Regio- and Stereoselective 1,2 Wagner–Meerwein Shifts during Trifluoroacetic Acid Catalyzed Isomerization of Unsymmetrically Substituted Tricyclo[3.2.0.0^{2,4}]heptanes

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Abstract: The regioselectivity and stereoselectivity which materialize upon trifluoroacetic acid promoted isomerization of variously substituted tricyclo[3.2.0.0^{2,4}]heptanes have been experimentally determined. The highly strained hydrocarbon substrates have been prepared by cycloaddition of cyclobutadiene to 3-methyl-5-phenylisopyrazoles differently substituted at C_4, diimide reduction of these adducts to their dihydro derivatives, and photochemical extrusion of nitrogen. Particular attention is given to the question whether, in the Wagner–Meerwein shift from C_3 to C_2 or C_4, there exists a preference for migration of the endo or exo substituent. The stereochemical outcome (retention or inversion) of the rearrangement was also analyzed, with suitable deuterium labeling where required. A mechanistic scheme is proposed which accounts for the nonfavored status of the benzylic carbonium option in terms of inability on the part of the phenyl ring due to steric congestion to orient itself in-plane with the developing empty p orbital in the C_2–C_4 bond cleavage transition state. Subsequent migrations away from C_3 to C_2 or C_4 are stereoelectronically and conformationally controlled. Full retention of stereochemistry is witnessed.

Substituted derivatives of the fundamental tricyclic systems **1** and **2** have proven to be of interest because of their highly strained nature which is reflected inter alia in unusual thermal behavior[2] and facile dissolving metal reduction.[3] For example, the heating of certain tricyclo[3.2.0.0^{2,4}]hept-6-enes has been found to cause C_2–C_4 bond fission and trapping of the resultant 1,3 biradical by the neighboring nonconjugated cyclobutene double bond. Quadricyclanes are thereby produced in high yield under nonphotochemical conditions.

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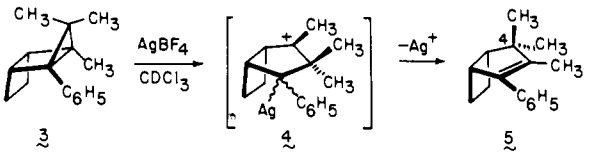


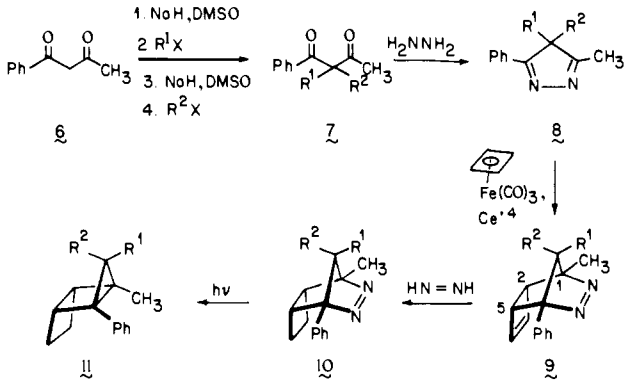
3 **4** **5**

In another development, Paquette and Leichter reported that **3** responds to the catalytic influence of silver fluoroborate by undergoing regiospecific 1,2-methyl migration and formation of **5**.[4] The finding that one of the methyl groups migrates away from the incipient benzylic carbonium-ion center was interpreted in terms of intervention by the covalently silver-bonded carbocation **4**. The high level of regiospecificity was thought possibly to be due to kinetically significant initial complexation of Ag^+ ion to the arene substituent, although the important consequences of steric control or concerted C_3-methyl migration were not ruled out.

More recently, we have found that solutions of trifluoroacetic acid in benzene also promote the quantitative isomerization of **3** to **5**. Thus, the Ag atom in **4** can equally well be replaced by H. This observation was considered to warrant a complete analysis of the factors controlling the fate of such an assembly of atoms in an acidic medium. In the present paper, therefore, we report on the overall regio- and stereoselectivity of this process. The various specific properties examined herein include the relative migratory capability of the endo and exo C_3 substituents in **3**, the level of retention or inversion of stereochemistry at C_4 in **5**, and the extent of "leakage" leading to formation of the isomeric benzylic cation intermediates.

Results

Synthesis. Access to the desired tricyclo[3.2.0.0^{2,4}]heptanes (**11a–f**) was gained by a sequence modeled after earlier strategy.[2,3] To attain maximum yields of the doubly substituted β-diketones **7**, the larger substituent must be incorporated first.[5] In this fashion, the subsequent attachment of the smaller group is not so adversely affected by steric factors and the levels of competing O-alkylation are reduced. Condensation of the geminally dialkylated β-diketones with hydrazine[2a,6] afforded the corresponding isopyrazoles **8** which were in turn subjected to Diels–Alder reaction with cyclobutadiene, as generated in situ by ceric ion oxidation of the iron tricarbonyl complex.



6 **7** **8** **9** **10** **11**

a, $R^1 = CH_3CH_2-$; $R^2 = CH_3$
b, $R^1 = PhCH_2-$; $R^2 = CH_3$
c, $R^1 = PhCH_2-$; $R^2 = CD_3$
d, $R^1 = HC\equiv CCH_2-$; $R^2 = CH_3$
e, $R^1 = H_2C=CHCH_2-$; $R^2 = CH_3$
f, $R^1 = CH_3CH_2CH_2-$; $R^2 = CH_3$

When these cycloadditions were carried out at the recommended temperatures (−5 to 0 °C), fair to good yields of azo compounds **9** were realized. Matters were found to improve substantially, however, upon lowering of the reaction temperature to −20 °C and lengthening of the reaction time. In general, 50–100% enhancements in yield were noted with this modification.

Although two stereochemical issues materialize at this point, the cycloadducts proved to be uniformly homogeneous. In

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Table I. Chemical Shifts of Selected Substituents in **9** and **10**[a]

compd	R^1	δ	R^2	δ	compd	R^1	δ	R^2	δ
9	CH_3-	0.42	CH_3-	0.93	**10**	CH_3-	0.36	CH_3-	0.73
9a	CH_3CH_2-	1.00	CH_3-	1.03	**10a**	CH_3CH_2-	0.90	CH_3-	0.91
9b	$PhCH_2$-	2.19	CH_3-	1.07	**10b**	$PhCH_2$-	2.13	CH_3-	0.89
9d	$HC{\equiv}CCH_2$-	1.78	CH_3-	1.20	**10d**	$HC{\equiv}CCH_2$-	1.70	CH_3-	0.98
9e	$H_2C{=}CHCH_2$-	1.58	CH_3-	1.01	**10e**	$H_2C{=}CHCH_2$-	1.64	CH_3	0.90

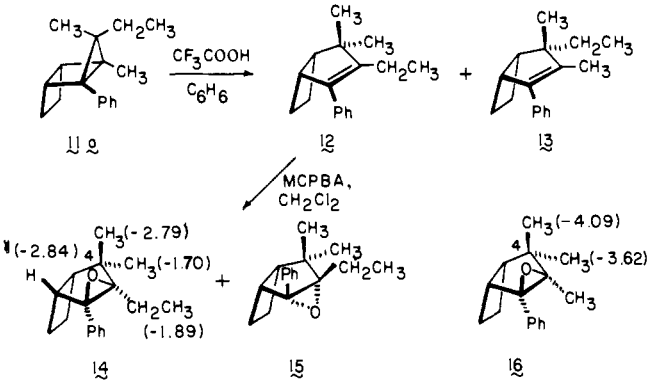
[a] $CDCl_3$ solution, 60 MHz.

earlier work, the endo orientation of the cyclobutene ring in a derivative of **9** ($R^1 = R^2 = CH_3$ and Ph at both bridgehead sites) was experimentally determined to be endo by application of nuclear Overhauser effect techniques.[2a] Additionally, its ^1H NMR spectrum consists of two methyl singlets at δ 1.04 and 0.28 (in $CDCl_3$) due to $R^1 = CH_3$ and $R^2 = CH_3$, respectively. The obvious shielding of the latter substituent is the result of its close proximity to the azo group. Secondary orbital factors are recognized to be particularly influential in those cycloadditions where cyclobutadiene is required to function as the diene component.[7,8] In line with such past observations, the spatial orientation adopted by the cyclobutene ring in **9** is assigned as endo. If such were not the case, abnormal shielding of R^1 should materialize; however, no marked chemical shift perturbations were encountered (Table I).

