830, 900, 930, 948, 1018, 1100, 1170, 1316, 1346, 1415, 1599, 1687, 3200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.6 (complex m), 2.42 (s, $-CH_3$), 7.59 (d of d, aromatic).

Anal. Calcd for $C_{17}H_{22}N_2O_2S$: C, 64.11; H, 6.98. Found: C, 64.19; H, 7.06.

Tetracyclo[5.2.1.$0^{2,6}$.$0^{3,8}$]decane (11). In a 50-ml round-bottomed flask equipped with a Claisen head fitted with a serum stopper and nitrogen inlet were placed 1.50 g (4.72 mmol) of tosylhydrazone **14** and 20 ml of anhydrous ether. To this magnetically stirred suspension, cooled in an ice bath under nitrogen, was slowly injected by syringe 2.2 ml (5.19 mmol) of 2.4 M *n*-butyllithium in hexane (Ventron). After stirring in the ice bath for 0.5 h, the stirring bar was removed, and the ether was carefully stripped off on the rotary evaporator to give a white solid. As much as possible of this solid was scraped from the sides of the flask to the bottom, and the flask was put on the rotary evaporator for several more minutes. The flask was then connected to a pyrolysis apparatus consisting of a short curved adapter, fitted with a loose glass-wool plug, leading to a tared three-necked round-bottomed receiving flask, which was fitted with a stopper and vacuum take-off adapter. The system was evacuated to 1 mm and allowed to stand at room temperature for 0.5 h. The receiving flask was then cooled in dry ice, and after several minutes the reaction flask was immersed in a silicone-oil bath preheated to 165 °C. The bath was allowed gradually to heat up further, and after several minutes decomposition commenced (gas evolution). The bath slowly reached a maximum of 210 °C (during which time the curved adapter was heated with a heat gun to prevent vapor condensation) and was then allowed to cool to room temperature. The receiving flask contained 540 mg of a slightly yellow liquid, which was shown by GC (column B at 90 °C, column C at 115 °C, column D at 140 °C) to be greater than 95% of one component. Short-path distillation gave 350 mg (55%) of a colorless liquid, bp 71–72 °C (15 mm). Gas chromatographic analysis showed this material to be ca. 98% pure. Two minor impurities (ca. 1% each) of similar retention times to that of the major component were observed. The mass spectrum (Varian M-66) exhibited a molecular-ion peak at *m/e* 134. An analytical sample was obtained by preparative GC at 125 °C: ir (neat) 1300, 1465, 2880, 2900, 2910, 2970 cm^{-1}; ^1H NMR (CCl_4) δ 1.2–1.7 (m, 8 H, $-CH_2-$), 1.7–2.4 (m, 6 H, >CH–); ^{13}C NMR, off-resonance decoupled, δ 25.0 (t, $-CH_2-$), 37.3 (d, >CH–), 41.0 (d, >CH–), 45.6 (t, $-CH_2-$), 47.2 (d, >CH–), 54.0 (d, >CH–).

Anal. Calcd for $C_{10}H_{14}$: C, 89.47; H, 10.53. Found: C, 89.60; H, 10.58.

***exo*-5,6-Trimethylene-*exo*-2-bromo-7-norbornanone Tosylhydrazone (21).** In a 50-ml, round-bottomed flask fitted with a reflux condenser and magnetic stirrer were placed 2.0 g (8.73 mmol) of bromo ketone **6**, 1.79 g (9.60 mmol) of tosylhydrazine, and 17 ml of methanol. To this stirred solution was added 5 drops of concentrated HCl, and the reaction mixture was brought to a gentle boil under reflux. After stirring for 21 h, the reaction mixture was cooled to room temperature, then placed in the refrigerator at 0 °C overnight. Suction filtration gave 3.02 g (88%) of a white, crystalline powder. Recrystallization from methanol at 0 °C gave small, white needles: mp 191–192 °C dec; ir (Nujol) 805, 885, 922, 927, 1014, 1088, 1161, 1232, 1345, 1403, 1598, 1705, 3218 cm^{-1}.

