perature. The reaction mixture was evaporated and purified by column chromatography ($CHCl_3$–MeOH, 97:3), yielding 550 mg (78%) of N^6-benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**2**).

Synthesis of N^6-Benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (2) from 1. Method A. A suspension of 920 mg (2 mmol) of **1** in anhydrous dichloromethane (50 mL) and pyridine (2 mL) was cooled to −30 °C and 5 mL of trifluoromethanesulfonic anhydride (10 vol % in dichloromethane) was added dropwise. After removal of the cooling bath, the reaction mixture was stirred for 30 min during which time it became complete clear. After addition of H_2O (1 mL), the emulsion was further stirred for 3 h at room temperature. Then 5 mL of H_2O was added, and the organic layer was separated, dried, evaporated, and coevaporated with toluene to remove pyridine. The residual oil was diluted with 50 mL of anhydrous methanol and 100 mg of sodium bicarbonate was added. The suspension was stirred for 2 h 15 min at room temperature, neutralized with acetic acid, evaporated, and purified by column chromatography ($CHCl_3$–MeOH, (97:3), yielding 720 mg (1.57 mmol, 78%) of N^6-benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**2**).

Method B. To a suspension of 460 mg (1 mmol) of **1** in 15 mL of anhydrous dichloromethane, containing 0.24 mL (3 mmol) of pyridine, was added dropwise 2.5 mL (1.5 mmol) of a solution of trifluoromethanesulfonic anhydride (10 vol %) in dichloromethane at −30 °C. The reaction mixture was warmed up to 0 °C over a period of 25 min. After 15 min, all the material was dissolved. Then 370 mg (3 mmol) of benzoic acid and 1 mL of H_2O were added successively and the emulsion was stirred for a further 6 h at 0 °C. The organic layer was isolated, dried, evaporated, and purified by column chromatography ($CHCl_3$–MeOH, 97:3), yielding 270 mg (0.59 mmol, 59%) of **2** and 140 mg (0.3 mmol, 30%) of **5**.

3′-Azido-2′,3′-dideoxyadenosine (3). A solution of 920 mg (2 mmol) of **2** in 20 mL of anhydrous dichloromethane, containing 2 mL of pyridine, was cooled to −30 °C. Then 5 mL (3 mmol) of a solution of trifluoromethanesulfonic anhydride in dichloromethane (10 vol %) was added dropwise. The cooling bath was removed and the reaction was stirred for a further 15 min. A solution of 980 mg (20 mmol) of lithium azide in 20 mL of dimethylformamide was added at once and the reaction was stirred, for 2 h at room temperature. H_2O (50 mL) and $CHCl_3$ (150 mL) were added, and the organic layer was separated, washed with H_2O (2 × 100 mL), dried, and evaporated. The oily residue was dissolved in methanol, saturated with ammonia, and kept overnight at room temperature. After evaporation and column chromatographic purification ($CHCl_3$–MeOH, 95:5), 460 mg (1.67 mmol, 83%) of crystalline **3** was obtained: mp 189–190 °C (lit.[3] mp 189–191 °C).

3′-Azido-2′,3′-dideoxyinosine (4). To a solution of 276 mg of 3′-azido-2′,3′-dideoxyadenosine in 200 mL of a 0.05 M phosphate buffer (pH 7.5), formed from KH_2PO_4 and Na_2HPO_4, was added 0.5 mL of a suspension of adenosine aminohydrolase (from bovine spleen type IV, 275 units/mg), and the mixture was stirred for 1 h at 30 °C. The reaction was monitored by UV analysis and the λ_{max} shifted from 260 nm to 249 nm. The reaction mixture was concentrated, applied on a XAD column, and eluted first with H_2O and then with methanol. The UV-absorbing fractions were pooled and evaporated, and the title compound was crystallized from MeOH: 270 mg (0.97 mmol, 97%); mp 191–192 °C; IR (KBr) 2100 cm^{-1} (N_3); UV (MeOH) λ_{max} 250 nm (log ε 4.10); ^1H NMR (DMSO-d_6) δ 2.40–2.68 (m, H-2′), 2.70–3.00 (m, H-2″), 3.59 (d, H-5′, H-5″), 3.93 (m, H-4′), 4.59 (m, H-3′), 6.29 (t, J = 6.2 Hz, H-1′), 8.07 (s) and 8.32 (s) (H-8 and H-2). Anal. Calcd for $C_{10}H_{11}N_7O_3$: C, 43.32; H, 4.00; N, 35.37. Found: C, 43.38; H, 4.27; N, 35.30.