The preceding structural assignments were further substantiated by the results of $Eu(fod)_3$ studies[9] on **9a**, **9b**, and **9d**. To illustrate, the ΔEu values[10] for **9a** ($R^1 = CH_3CH_2$-, −2.75 and −7.42; $R^2 = CH_3$, −5.79; 1-CH_3, −6.21; H_2 and H_5, −8.83 and −9.32; H_3 and H_4, −6.15 and −7.77) show a lesser shielding to be operating on the 9-methyl substituent relative to the methylene portion of the ethyl group. Given that the europium atom is coordinated unsymmetrically to the azo group, the data require the spatial relationship of R^1 and R^2 shown. For **9b**, the ΔEu value for the benzylic CH_2 protons is significantly larger than that observed for the 9-methyl substituent, again in agreement with capture of the isopyrazole by cyclobutadiene from the less hindered surface ($R^1 = C_6H_5CH_2$-, −5.82; $R^2 = CH_3$, −4.20; 1-CH_3, −4.53; H_2 and H_5, −5.98 and −6.55; H_3 and H_4, −3.48 and −5.50). In the case of **9d**, the stereochemistry of C_9 was revealed not only by similar chemical shift changes ($R^1 = HC{\equiv}CCH_2$-, −0.51 and −6.05; H_3 and H_4, −4.18 and −5.13), but also by an enhancement in the nonequivalence of the $HC{\equiv}CCH_2$- protons from 0.15 to 0.68 ppm upon addition of 29 mol % $Eu(fod)_3$.

Reduction of the adducts **9** with excess diimide furnished the dihydro derivatives **10** in good yield. In the reaction involving **9d**, a difficultly separable mixture of **10d** and the overreduced products **10e** and **10f** were formed. Similarly, **9e** gave rise to a mixture of **10e** and **10f**. It proved most efficacious not to attempt the separation of these components until after nitrogen had been eliminated. The photoextrusions were realized in essentially quantitative yield by irradiation with a 200-W Hanovia lamp in ether solution through Pyrex. The resulting tricyclo[3.2.0.$0^{2,4}$]heptanes **11** were purified by vapor phase chromatography where necessary.

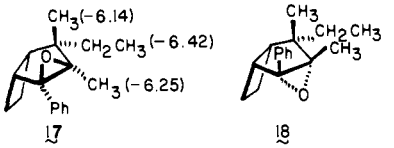
Acid Promoted Rearrangements. When a C_6D_6 solution of **3** was exposed to a small quantity of freshly distilled trifluoroacetic acid at room temperature, quantitative isomerization (^1H NMR analysis) to **5** occurred within 90 min. A mechanistically more informative example was **11a**, analogous treatment of which led efficiently to a mixture of **12** (83%) and **13** (17%). A distinction between the two isomers was made readily apparent by inspection of their ^1H NMR spectra (in $CDCl_3$). Whereas the methyl signals of **12** appear as two narrowly spaced singlets at δ 1.10 and 1.00 in accordance with the mutual attachment of these substituents to tetrahedral carbon, the analogous signals in **13** are more widely disparate [δ 1.66 (d, J = 1.8 Hz) and 0.94 (s)]. The downfield chemical shift and



long range spin interaction associated with the first of this pair of peaks attests to the allylic nature of this methyl group.

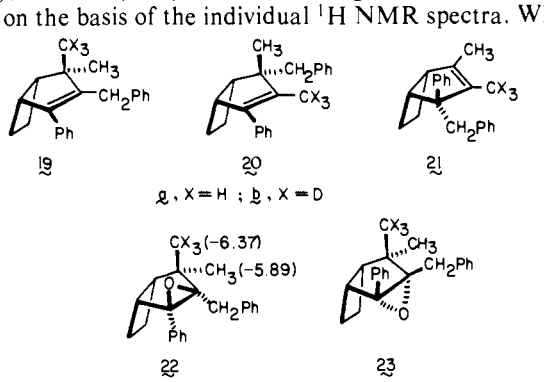
Peracid epoxidation of **12** gave a mixture of **14** (64%) and **15** (36%). After separation of these isomers by preparative layer chromatography, suitable lanthanide shift experiments were conducted with $Eu(fod)_3$. Exo epoxide **14** responded classically and the observed ΔEu values have been incorporated alongside the structural formula. Correlation of these data with those reported earlier for **16** shows the exo-oriented methyl group at C_4 to be more highly responsive to the presence of the lanthanide as expected. In contrast to the behavior of **14**, epoxide **15** showed little chemical shift alteration when quantities of $Eu(fod)_3$ of up to 35.7 mol % were added. Evidently, the epoxide oxygen in this isomer is too sterically encumbered for ready complexation to the europium reagent.

To ascertain the stereochemistry of hydrocarbon **13**, recourse was again made to epoxidation. The major product (89%) was identified as **17** on the basis of the measured ΔEu



values (see structural formula). Significantly, therefore, the ethyl group migrates with retention of its syn relationship to the cyclobutane ring.

A persistence for predominant methyl group migration was also encountered in the case of a benzyl derivative **11b**, which was transformed under analogous conditions to **19a** (66%), **20a** (13%), and **21a** (21%). Structural assignments were formulated on the basis of the individual ^1H NMR spectra. While



19a is characterized by a pair of three-proton singlets at δ 0.88 and 0.84, **20a** shows a singlet of area 3 at δ 0.82 and a narrow doublet (J = 2 Hz) of equal weight at 1.78. Third component **21a** is unique in featuring two trigonally bound methyl groups at δ 1.68 and 1.20.

The stereochemical course of the more prominent rearrangement pathway was elucidated by making recourse to **11c** which gave rise to **19b–21b** in similar proportions when treated with trifluoroacetic acid in benzene. Through peracid oxidation of **19a** and **19b**, the epoxides **22** and **23** (ratio 1:1) were made available. As before, exo epoxide **22a** responded systematically to the addition of incremental amounts of Eu(fod)$_3$, whereas no change was observed with **23a** in the presence of shift reagent levels as high as 75 mol %. The more intensely deshielded exo methyl singlet of **22a** was absent in the ^{1}H NMR spectrum of **22b**.

Further studies of similar type established that the propargyl derivative **11d** rearranged with formation of essentially homogeneous **24a**, whereas allyl example **11e** was subject to lesser domination by the 9-methyl group (63% **24b**, 37% **25b**). Propyl

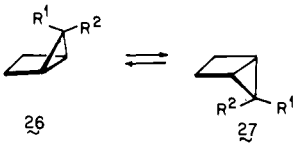
24 **25**

c, R = $-CH_2C{\equiv}CH$; **b**, R = $-CH_2CH{=}CH_2$, **c**, R = $-CH_2CH_2CH_3$

analogue **11b** more closely approximated the acetylenic example in behavior (91% **24c**, 9% **25c**). The stereochemistries of **25b** and **25c** were formulated on the basis of the close similarity of their C$_4$-methyl shifts to that of **13**.