Preparation and Thermal Decomposition of the Lithium Salt of Tosylhydrazone 21. The procedure used was the same as that described for the saturated tosylhydrazone **14**. Thus, the lithium salt was prepared from 2.8 g (7.05 mmol) of bromotosylhydrazone **21** and 3.3 ml (7.8 mmol) of *n*-butyllithium solution in 45 ml of anhydrous ether. Pyrolysis at 170 °C (1 mm) occurred readily to give 810 mg of a yellow oil, which was shown by GC (column B at 145–190 °C) to be a complex mixture of products. ^1H NMR analysis also indicated a complex mixture containing only a small amount of the desired tetracyclic bromide, **9**.

***exo*-5,6-Trimethylene-2-norbornen-*syn*-7-ol (22).** In a 500-ml, three-necked, round-bottomed flask fitted with a reflux condenser equipped with a nitrogen inlet and an addition funnel were placed 13.5 g (0.12 mol) of potassium *tert*-butoxide (Aldrich) and 100 ml of dry dimethyl sulfoxide (distilled at reduced pressure from CaH_2 and stored under nitrogen over 4A molecular sieves). To this magnetically stirred, room-temperature solution was added dropwise over ca. 1 h 23.0 g (0.10 mol) of once recrystallized bromohydrin **5** dissolved in 100 ml of dry Me_2SO. After stirring at room temperature for 24 h, 100 ml of water was added to the reaction mixture, and the product was predominantly separated by steam distillation. The residual liquid was transferred to a separatory funnel and extracted with three portions of pentane. The combined organic materials were washed three times with water and dried over $MgSO_4$. Rotary evaporation of the pentane gave 11.9 g of a colorless oil, which was distilled at 0.7 mm through a short neck into an ice bath cooled receiving flask to yield 9.92 g (66%) of a white solid, mp 37–39 °C. A small amount of this product was sublimed (30–35 °C at 1 mm), recrystallized at −78 °C from petroleum ether (bp 30–60 °C), and resublimed (30–35 °C at 1

mm) to give an analytical sample which was homogeneous by GC on column B at 120 °C: mp 43.0–44.0 °C; ir (CCl_4) 708, 896, 1020, 1080, 1155, 1218, 1232, 1275, 1335, 1415, 2872, 2960, 3070, 3570 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.0–2.1 (m), 2.47 (narrow m, allylic CH), 4.02 (s), 6.09 (narrow t, -CH=CH-); ^{13}C NMR, fully decoupled, δ 29.8, 30.7, 44.8, 52.1, 83.6, 134.8.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.94; H, 9.41. Found: C, 79.84; H, 9.39.

***exo*-5,6-Trimethylene-2-norbornen-7-one (23).** In a 500-ml, three-necked, round-bottomed flask fitted with a reflux condenser with attached nitrogen inlet, a mechanical stirrer, and an addition funnel was placed 150 ml of pyridine (dried over KOH pellets). To the stirred solvent, cooled in an ice–water bath, was added slowly in small portions, under positive nitrogen pressure, 15.7 g (0.157 mol) of solid analytical-grade chromium trioxide.[15] After stirring at 10 °C for 15 min, the orange-yellow suspension was allowed to warm to room temperature, and after stirring an additional 15 min 5.86 g (39.1 mmol) of distilled unsaturated alcohol **22** dissolved in 20 ml of pyridine was added dropwise from the addition funnel over 15 min. The reaction mixture was stirred at room temperature for 45 h, then poured into 1000 ml of ice water and extracted with four portions of ether. The combined ether extract was washed once with water, three times with 10% sulfuric acid solution, once with water, twice with saturated $NaHCO_3$ solution, and once with brine, then dried over $MgSO_4$. Rotary evaporation of the ether gave 4.82 g of a slightly yellow liquid. Short-path distillation afforded 4.32 g (75%) of an analytically pure, colorless liquid: bp 49 °C (1 mm); ir (neat) 693, 765, 800, 1105, 1455, 1773, 2873, 2900, 3002 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.0–2.2 (complex m), 2.55 (t, J = 2.5 Hz, allylic CH), 6.51 (t, J = 2.5 Hz, -CH=CH-); ^{13}C NMR, fully decoupled, δ 28.8, 30.1, 43.3, 51.4, 134.3 (-CH=CH-), 207.2 (>C=O).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.03; H, 8.18. Found: C, 81.11; H, 8.20.