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Intramolecular Carbene Chemistry. Evidence for Exclusive C–H Insertion in 8-Methylene-2-noradamantylidene

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8-Methylene-2-noradamantylidene (**5**) reacts by intramolecular γ-C,H insertion to produce 6-methylene-2,4-didehydronoradamantane (**4**) as the sole product (92%). Specifically labeled carbene 8-methylene-2-noradamantylidene-*4-d* (**5a**) produces **4** with the label located at only one position. This rules out the possible formation of the unstable olefin-cycloaddition product, 2,8-methano-2,8-didehydronoradamantane (**6**), followed by retro carbene ring opening to give **5**. The higher homologue of **5**, 4-methylene-2-adamantylidene (**2**), is known to react exclusively by intramolecular olefin cycloaddition to give 2,4-methano-2,4-didehydroadamantane, a [3.1.1]propellane, although the carbenic center and the olefinic bond in this carbene are less favorably arranged for cycloaddition than those in carbene **5**. This difference in behavior suggests a relatively late and high activation energy transition state between carbene **5** and the resultant intramolecular olefin-cycloaddition product **6**, a highly strained [2.1.1]propellane.

Intermolecular carbene cycloadditions to olefinic bonds as well as insertions into C–H bonds are generally unselective processes,[1] indicating that the respective activation energies are negligible or very small.[2] Yet, analogous *intramolecular carbene reactions may be highly selective.*[3-5]

(1) (a) Krzyzanowski, S.; Cvetanović, R. J. *Can. J. Chem.* **1967**, *45*, 665–673. (b) Doering, W. v. E.; Buttery, R. G.; Laughlin, R. G.; Chaudhri, N. *J. Am. Chem. Soc.* **1956**, *78*, 3224.

(2) (a) Hoffmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 1475–1485. (b) Dobson, R. C.; Hayes, D. M.; Hoffmann, R. *Ibid.* **1971**, *93*, 6188–6192. (c) Bodor, N.; Dewar, M. J. S.; Wasson, J. S. *Ibid.* **1972**, *94*, 9095–9102.

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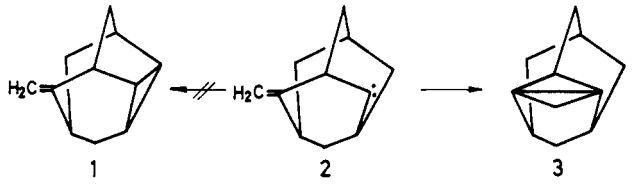
The course of an intramolecular carbene reaction is mostly directed by the spatial arrangement of the carbenic center in relation to the potential reaction sites.[2,3d,6] However, when the potential products are extremely strained, the strain energies of the respective transition states may become the governing factor for the reaction course. This is clearly demonstrated in the present work on the intramolecular chemistry of 8-methylene-2-noradamantylidene (**5**). Its higher homologue, 4-



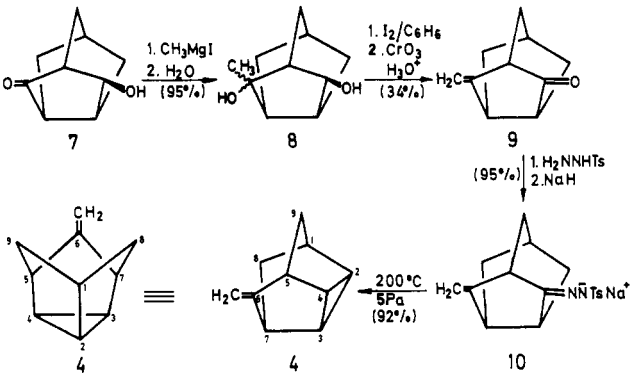
methylene-2-adamantylidene (**2**), reacts exclusively by intramolecular cycloaddition to the olefinic bond, producing 70% of 2,4-methano-2,4-didehydroadamantane, a [3.1.1]propellane (**3**).[4] Carbene **5**, however, yields only the γ-C,H insertion product, 6-methylene-2,4-didehydronoradamantane (**4**), rather than the olefin-cycloaddition product **6**.