Discussion

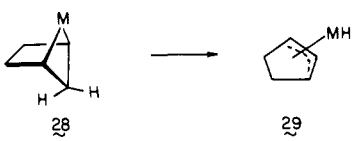
The thermally induced stereomutation of 2-[11] and 5-substituted bicyclopentanes[12] has attracted considerable experimental attention and theoretical scrutiny.[13] In general, the energy demands for stereomutation of the type **26** $\rightleftharpoons$ **27** fall



26 **27**

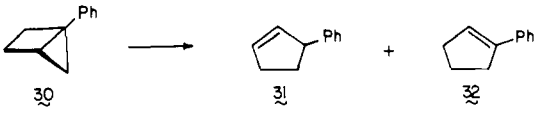
into the range of 35–40 kcal/mol. However, the presence of π-donor substituents at C$_5$ is known to lower somewhat the barrier to ring flip isomerization, as expected from the usual remote cyclopropane bond weakening effects which come into play as the result of antibonding interactions with such groups.[14]

Bicyclo[2.1.0]pentanes are also subject to transition metal promoted isomerization.[15-17] With rhodium(I) catalysts in particular, rearrangement to a cyclopentene is believed to result from initial oxidative addition to the strained central bond (see **28**), abstraction of the exo-C$_5$ hydrogen to form an allylrhodium hydride of type **29**, and decomposition of the latter to



28 **29**

olefin and metal complex. Normally, Lewis acid catalysts of the Fe(III), Ni(II), Cd(II), Mg(II), Zn(II), Hg(II), and Ag(I) are inactive under comparable conditions. In a particularly relevant study, however, McKinney and Chou reported that 1-phenylbicyclo[2.1.0]pentane (**30**) could be isomerized with zinc iodide and silver tetrafluoroborate, as well as rhodium dicarbonyl chloride dimer.[17] These workers observed high regiospecificity in the first instance; only **31** was produced.

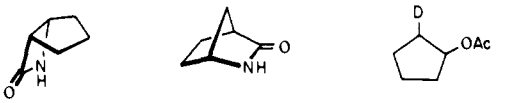


30 **31** **32**

ZnI_2	100 %	
$AgBF_4$	28 %	72 %
$[Rh(CO)_2Cl]_2$	56 %	44 %

Mixtures of **31** and **32** were seen with the other catalysts examined. At the mechanistic level, metallocyclic intermediates such as **28**, or a metal assisted concerted [$_\sigma 2_s + {}_\sigma 2_2$] pericyclic pathway were proposed.

Electrophilic additions to bicyclo[2.1.0]pentanes have been less extensively studied.[18] In 1965, LaLonde reported that halogen addition to the parent hydrocarbon proceeds with rearrangement to give principally 1,2-dihalocyclopentanes rather than the 1,3 isomers.[19] Similar rearrangement has been encountered with chlorosulfonyl isocyanate, cycloaddition giving rise to β-lactam **33**[20] and not 2-azabicyclo[2.2.1]heptan-3-one (**34**).[21] Analogously, acetic acid-*O*-*d* adds to bicyclo[2.1.0]pentane to give **35**.[22] In each of these examples, the

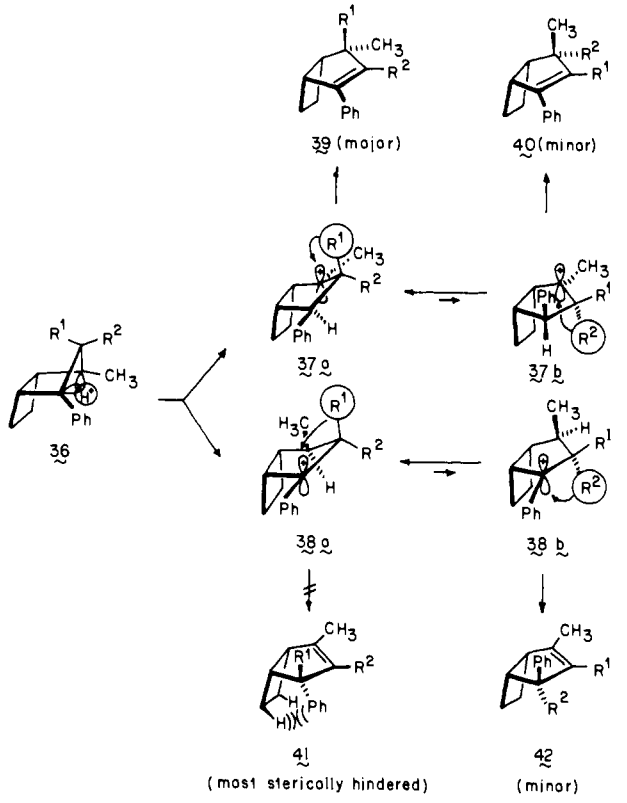


33 **34** **35**

simplest mechanistic interpretation consistent with the available facts consists of electrophilic attack at the central bond, 1,2 migration of a hydrogen from the one-carbon bridge, and counterion attack at the new electron-deficient center to deliver rearranged product.

The structural similarity of tricyclo[3.2.0.0^{2,4}]heptanes suggests that their acid catalyzed rearrangement is also initiated by proton attack at the highly strained C$_2$–C$_4$ bond (cf. **36**). Advocacy of such a carbonium-ion pathway takes its justification largely from the internal consistency of the scheme, a key portion of which is the observed Wagner–Meerwein migration of R^1 (preferred) or R^2 away from C$_3$. The bond-breaking process in **36** can lead to **37** or **38** (Scheme 1). It is not presently known whether these cations are formed reversibly from **36**. Consequently, discussion in agreement with the experimental findings is offered for both sets of circumstances. If the interconversion of **37** and **38** is *not* rapid, it must be argued that the transition state leading to **38** cannot take full advantage of resonance delocalization with the aromatic ring. Analysis of molecular models reveals that steric factors might preclude proper rotational alignment of the phenyl pπ orbitals with the developing empty π orbital at C$_4$ until such time as the bond is fully cleaved and C$_2$ has become completely disconnected from C$_4$. On this basis, a greater fraction of activation energy must be provided to overcome the adverse electronegativity characteristics of the adjoining "twisted" phenyl ring. Since opening in the direction which leads to tertiary carbocation **37** is not dependent on the attainment of an appropriate rotamer, the rate of production of this intermediate cannot be adversely affected in an analogous way and could dominate kinetically. For migration to occur from C$_3$ to C$_2$ in **37** or to C$_4$ in **38**, the C–C bonds to R^1 and R^2 must be colinearly aligned with the vacant pπ orbital. As visualized in **37a**/**37b** and **38a**/**38b**, only two conformations encompass this stereoelectronic requirement. Of the pair of alternatives, the "**a**" series is obviously much less sterically congested than the "**b**" series. However, whereas the conversion of **37a** into **39** is seen to be favored, the production of **41** from **38a** is not. Since molecular models reveal **41** to be the most sterically hindered of the possible products (**39–42**), this process is understandably disfavored from the thermodynamic viewpoint. It might be

Scheme I



argued that **37a** and **38a** are so similar to starting material that R^1 migration in concert with C_2–C_4 bond cleavage is feasible. This eventuality does not take on significance with **38a**. Additionally, to the extent that leakage from **37a** to **40** via **37b** occurs in those examples where R^2 is a respectable migrating group, we see no compelling reason to adhere to a concerted mechanism.

Should **37** and **38** be in *rapid*, reversible equilibrium, **38** should be favored for the usual reasons of benzylic carbonium-ion stability. However, the migration of R^1 or R^2 to the cationic center of **38** should be much slower than the related process in **37** because of the delocalizing effect on the positive charge by the phenyl group. Considerable precedent is available for this migratory discrimination in the form of earlier work by Collins,[23] Bonner,[24] and their co-workers. Pinacol rearrangements and deamination studies have both provided strong evidence for the conclusion that an increase in charge delocalization at the migration terminus of a carbocation intermediate leads to a reduction in the level of migration which subsequently materializes. The dichotomy involving **37** and **38** may thus be viewed as a further example which illustrates the point that a more stable cation provides less driving force for 1,2 shifting that does a less stable cation.