Upon standing at room temperature for several days the distilled product gradually turned yellow. However, it could be stored in the solid state in the dark at −22 °C without apparent decomposition.

***exo*-5,6-Trimethylene-2-norbornen-7-one Tosylhydrazone (24).** In a 25-ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser were placed 1.00 g (6.76 mmol) of pure ketone **23**, 1.30 g (7.0 mmol) of tosylhydrazine (Aldrich), 5 ml of methanol, and 4 drops of concentrated hydrochloric acid. The resulting stirred solution was then placed in a 50–55 °C oil bath for 26 h, cooled to room temperature, and finally placed in the refrigerator at 0 °C. Suction filtration gave 1.34 g (63%) of a crystalline, white powder after drying in vacuo: mp 181.5–182.0 °C dec; ir (Nujol) 711, 721, 832, 1010, 1170, 1346, 1380, 1404, 1599, 1687, 3230 cm^{-1}. The crude material was stored at −22 °C and used as soon as possible.

Preparation and Thermal Decomposition of the Lithium Salt of Tosylhydrazone 24. The procedure used was similar to that described for the saturated tosylhydrazone **14** except that the pyrolysis system was evacuated and flushed with nitrogen or helium before the final evacuation and decomposition. Thus, the lithium salt was prepared from 1.0 g (3.16 mmol) of tosylhydrazone **24** and 1.45 ml (3.48 mmol) of 2.4 M n-butyllithium solution in 15 ml of anhydrous ether. After evaporation of the ether, the flask containing the dry salt was connected to the pyrolysis apparatus, dried for 45 min, then pyrolyzed at 175–195 °C. After the reaction vessel had cooled, nitrogen was admitted to the evacuated, cold (−78 °C) receiving flask and, under positive nitrogen pressure, the pyrolysis flask and short neck were removed and quickly replaced with a rubber serum stopper. Approximately 3 ml of precooled (−20 °C) $CDCl_3$ was then injected into the receiving flask, and the colorless liquid product dissolved. A small portion of this cold solution was withdrawn with a syringe and placed in a nitrogen-flushed ^{1}H NMR tube. The remainder of the solution was withdrawn and placed in a nitrogen-flushed ^{13}C NMR tube which was then chilled to ca. −30 °C. The ^{1}H NMR spectrum (single sweep) was obtained at ambient probe temperature, the ^{13}C NMR spectrum (3794 transients) at −30 °C: ^{1}H NMR ($CDCl_3$) δ 0.8–2.4 (complex m), 2.65 (m), 3.00 (m), 3.26 (broad d, J = 8 Hz, 1 H), 5.06 (d, J = 4 Hz, 1 H, five-ring butadiene H), 6.45 (t, J = 2 Hz, 1 H, four-ring terminal butadiene H), 6.87 (d, J = 2 Hz, 1 H, four-ring internal butadiene H); ^{13}C NMR, fully decoupled, δ 27.3, 30.9, 32.3, 45.3, 57.5, 61.0, 112.8, 134.8, 141.8, 150.1. Upon contact with air, the product rapidly polymerized to an amorphous, yellow-brown solid, either neat or in solution (the material seemed to be somewhat more stable in $CDCl_3$ than in CS_2). While elemental analysis could not be obtained, the product structure is strongly indicated to be **25** by the close resemblance of its ^{1}H NMR spectrum to that of **27**[25] and by the ten-line pattern of its ^{13}C NMR spectrum.

Registry No.—**3**, 2826-19-9; **4**, 59121-43-6; **5**, 59054-55-6; **6**, 59054-56-7; **7**, 59054-57-8; **9**, 59054-58-9; **10**, 59054-59-0; **11**, 59054-60-3; **12**, 59121-44-7; **13**, 59054-61-4; **14**, 59054-62-5; **21**, 59054-63-6; **22**, 59054-64-7; **23**, 59054-65-8; **24**, 59054-66-9; **25**, 59054-67-0; cyclopentene, 142-29-0; cyclopentadiene, 542-92-7; HBr, 10035-10-6; phosphorus pentachloride, 10026-13-8; tosylhydrazine, 1576-35-8.