Results and Discussion

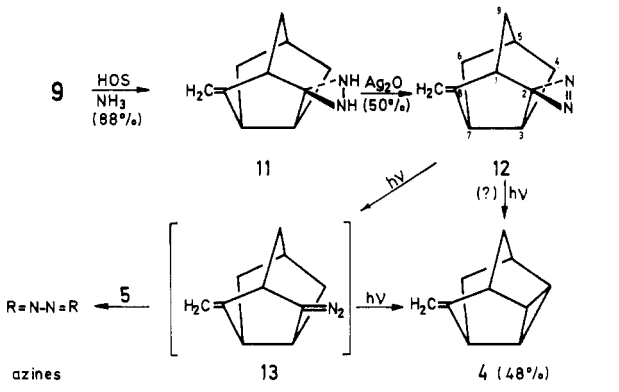
8-Methylene-2-noradamantylidene (**5**) was generated by two methods: (i) pyrolysis of the dry tosylhydrazone sodium salt of 8-methylene-2-noradamantanone (**10**) in vacuo and (ii) photolysis of the corresponding diazirine (**12**) in toluene-d_8 at −70 °C. The key intermediate in the syntheses of **10** and **12**, 8-methylene-2-noradamantanone (**9**), was prepared in 32% overall yield by methyl-Grignard addition to 8-*exo*-hydroxy-2-noradamantanone[7] (**7**) followed by iodine-catalyzed dehydration and Jones oxidation of the resulting methyl diol **8** (Scheme I).

Ketone **9** was converted (95%) into the tosylhydrazone sodium salt **10** by the usual procedures[4] (Scheme I). Pyrolysis of the dry salt **10** at 200 °C in vacuo yielded 92% of 6-methylene-2,4-didehydronoradamantane (**4**). It was more than 98% pure (by GC). The structure of **4** was established by spectral means. In particular, the mass

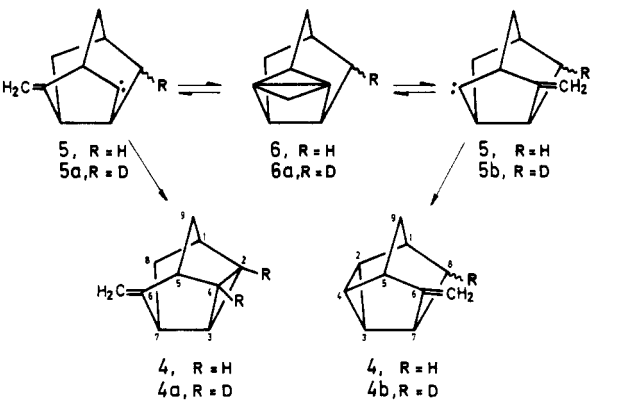
Scheme I



Scheme II



Scheme III



spectrum showed a molecular ion peak at m/z 132 (relative intensity 70%) and the IR spectrum exhibited the characteristic olefinic and cyclopropane C–H vibrational bands at 3065 and 3045 cm^{-1}, respectively. The ^{1}H NMR spectrum (C_6D_6) showed a sharp singlet at δ 4.39 corresponding to two olefinic protons and three multiplets between δ 2.8 and 2.6 (2 H), 2.6 and 2.3 (1 H), and 2.2 and 1.3 (7 H), respectively. The ^{13}C NMR spectrum unambiguously confirmed the structure of **4**: (C_6D_6) δ 165.2 (s, 1 C, C-6), 96.6 (t, J = 156 Hz, 1 C, C-10), 49.7 (t, J = 130 Hz, 2 C, C-8,9), 45.8 (d, J = 138 Hz, 2 C, C-5,7), 40.4 (d, J = 136 Hz, 1 C, C-1), 36.8 (d, J = 171 Hz, 1 C, C-2), 35.1 (d, J = 173 Hz, 2 C, C-3,4). The ^{13}C NMR signals were assigned on the basis of their characteristic chemical shifts, the relative intensities in the quantitative spectrum, and the splitting patterns in the proton off-resonance decoupled spectrum, as well as the C–H coupling constants. These spectral data were essential for the precise location of the deuterium label in **4a** which was obtained from deuteriated ketone **9a** (vide infra).