In either mechanistic situation, the strict adherence to retention of stereochemistry during alkyl migration is the obvious result of stereoelectronic control.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 467 spectrometer. The ^{1}H NMR spectra were determined with a Varian T-60 instrument and apparent splittings are given in all cases. Mass spectra were measured on an AEI-MS9 spectrometer at an ionizing energy of 70 eV. Microanalytical determinations were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

3,4-Dimethyl-4-ethyl-5-phenylisopyrazole (8a). A 2.20-g (45.7 mmol) sample of 50% sodium hydride oil dispersion was washed three times with dry pentane under a nitrogen atmosphere and freshly distilled dimethyl sulfoxide (50 mL) was added. A solution of benzoylacetone (7.40 g, 45.7 mmol) in dimethyl sulfoxide (50 mL) was added dropwise with stirring. After completion of the addition, reaction was allowed to occur during 45 min at which point 7.13 g (45.7 mmol) of ethyl iodide was added. After being stirred overnight, the reaction mixture was treated with water (150 mL) and extracted with ether. The combined ethereal layers were washed with water, dried, and concentrated under reduced pressure to give 8.30 g (95.6%) of monoethyl derivative: bp 87–95 °C (0.3–0.4 mm) [lit.[25] bp 155–157 °C (20 mm); lit.[26] bp 135–138 °C (10 mm)]; ^{1}H NMR (δ, $CDCl_3$) 8.0–7.25 (m, 5 H), 4.33 (t, J = 7 Hz, 1 H), 2.16 (s, 3 H), 2.10 (m, 2 H), and 0.34 (t, J = 7 Hz, 3 H).

To a slurry of pentane-washed sodium hydride (50% in oil, 2.10 g, 43.7 mmol) in freshly distilled dimethyl sulfoxide (50 mL) was added dropwise a solution of the above β-diketone (8.30 g, 43.7 mmol) in 50 mL of the same solvent. After 45 min of stirring, methyl iodide (6.33 g, 43.7 mmol) was introduced and reaction allowed to proceed overnight. Workup and concentration as above afforded 7.36 g (82.6%) of **7a**: bp 95–102 °C (0.4–0.5 mm); ν_{max}^{neat} 1712 and 1676 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.8–7.25 (m, 5 H), 2.10 (q, J = 8 Hz, 2 H), 2.07 (s, 3 H), 1.43 (s, 3 H), and 0.97 (t, J = 8 Hz, 3 H); m/e calcd 204.1150, obsd 204.1153.

A solution of **7a** (7.36 g, 36 mmol) and hydrazine hydrate (1.80 g, 36 mmol) in 50 mL of carbon tetrachloride was heated at reflux for 1 h. An additional 1.80 g of hydrazine hydrate was introduced and the mixture was heated overnight. The organic layer was separated, washed with water, dried, and concentrated under reduced pressure. Distillation of the residue gave 4.89 g (68%) of **8a**: bp 130–135 °C (0.2 mm); ν_{max}^{neat} 1578 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.8–7.2 (m, 5 H), 2.18 (s, 3 H), 1.92 (q, J = 7.8 Hz, 2 H), 1.40 (s, 3 H), and 0.45 (t, J = 7.8 Hz, 3 H); m/e calcd 200.1313, obsd 200.1317.

4-Benzyl-3,4-dimethyl-5-phenylisopyrazole (8b). The anion generated from 7.0 g (43 mmol) of benzoylacetone and 2.06 g (43 mmol) of 50% sodium hydride oil dispersion in a total of 100 mL of dry dimethyl sulfoxide was treated with 7.4 g (43 mmol) of benzyl bromide and stirred overnight. The predescribed workup afforded 9.33 g (86.4%) of the monobenzyl derivative: bp 170–180 °C (0.4–0.5 mm) (lit.[26] mp 55–56 °C); ν_{max}^{neat} 1715 and 1670 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.9–7.1 (m, 10 H), 4.76 (t, J = 7 Hz, 1 H), 3.28 (d, J = 7 Hz, 2 H), and 2.08 (s, 3 H).

The anion generated from this diketone (9.33 g, 37 mmol) was methylated in the predescribed manner. After removal of solvent, there remained a white crystalline solid which was recrystallized once from ethanol–hexane to give 5.79 g (58.8%) of **7b**: mp 96.5–97 °C (lit.[27] mp 104–105.5 °C; lit.[28] mp 105–106 °C); $\nu_{max}^{CCl_4}$ 1725 and 1670 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 8.0–6.9 (m, 10 H), 3.43 (m, 2 H), 2.12 (s, 3 H), and 1.38 (s, 3 H).

A solution of **7b** (15.5 g, 0.058 mol) in 100 mL of carbon tetrachloride was heated with a total of 3.8 g (0.116 mol) of hydrazine hydrate as described above. There was obtained 10.5 g (69%) of **8b** as a colorless crystalline solid: mp 111–112 °C (from ether–chloroform); $\nu_{max}^{CHCl_3}$ 2920, 1578, 1440, 1380, 1350, and 905 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.9 (m, 2 H), 7.4 (m, 3 H), 7.0 (m, 3 H), 6.7 (m, 2 H), 3.38 and 3.04 (AB q, J = 14 Hz, 2 H), 2.24 (s, 3 H), and 1.62 (s, 3 H); m/e calcd 262.1470, obsd 262.1473. Anal Calcd for $C_{18}H_{18}N_2$: C, 82.40; H, 6.92. Found: C, 82.38; H, 6.89.

4-Benzyl-3-methyl-4-methyl-d_3-5-phenylisopyrazole (8c). The anion generated from 4.34 g (0.090 mol) of monobenzylated benzoylacetone was treated with 13.11 g (0.090 mol) of methyl-d_3 iodide in the predescribed manner. Workup and product isolation furnished 23.37 g (96%) of **7c**: ^{1}H NMR (δ, $CDCl_3$) 8.15–6.92 (m, 10 H), 3.42 (s, 2 H), and 2.27 (s, 3 H).

A solution of **7c** (23.37 g, 86.9 mmol) in carbon tetrachloride (50 mL) was heated overnight at reflux with a total of 5.56 g (173.8 mmol) of hydrazine hydrate which was added in two portions (see above). Product isolation gave 14.74 g (64%) of **8c** as pale yellow crystals: mp 106.5–108 °C; ^{1}H NMR (δ, $CDCl_3$) 8.16–6.63 (m, 10 H), 3.15 (q, J = 14 Hz, 2 H), and 1.42 (s, 3 H); m/e calcd 265.1658, obsd 265.1663.

3,4-Dimethyl-5-phenyl-4-propargylisopyrazole (8d). From 30 g (0.185 mol) of benzoylacetone, 8.89 g (0.184 mol) of 50% sodium hydride oil dispersion, and 27.5 g (0.185 mol) of propargyl bromide (80% purity) in 150 mL of dimethyl sulfoxide, there was obtained 31.3 g (84.6%) of monoalkylated product: bp 110–115 °C (0.4 mm); ^{1}H NMR (δ, $CDCl_3$) 8.1–7.25 (m, 5 H), 4.70 (d of t, J = 7 and 2 Hz, 1 H), 2.83 (m, 2 H), 2.21 (s, 3 H), and 2.02 (t, J = 2 Hz, 1 H).