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The Ethanonoradamantanes. An Experimental Evaluation of Empirical Force Field Predictions[1]

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2,4-Ethanonoradamantane (**6**) is the most stable of 2486 possible tetracyclic ring systems of empirical formula $C_{11}H_{16}$. While empirical force field calculations predicted **6** and 2,8-ethanonoradamantane (**7**) to be the most stable tetracycloundecanes and to have equal stability, $AlBr_3$-catalyzed isomerization of tetracyclo[6.3.0.0^{2,6}.0^{5,9}]undecane (**13**), noriceane (**9**), and methanotwistane (**14**) gave mixtures of **6** and **7** in a 97:3 (±1) ratio. The structures of **6** and **7** were established by syntheses based on the stereochemical control imposed on the C–H carbene insertion of *exo*- and *endo*-2-noradamantyl methyldiazo ketones (**19** and **20**). While **13** and **9** rearrange directly to **6** and **7** in high yield, **14** isomerized initially to **7**, which then underwent slow isomerization to the more stable **6**, accompanied by extensive disproportionation to 1-methyladamantane. Noriceane (**9**) was detected as an intermediate in the rearrangement of **14**. The mechanisms of these isomerizations are analyzed using a graph interconnecting 15 tetracycloundecanes. The overall results demonstrate the power of force field calculations, but indicate that there are still limitations in accuracy even when an isomerization between structurally related molecules is involved.

The $AlCl_3$-catalyzed rearrangement of tetrahydrodicyclopentadiene to adamantane demonstrated the synthetic potential of thermodynamically controlled polycyclic isomerizations.[3] Diamantane,[4] triamantane,[5] and many other cage molecules have now been prepared by this method.[6] A readily available precursor, generally with the same empirical formula and number of rings, is treated with a strong Lewis acid. Although exceptions are known,[7,8] rearrangement to the most stable isomer (the "stabilomer")[9] usually occurs.[6] Although it is rather obvious that adamantane should be the $C_{10}H_{16}$ stabilomer, predictions in other instances are much more difficult. For example, qualitative inspection of the structures of iceane (**1**) and of ethanoadamantane (**2**) does not provide a clear basis for understanding why the latter is the $C_{12}H_{18}$ stabilomer.[10]

Further progress in this area requires the development of a systematic method for the prediction of the stabilomer of any given saturated hydrocarbon set. We illustrate in this paper the procedure we have devised for the tetracyclic $C_{11}H_{16}$ series.

Prediction of the $C_{11}H_{16}$ Tetracyclic Stabilomer. In general, the prediction of a stabilomer will require three steps:

1. Determination and listing of all possible isomers. The number is likely to be prohibitively large.

2. Elimination of isomers expected qualitatively to be unstable on the basis of structural considerations.

3. Quantitative estimation of the free energies of formation of the remaining isomers. The isomer with the lowest free energy is predicted to be the stabilomer.

The computer program developed by Wipke for the elucidation of the number of polycyclic isomers[11] predicts that 2486 tetracyclic $C_{11}H_{16}$ ring systems are possible. This program further indicates the ring sizes present in each isomer. Since structures with three-membered rings tend to be highly strained (and do not, in any event, survive AlX_3 isomerization) these are unlikely stabilomer candidates. Elimination of such structures reduces the number of isomers to 812. Similarly, isomers with four-membered rings can also be rejected; this leaves only 68 possibilities. In order to check this latter assumption, we included the methano-bridged adamantane (**3**) in the set to be calculated, because it should be the most stable $C_{11}H_{16}$ tetracycle with a four-membered ring.[12,13]

Inspection of the structures of the 68 theoretical $C_{11}H_{16}$ isomers with only five- and six-membered rings show that many have intertwined bridges or other obviously unfavorable features. While quite a manageable number of isomers remained, we chose to continue the screening process. If we had not had any access to experimental information, we would have at this point calculated the heats of formation of all viable $C_{11}H_{16}$ tetracyclic candidates by empirical force field calculations.[14,15] Estimation of the entropy and the free energies would have completed the process. Instead, we took