(3) For example: (a) Andruskiewicz, C. A., Jr.; Murray, R. K., Jr. *J. Org. Chem.* **1983**, *48*, 1926–1927. (b) Nickon, A.; Pandit, G. D. *Tetrahedron Lett.* **1968**, 3663–3666. (c) Powell, J. W.; Whiting, M. C. *Tetrahedron* **1959**, *7*, 305–310. Dauben, W. G.; Willey, F. G. *J. Am. Chem. Soc.* **1962**, *84*, 1497–1498. Nickon, A.; Werstiuk, N. H. *Ibid.* **1972**, *94*, 7081–7086. (d) Paquette, L. A.; Chamot, E.; Browne, A. R. *Ibid.* **1980**, *102*, 637–643. Paquette, L. A.; Taylor, R. T. *Ibid.* **1977**, *99*, 5708–5715.

(4) Mlinarič-Majerski, K.; Majerski, Z. *J. Am. Chem. Soc.* **1983**, *105*, 7389–7395. Mlinarič-Majerski, K.; Majerski, Z. *Ibid.* **1980**, *102*, 1418–1419.

(5) (a) Majerski, Z.; Žuanič, M. *J. Am. Chem. Soc.* **1987**, *109*, 3496–3498. (b) Vinković, V.; Majerski, Z. *Ibid.* **1982**, *104*, 4027–4029. (c) Burger, U.; Gandillon, G. *Tetrahedron Lett.* **1979**, 4281–4284.

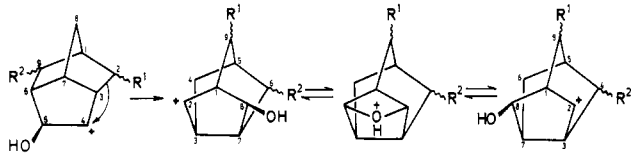
(6) (a) Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* **1961**, *83*, 3159–3160. (b) Nickon, A.; Huang, F.; Weglein, R.; Matsuo, K.; Yagi, H. *Ibid.* **1974**, *96*, 5264–5265. Nickon, A.; Bronfenbrenner, J. K. *Ibid.* **1982**, *104*, 2022–2023. (c) Press, L. S.; Shechter, H. *Ibid.* **1979**, *101*, 509–510. Kyba, E. P. *Ibid.* **1977**, *99*, 8330–8332. (d) Hill, E. A. *J. Org. Chem.* **1972**, *37*, 4008–4012. (e) Hiršl-Starčevič, S.; Majerski, Z. *Ibid.* **1982**, *47*, 2520–2525. (f) Škare, D.; Majerski, Z. *J. Chem. Soc., Chem. Commun.* **1974**, 1000–1001.

(7) Majerski, Z.; Hameršak, Z. *J. Org. Chem.* **1984**, *49*, 1182–1185.

8-Methylenenoradamantane-2-spiro-3′-diazirine (**12**) was prepared in 44% overall yield by treatment of methylene ketone **9** with freshly prepared hydroxylamine-*O*-sulfonic acid in methanolic ammonia followed by oxidation of the resulting diaziridine **11** with silver oxide (Scheme II). Photolysis of diazirine **12** in toluene-d_8 at −70 °C produced a mixture of hydrocarbon **4** and 8-methylene-2-noradamantylidene azines.[8] Hydrocarbon **4** was isolated in 48% yield and proved to be identical with the pyrolysis product of tosylhydrazone salt **10** by comparison of their ^{13}C NMR, ^1H NMR, IR, and mass spectra.