The anion generated from this diketone (15.0 g, 75 mmol) and 50% sodium hydride oil dispersion (3.6 g, 75 mmol) in dimethyl sulfoxide

solution (100 mL) was methylated with methyl iodide (10.87 g, 75 mmol) in the predescribed fashion. There was obtained 11.85 g (73.8%) of **7d**: bp 105–115 °C (0.4–0.5 mm); ν_{max}^{neat} 3291, 1717, and 1676 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.8–7.2 (m, 5 H), 3.02 (dd, J = 6.5 and 2.5 Hz, 2 H), 2.17 (s, 3 H), 2.01 (t, J = 2.5 Hz, 1 H), and 1.63 (s, 3 H); m/e calcd 214.0994, obsd 214.0997.

From the reaction of 11.85 g (0.055 mol) of **7d** with a total of 5.54 g (0.11 mol) of hydrazine hydrate in 50 mL of carbon tetrachloride, there was obtained 6.24 g (54%) of **8d** as a colorless crystalline solid: mp 114.5 °C (from ethanol); ν_{max}^{KBr} 3231 and 1580 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 8.0–7.2 (m, 5 H), 2.68 (d, J = 2 Hz, 2 H), 2.28 (s, 3 H), 1.93 (t, J = 2 Hz, 1 H), and 1.43 (s, 3 H); m/e calcd 210.1157, obsd 210.1161. Anal Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71. Found: C, 79.79; H, 6.67.

4-Allyl-3,4-dimethyl-5-phenylisopyrazole (8e). From 13.5 g (0.083 mol) of benzoylacetone, 4.00 g (0.083 mol) of 50% sodium hydride oil dispersion, and 10.08 g (0.083 mol) of allyl bromide in 100 mL of freshly distilled dimethyl sulfoxide, there was obtained 14.3 g (85%) of monoallylated diketone: bp 104–114 °C (0.4–0.5 mm); ^{1}H NMR (δ, $CDCl_3$) 8.1–7.2 (m, 5 H), 5.60 (m, 1 H), 5.10 (m, 2 H), 4.58 (t, J = 7 Hz, 1 H), 2.90 (br t, J = 7 Hz, 2 H), and 2.18 (s, 3 H).

Reaction of the anion of the above diketone (12.0 g, 0.059 mol) with methyl iodide (28.2 g, 0.20 mol) in dimethyl sulfoxide (100 mL) gave 11.3 g (88%) of **7e**: bp 95–105 °C (0.5–0.6 mm); ν_{max}^{neat} 1714 and 1676 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.8–7.2 (m, 5 H), 5.40 (m, 1 H), 5.07 (m, 2 H), 2.76 (br d, 2 H), 2.11 (s, 3 H), and 1.47 (s, 3 H); m/e calcd 216.1150, obsd 216.1154.

To a solution of **7e** (11.65 g, 0.054 mol) in carbon tetrachloride (50 mL) was added 2.70 g (0.054 mol) of hydrazine hydrate and the mixture was heated at the reflux temperature for 1 h. An additional 2.70 g of hydrazine hydrate was introduced and heating was continued overnight. The usual workup led to the isolation of 8.36 g (73%) of **8e**: bp 95–105 °C (0.5–0.6 mm); the pale yellow oil turned red on standing; ν_{max}^{neat} 1579 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 8.0–7.2 (m, 5 H), 5.15–4.75 (complex m, 3 H), 2.63 (m, 2 H), 2.22 (s, 3 H), and 1.41 (s, 3 H); m/e 212.1313, obsd 212.1316.

***endo*-7,8-Diaza-1,8-dimethyl-9-ethyl-6-phenyltricyclo[4.2.1.0^{2,5}]-nona-3,7-diene (9a).** Isopyrazole **8a** (2.71 g, 0.0136 mol) and cyclobutadieneiron tricarbonyl (2.33 g, 0.0136 mol) dissolved in acetone (300 mL) were introduced into a 500-mL round-bottomed flask under nitrogen and the yellow solution was cooled to −20 °C. Ceric ammonium nitrate (37.2 g, 0.068 mol) was added in small portions over 2 h while the temperature was maintained at −18 to −20 °C. Upon completion of the addition, the mixture was stirred at −20 °C for 30 min. The cooling bath was removed for 10 min and the reaction mixture was poured into 500 mL of ether and filtered. The ethereal solution was washed with water (3 × 10 mL), dried, filtered, and evaporated. The crude product was chromatographed on silica gel (elution with 10% ether in pentane) to give 1.40 g (41%) of **9a** as a clear viscous oil which was purified by preparative VPC on a 2 ft × 0.25 in. 5% SE-30 column at 157 °C: ν_{max}^{neat} 1604 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.82–7.04 (m, 5 H), 5.96 (br d, J = 3 Hz, 1 H), 5.88 (br d, J = 3 Hz, 1 H), 3.55 (br d, J = 4 Hz, 1 H), 3.00 (br d, J = 4 Hz, 1 H), 1.67 (s, 3 H), 1.03 (s, 3 H), 1.00 (q, J = 7 Hz, 2 H), and 0.38 (t, J = 7 Hz, 3 H); m/e ($M^+ - N_2$) calcd 224.1565, obsd 224.1570. Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99. Found: C, 81.36; H, 8.23.

***endo*-9-Benzyl-7,8-diaza-1,9-dimethyl-6-phenyltricyclo[4.2.1.0^{2,5}]-nona-3,7-diene (9b).** Reaction of **8b** (2.00 g, 7.63 mmol) and cyclobutadieneiron tricarbonyl (1.32 g, 7.63 mmol) dissolved in 160 mL of dry acetone with ceric ammonium nitrate (33.5 g, 61 mmol) at −20 °C in the predescribed manner gave 723 mg (30.2%) of **9b** as a colorless solid: mp 90–91 °C (from hexane); ν_{max}^{neat} 3020, 3000, 2925, 1625, 1490, 1445, 1380, 1275, 905, 850, 750, and 700 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.9–6.5 (m, 10 H), 5.97 (m, 2 H), 3.40 (d, J = 3 Hz, 1 H), 2.95 (d, J = 3 Hz, 1 H), 2.19 (d, J = 4.5 Hz, 2 H), 1.60 (s, 3 H), and 1.07 (s, 3 H); m/e ($M^+ - N_2$) calcd 286, obsd 286. Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05. Found: C, 84.21; H, 7.15.

***endo*-9-Benzyl-7,8-diaza-1-methyl-9-methyl-d_3-6-phenyltricyclo-[4.2.1.0^{2,5}]nona-2,7-diene (9c).** From 3.60 g (0.0136 mol) of **8c**, 2.34 g (0.0136 mol) of cyclobutadieneiron tricarbonyl, and 59.6 g (0.109 mol) of ceric ammonium nitrate, there was obtained 1.47 g (34%) of **9c** which was without further purification: ^{1}H NMR (δ, $CDCl_3$) 8.0–6.4 (m, 10 H), 5.85 (m, 2 H), 3.36 (d, J = 3 Hz, 1 H), 2.89 (d, J = 3 Hz, 1 H), 2.10 (d, J = 4.5 Hz, 2 H), and 1.62 (s, 3 H).

***endo*-7,8-Diaza-1,9-dimethyl-6-phenyl-9-propargyltricyclo-[4.2.1.0^{2,5}]nona-3,7-diene (9d).** From 2.25 g (10.71 mmol) of **8d**, 2.02 g (11.78 mmol) of cyclobutadieneiron tricarbonyl, and 46.98 g (85.68 mmol) of ceric ammonium nitrate, there was obtained 927 mg (33%) of **9d** as a viscous colorless oil: ν_{max}^{neat} 3301 and 1602 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.8–6.8 (m, 5 H), 6.03 (br d, J = 3.5 Hz, 1 H), 5.94 (br d, J = 3.5 Hz, 1 H), 3.60 (br d, J = 3.5 Hz, 1 H), 3.07 (br d, J = 3.5 1 H), 1.83 (s, 3 H), 1.80 (d, J = 3 Hz, 2 H), 1.68 (t, J = 3 Hz, 1 H), and 1.20 (s, 3 H); m/e ($M^+ - N_2$) calcd 234.1408, obsd 234.1414.

***endo*-9-Allyl-7,8-diaza-1,9-dimethyl-6-phenyltricyclo[4.2.1.0^{2,5}]-nona-3,7-diene (9e).** From 1.50 g (7.08 mmol) of **8e**, 1.22 g (7.08 mmol) of cyclobutadieneiron tricarbonyl, and 23.28 g (42.48 mmol) of ceric ammonium nitrate, there was obtained 636 mg (34%) of **9e** as a colorless crystalline solid: mp 63.5–64 °C (from hexane); ^{1}H NMR (δ, $CDCl_3$) 7.9–7.2 (m, 5 H), 6.00 (br d, J = 2 Hz, 1 H), 5.87 (br d, J = 2 Hz, 1 H), 5.4–4.4 (m, 3 H), 3.52 (br d, J = 3.5 Hz, 1 H), 3.00 (br d, J = 3.5 Hz, 1 H), 1.72 (s, 3 H), 1.58 (br d, J = 4 Hz, 2 H), and 1.01 (s, 3 H); m/e ($M^+ - N_2$) calcd 236.1564, obsd 236.1569. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63. Found: C, 81.72; H, 7.49.

***endo*-7,8-Diaza-1,9-dimethyl-9-ethyl-6-phenyltricyclo[4.2.1.0^{2,5}]-non-7-ene (10a). General Diimide Reduction Procedure.** To a solution of **9a** (150 mg, 0.595 mmol) and dipotassium azodicarboxylate (2.31 g, 11.90 mmol) in dry methanol (50 mL) was added acetic acid (11.90 mmol) dropwise. The reaction mixture was stirred for an additional 30 min and poured into 50 mL of water. The product was extracted into ether (3 × 25 mL) and the combined organic layers were washed with saturated sodium bicarbonate solution (25 mL) and brine (25 mL) prior to drying and evaporation of solvent. Preparative layer chromatography gave 146 mg (97%) of **10a**: ν_{max}^{neat} 1602 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.8–7.2 (m, 5 H), 3.05 (br m, 1 H), 2.67 (br m, 1 H), 1.84–1.60 (m, 4 H), 1.74 (s, 3 H) 0.90 (q, J = 7 Hz, 2 H), 0.85 (s, 3 H), and 0.38 (t, J = 7 Hz, 3 H); m/e ($M^+ - N_2$) calcd 226.1721, obsd 226.1727.

***endo*-9-Benzyl-7,8-diaza-1,9-dimethyl-6-phenyltricyclo[4.2.1.0^{2,5}]-non-7-ene (10b).** Reduction of 130 mg of **9b** furnished 118 mg (90%) of **10b**: colorless solid; mp 86–87 °C (from isooctane); $\nu_{max}^{CHCl_3}$ 1600 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.90–6.58 (m, 10 H), 3.09 (br m, 1 H), 2.56 (br m, 1 H), 2.11 (d, J = 4 Hz, 2 H), 1.95–1.60 (m, 4 H), 1.60 (s, 3 H), and 0.88 (s, 3 H); m/e ($M^+ - N_2$) 288. Anal. Calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64. Found: C, 83.52; H, 7.71.

***endo*-9-Benzyl-7,8-diaza-1-methyl-9-methyl-d_3-6-phenyltricyclo[4.2.1.0^{2,5}]non-7-ene (10c).** Reduction of 318 mg of **9c** provided 296 mg (93%) of **10c**: ^{1}H NMR (δ, $CDCl_3$) 7.85–6.45 (m, 10 H), 3.05 (br m, 1 H), 2.60 (br m, 1 H), 2.10 (d, J = 4 Hz, 2 H), 1.95–1.60 (m, 4 H), and 1.60 (s, 3 H); m/e ($M^+ - N_2$) calcd 291.2066, obsd 291.2071.

Diimide Reductions of 9d and 9e. When **9d** was subjected to the reaction conditions described above, there was produced a difficultly separable mixture of **10d**, **10e**, and **10f**. This mixture was directly subjected to photolysis (see below). In the case of **9e**, a mixture of **10e** and **10f** was also produced and photolyzed without separation of the components.

General Photolysis Procedure. A solution of **10** (150–650-mg sample) in 20 mL of ether contained in a quartz tube was irradiated with a 200-W Hanovia lamp fitted with a Pyrex filter and housed in a water-cooled quartz well. After 3 h, the conversion into product was complete (TLC analysis). In all cases, the conversion was essentially quantitative.

***anti*-2,3-Dimethyl-3-ethyl-4-phenyltricyclo[3.2.0.0^{2,4}]heptane (11a):** clear colorless oil; ^{1}H NMR (δ, $CDCl_3$) 7.20–7.05 (m, 5 H), 2.70 (br m, 1 H), 2.40 (br m, 1 H), 2.35–1.7 (m, 4 H), 1.43 (s, 3 H), 1.03 (s, 3 H), and 1.15–0.75 (m, 5 H); m/e calcd 226.1721, obsd 226.1725. Anal Calcd for $C_{17}H_{22}$: C, 90.27; H, 9.73. Found: C, 90.23; H, 9.94.

***anti*-3-Benzyl-2,3-dimethyl-4-phenyltricyclo[3.2.0.0^{2,4}]heptane (11b):** clear colorless oil; ^{1}H NMR (δ, $CDCl_3$) 7.58–6.76 (m, 10 H), 2.86–1.65 (m, 6 H), 2.48 (d, J = 3 Hz, 2 H), 1.57 (s, 3 H), and 1.02 (s, 3 H); m/e calcd 228.1978, obsd 228.1881. Anal. Calcd for $C_{22}H_{24}$: C, 91.61; H, 8.39. Found: C, 91.20; H, 8.42.

***anti*-3-Benzyl-2-methyl-3-methyl-d_3-4-phenyltricyclo[3.2.0.0^{2,4}]-heptane (11c):** clear colorless oil; ^{1}H NMR (δ, $CDCl_3$) 7.58–6.76 (m, 10 H), 2.86–1.65 (m, 6 H), 2.48 (d, J = 3 Hz, 2 H), and 1.57 (s, 3 H); m/e calcd 291.2066, obsd 291.2073.

***anti*-2,3-Dimethyl-4-phenyl-3-propargyltricyclo[3.2.0.0^{2,4}]heptane (11d)** was separated from **11e** and **11f** by preparative layer chromatography on silica gel (elution with hexane) and obtained as a colorless oil: ^{1}H NMR (δ, $CDCl_3$) 7.2–7.0 (m, 5 H), 2.80–1.70 (series of m,

9 H), 1.44 (s, 3 H), and 1.26 (s, 3 H); *m/e* calcd 236.1565, obsd 236.1571. Anal Calcd for $C_{18}H_{20}$: C, 91.53; H, 8.47. Found: C, 91.21; H, 8.53.

***anti*-3-Allyl-2,3-dimethyl-4-phenyltricyclo[3.2.0.0^{2,4}]heptane (11e):** colorless oil; ^{1}H NMR (δ, $CDCl_3$) 7.4–7.1 (m, 5 H), 6.05–5.35 (m, 1 H), 5.05–4.60 (m, 2 H), 2.80–1.60 (series of m, 8 H), 1.44 (s, 3 H), and 1.05 (s, 3 H); *m/e* calcd 238.1721, obsd 238.1727. Anal. Calcd for $C_{18}H_{22}$: C, 90.76; H, 9.24. Found: C, 90.49; H, 9.43.

***anti*-2,3-Dimethyl-4-phenyl-3-propyltricyclo[3.2.0.0^{2,4}]heptane (11f):** colorless oil; ^{1}H (δ, $CDCl_3$) 7.35–7.10 (m, 5 H), 2.80–1.90 (series of m, 6 H), 1.40 (s, 3 H), 1.30–.95 (m, 4 H), 1.04 (s, 3 H), and 0.70 (t, J = 8 Hz, 3 H); *m/e* calcd 240.1877, obsd 240.1882. Anal. Calcd for $C_{18}H_{22}$: C, 89.94; H, 10.06. Found: C, 89.97; H, 10.02.

Rearrangement of 11a. To a solution of 340 mg (1.5 mmol) of **11a** in 3.75 mL of benzene was added 0.5 mL of freshly distilled trifluoroacetic acid. After 2 h, the mixture was transferred to a separatory funnel, an additional 15 mL of benzene was added, and the mixture was washed with water (10 mL), saturated sodium bicarbonate (10 mL), and brine solutions (10 mL) prior to drying. After solvent removal, there remained 340 mg (100%) of a mixture of **12** (83%) and **13** (17%) which was separated by preparative VPC (4 ft × 0.25 in. 5% SE-30 at 165 °C.

12: ^{1}H NMR (δ, $CDCl_3$) 7.24 (m, 5 H), 3.46 (br m, 1 H), 2.55 (br m, 1 H), 2.30–1.40 (series of m, 6 H), 1.10 (s, 3 H), 1.07 (t, J = 7.5 Hz, 3 H), and 1.00 (s, 3 H); *m/e* calcd 226.1721, obsd 226.1725. Anal. Calcd for $C_{17}H_{22}$: C, 90.27; H, 9.73. Found: C, 90.36; H, 10.08.

13: ^{1}H NMR (δ, $CDCl_3$) 7.25 (m, 5 H), 3.52 (br m, 1 H), 2.60 (br m, 1 H), 2.40–1.80 (series of m, 4 H), 1.66 (d, J = 1.8 Hz, 3 H), 1.44 (q, J = 7.8 Hz, 2 H), 0.94 (s, 3 H), and 0.80 (t, J = 7.8 Hz, 3 H); *m/e* calcd 226.1721, obsd 226.1725. Anal. Calcd for $C_{17}H_{22}$: C, 90.27; H, 9.73. Found: C, 90.21; H, 9.79.

Epoxidation of 12. To a stirred ice-cold mixture of **12** (22.6 mg, 0.1 mmol) and sodium bicarbonate (16 mg) in dichloromethane (1 mL) was added dropwise a solution of *m*-chloroperbenzoic acid (25 mg) in 1 mL of the same solvent. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. After the addition of more dichloromethane (10 mL), the organic phase was washed with water (5 mL), saturated sodium bicarbonate solution (5 mL), and water (5 mL) prior to drying. After concentration, there was isolated 23 mg (95%) of a mixture of **14** (64%) and **15** (36%) which was separated by preparative layer chromatography on silica gel (elution with 5% ether in hexane).

14: ^{1}H NMR (δ, $CDCl_3$) 7.30 (m, 5 H), 3.02 (br s, 1 H), 2.40–1.60 (series of m, 5 H), 1.20 (m, 2 H), 1.22 (s, 3 H), 1.15 (s, 3 H), and 0.80 (t, J = 7.8 Hz, 3 H); *m/e* calcd 242.1670, obsd 242.1674. Anal. Calcd for $C_{17}H_{22}O$: (C, 84.30; H, 9.09. Found: C, 84.41; H, 9.12.

15: ^{1}H (δ, $CDCl_3$) 7.30 (m, 5 H), 3.05 (br m, 1 H), 2.41 (br m, 1 H), 2.20–1.50 (series of m, 4 H), 1.10 (m, 2 H), 1.14 (s, 3 H), 1.00 (s, 3 H), and 0.90 (t, J = 7 Hz, 3 H); *m/e* calcd 242.1670, obsd 242.1674. Anal. Calcd for $C_{17}H_{22}O$: C, 84.30; H, 9.09. Found: C, 84.69; H, 9.19.

General Procedure for the Eu(fod)$_3$ Shift Experiments. The ^{1}H NMR spectrum of the epoxide in $CDCl_3$ solution was recorded. The solution was transferred to a vial containing a weighed amount of Eu(fod)$_3$. After dissolution, the solution was returned to the tube; 1 or 2 drops of $CDCl_3$ were used to rinse the vial and to maintain the concentration roughly constant. The spectrum was recorded and the process was repeated. After several spectra were in hand, the ΔEu values were calculated by the literature method.[10]

Epoxidation of 13. Oxidation of an impure sample of **13** (18 mg) with 10.1 mg of *m*-chloroperbenzoic acid as described above afforded a mixture of **17** (89%) and **18** (11%) which was separated by preparative VPC on the 5% SE-30 column. A total of 8 mg of **17** was obtained.

17: ^{1}H NMR (δ, $CDCl_3$) 7.33–7.18 (m, 5 H), 2.98 (br m, 1 H), 2.66–1.14 (series of m, 7 H), 1.00 (s, 3 H), 0.92 (s, 3 H), and 0.80 (t, J = 8 Hz, 3 H); *m/e* calcd 242.1671, obsd 242.1676.

18: ^{1}H NMR (δ, $CDCl_3$) 7.26 (m, 5 H), 2.91 (br m, 1 H), 2.6–1.4 (series of m, 5 H), 1.08 (s, 3 H), 1.02 (s, 3 H), 0.95 (q, J = 8 Hz, 2 H), and 0.83 (t, J = 8 Hz, 3 H); *m/e* calcd 242.1671, obsd 242.1676.

Rearrangement of 11b. In an NMR tube were placed 35.7 mg (0.124 mol) of **11b**, 0.35 mL of $CDCl_3$, and 0.05 mL of freshly distilled trifluoroacetic acid. After 5 min at room temperature, the solution turned brown; after 4 h, when the isomerization was nearing completion, a deep violet color was seen. After 24 h, the reaction mixture was poured into ether (20 mL) and the ethereal solution was washed with water (2 × 10 mL), saturated sodium bicarbonate solution (10 mL), and brine before drying. Solvent removal left 35 mg of a mixture of **19a** (66%), **20a** (13%), and **21a** (21%) which was separated on the 5% SE-30 column at 167 °C.

19a: ^{1}H NMR (δ, $CDCl_3$) 7.40–7.00 (m, 10 H), 3.64 (m, 1 H), 3.55 (s, 2 H), 3.00–1.12 (m, 5 H), 0.88 (s, 3 H), and 0.84 (s, 3 H); *m/e* calcd 288.1878, obsd 288.1881. Anal Calcd for $C_{22}H_{24}$: C, 91.61; H, 8.39. Found: C, 91.20; H, 8.63.

20a: ^{1}H NMR (δ, $CDCl_3$) 7.34–6.88 (m, 10 H), 3.53 (br m, 1 H), 3.16–1.06 (series of m, 5 H), 1.78 (d, J = 2 Hz, 3 H), 1.01 (s, 2 H), and 0.82 (s, 3 H); *m/e* 288.1878, obsd 288.1881.

21a: ^{1}H NMR (δ, $CDCl_3$) 7.35–6.88 (m, 10 H), 3.53 (m, 1 H), 3.16–1.98 (series of m, 5 H), 1.68 (d, J = 2 Hz, 3 H), 1.56 (m, 2 H), and 1.20 (s, 3 H); *m/e* calcd 288.1878, obsd 288.1881.

Epoxidation of 19a. From 24.8 mg (0.086 mmol) of **19a**, 10.8 mg of sodium bicarbonate, and 22.3 mg of *m*-chloroperbenzoic acid in 2 mL of dichloromethane at room temperature, there was isolated 26 mg (100%) of a mixture of **22a** and **23a** in a 1:1 ratio (^{1}H NMR analysis). There were separated by preparative layer chromatography on silica gel (elution with low boiling petroleum ether).

22a: ^{1}H NMR (δ, $CDCl_3$) 7.49–7.04 (m, 10 H), 3.32–1.65 (series of m, 6 H), 1.24 (s, 3 H), 1.17 (d, J = 5 Hz, 2 H), and 0.65 (s, 3 H); *m/e* calcd 304.1827, obsd 304.1834.

23a: ^{1}H NMR (δ, $CDCl_3$) 7.36–7.00 (m, 10 H), 3.15–1.58 (series of m, 6 H), 1.20 (d, J = 5 Hz, 2 H), 1.03 (s, 3 H), and 0.62 (s, 3 H); *m/e* calcd 304.1827, obsd 304.1834.

Rearrangement of 11c. In an NMR tube were placed 100 mg (0.344 mmol) of **11c**, 0.50 mL of $CDCl_3$, and 0.10 mL of freshly distilled trifluoroacetic acid. Although the reaction mixture became brown after 5 min, green after 4 h, and dark violet after 1 day, the rearrangement was complete only after 7 days. After the usual workup, the products were separated by preparative VPC on a 4 ft × 0.25 in. 5% SE-30 column at 167 °C.

19b (66%): ^{1}H NMR (δ, $CDCl_3$) 7.35–7.01 (m, 10 H), 3.72 (m, 1 H), 3.55 (s, 2 H), 2.85–1.08 (series of m, 5 H), and 0.84 (s, 3 H); *m/e* calcd 291.2066, obsd 291.2071.

20b: ^{1}H NMR (δ, $CDCl_3$) 7.20–6.87 (m, 10 H), 3.50 (br m, 1 H), 3.16–1.15 (series of m, 5 H), 1.01 (s, 2 H), and 0.82 (s, 3 H); *m/e* calcd 291.2066, obsd 291.2071.

21b (21%): ^{1}H NMR (δ, $CDCl_3$) 7.44–6.73 (m, 10 H), 3.52–1.45 (series of m, 6 H), 1.65 (s, 2 H), and 1.10 (s, 3 H); *m/e* calcd 291.2066, obsd 291.2071.

Epoxidation of 19b. Epoxidation of 34.8 mg (0.12 mmol) of **19b** according to the usual procedure afforded a mixture of **22b** and **23b** in quantitative yield. These isomers were separated by preparative layer chromatography on silica gel.

22b: ^{1}H NMR (δ, $CDCl_3$)7.34–6.82 (m, 10 H), 3.16–1.65 (series of m, 6 H), 1.24 (s, 3 H), and 1.10 (d, J = 3 Hz, 2 H); *m/e* calcd 307.2015, obsd 307.2023.

Rearrangement of 11d. To 75.0 mg (0.318 mmol) of **11d** in 0.35 mL of $CDCl_3$ was added 0.05 mL of trifluoroacetic acid at room temperature. The isomerization was isolated by preparative VPC on the 5% SE-30 column: ^{1}H NMR ((δ $CDCl_3$) 7.44–7.18 (m, 5 H), 3.48 (br m, 1 H), 2.90 (m, 2 H), 2.58 (br m, 1 H), 2.38–1.06 (series of m, 5 H), 1.17 (s, 3 H); *m/e* calcd 236.1565, obsd 236.1569.

Rearrangement of 11e. Comparable treatment (5 days) of **11e** (27.2 mg, 0.116 mmol) furnished a mixture of **24b** (63%) and (37%). These were separated by preparative VPC as before.

24b: ^{1}H NMR (δ, $CDCl_3$) 7.20 (m, 5 H), 3.52 (br m, 1 H), 2.84 (d of m, 2 H), 2.52 (br m, 1 H), 2.19–1.27 (series of m, 7 H), 1.03 (s, 3 H), and 0.96 (s, 3 H); *m/e* calcd 238.1721, obsd 238.1727. Anal. Calcd for $C_{18}H_{22}$: C, 90.70; H, 9.30. Found: C, 90.26; H, 9.35.

25b: ^{1}H NMR (δ, $CDCl_3$) 7.20 (m, 5 H), 5.97–5.29 (m, 1 H), 5.15–4.77 (m, 2 H), 3.49 (br m, 1 H), 2.97–0.86 (series of m, 7 H), 1.71 (d, J = 2 Hz, 3 H), and 0.92 (s, 3 H); *m/e* calcd 238.1721, obsd 238.1727.

Rearrangement of 11f. Comparable treatment (2 h) of **11f** (30.5 mg) delivered a mixture of **24c** (91%) and **25c** (9%). Spectral characterization of these isomers followed upon VPC separation (5% SE-30, 103 °C).

24c: ^{1}H NMR (δ, $CDCl_3$) 7.17 (m, 5 H), 3.40 (br m, 1 H), 2.50 (br m, 1 H), 2.28–1.73 (m, 4 H), 1.73–1.18 (m, 4 H), 1.05 (s, 3 H), 0.96 (s, 3 H) and 0.84 (t, J = 7 Hz, 3 H); *m/e* calcd 240.1878, obsd 240.1882.

25c: ^{1}H NMR (δ, $CDCl_3$) 7.18 (m, 5 H), 3.51 (br m, 1 H), 3.00–1.75 (series of m, 5 H), 1.66 (d, J = 2 Hz, 3 H), 1.53–1.24 (m,

4 H), 0.94 (t, 3 H), and 0.93 (s, 3 H); *m/e* calcd 240.1878, obsd 240.1882.

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Stereoselective Bifunctional Catalysis of Dedeuteration of Cyclopentanone-*2,2,5,5*-d_4 by (1*R*,2*S*,3*R*,4*R*)-3-Dimethylaminomethyl-1,7,7-trimethyl-2-norbornanamine[1]

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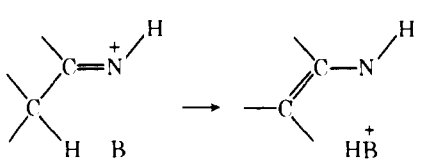
Abstract: The chiral diamine (1*R*,2*S*,3*R*,4*R*)-3-dimethylaminomethyl-1,7,7-trimethyl-2-norbornanamine (**2**) has been synthesized and found to be a very effective bifunctional catalyst for the dedeuteration of acetone-d_6. The Brønsted β for dedeuteration of cyclopentanone-*2,2,5,5*-d_4 in water at 35 °C is 0.57. The dedeuteration of cyclopentanone by **2** is rapid and stereoselective. The two *pro S* deuterium atoms are exchanged faster than the *pro R* deuterium atoms, by as much as 70-fold. Ketone containing >80% cyclopentanone-d_2 was isolated from the reaction mixture after partial exchange. This material showed a positive Cotton effect.

Certain primary amines containing basic substituents (B–NH_2) may act as bifunctional catalysts for removal of α hydrogen from aldehydes and ketones.[2-4] They transform the carbonyl compound to an iminium ion in which the basic group may remove the α hydrogen atom internally (eq 1). To learn whether such hydrogen removal could be made strongly stereoselective with a simple model, the dedeuteration of cyclopentanone-*2,2,5,5*-d_4 was studied in the presence of a chiral catalyst.[5] The enzyme acetoacetate decarboxylase, which is an effective bifunctional catalyst for the dedeuteration of acetone-d_6,[6] dedeuterates the methylene group of butanone stereoselectively.[7]



(1)

Results and Discussion

Synthesis of Chiral Catalyst. The most effective bifunctional catalyst for the dedeuteration of acetone-d_6 that we had studied was 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine,[1b] which had been prepared from norcamphor.[8] Rather than resolving this diamine we thought it would be easier to make the analogous 1,7,7-trimethyl compound from natural chiral camphor. From (+)-camphor, which is known[9] to be 1*R*,4*R*, we obtained the 2-dimethylaminomethyl derivative (**1**) by reduction of the 2-dimethylaminomethylene derivative. The

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