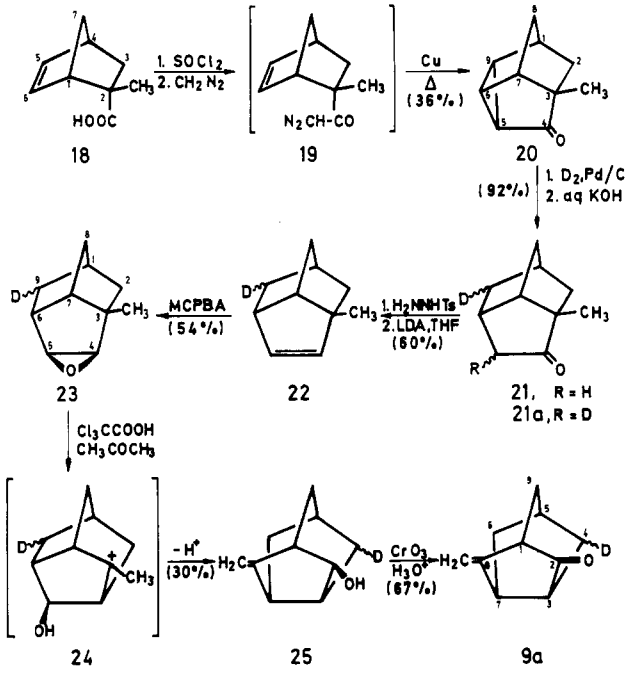
However, the possible formation of the olefin-cycloaddition product, 2,8-methano-2,8-didehydronoradamantane (**6**), as an intermediate, cannot be ruled out on the basis of these results alone. Such a thermodynamically unstable molecule could possibly isomerize back to 8-methylene-2-noradamantylidene (**5**) by a retro carbene ring opening process[9] even at −70 °C (Scheme III). This possibility can be checked with an appropriately labeled starting carbene **5**, such as 8-methylene-2-noradamantylidene-*4-d* (**5a**). The intramolecular γ-C,H insertion of this carbene would yield exclusively 6-methylene-2,4-didehydronoradamantane labeled at positions 2 and/or 4 (**4a**). However, if the olefin-cycloaddition product **6a** was formed, it should isomerize to *two* deuteriated carbenes, **5a** and **5b**, which would lead to *two* deuteriated 6-methylene-2,4-didehydronoradamantanes: **4a** and **4b**. Consequently, the label in **4** would then be scrambled at positions 2 and/or 4 and 8 rather than located at only 2 and/or 4.

Our usual route to 2,8-disubstituted noradamantanes,[7] the acid-catalyzed rearrangement of 4,5-*exo*-epoxybrendane, cannot be used to produce the specifically labeled carbene **5a**. The mechanism of this rearrangement involves protonation of the oxygen atom followed by the cleavage of either of the two carbon–oxygen bonds. When 4,5-*exo*-epoxybrendane-*2-d* (**14**)[10] was the starting material, two isotopomeric 5-*exo*-hydroxy-4-brendyl cations were formed: *2-d* and *9-d* (**15a** and **15b**). These cations subsequently rearranged by 1,2-C,C shifts to the thermodynamically more stable 8-*exo*-hydroxy-2-noradamantyl cations deuteriated at positions 9 and 6, respectively (**16a** and **16b**). Therefore, one could reasonably anticipate the label in 2,8-disubstituted noradamantane products to be located at positions 6 and 9. However, the label in 2-*exo*-acetoxy-8-*exo*-noradamantanol[7] was actually found at three positions: 4, 6, and 9. This can be explained by rapid isomerizations of cations **16a** and **16b** to **16c** and **16d** via the oxonium intermediates **17a** and **17b**, respectively.



[a] R^1=D, R^2=H. [b] R^1=H, R^2=D.

Scheme IV



To circumvent this deuterium scrambling, we used 3-methyl-4,5-*exo*-epoxybrendane-*9-d* (**23**) as the starting material in our approach to carbene **5a**. Epoxide **23** was obtained in 10% overall yield from 2-*exo*-methyl-5-norbornene-2-*endo*-carboxylic acid[11] (**18**) through the sequence in Scheme IV.[12] Carboxylic acid **18** was first converted to α-diazo ketone **19** by treatment of the crude acyl chloride with diazomethane. Copper-catalyzed decomposition of **19** in refluxing toluene generated the respective carbene, which yielded 35% (with respect to **18**) of tetracyclic ketone **20** by an intramolecular olefin cycloaddition. Hydrogenolysis of the C_5–C_9 bond in **20** with deuterium gas on Pd/C afforded 92% of 3-methyl-4-brendanone (**21a**) deuteriated at two positions: 5 and 9. A base-catalyzed exchange reaction of **21a** in aqueous dioxane gave the monodeuteriated ketone, 3-methyl-4-brendanone-*9-d* (**21**). Ketone **21** was converted into 3-methyl-4,5-*exo*-epoxybrendane-*9-d* (**23**) in 31% overall yield by treatment of the derived tosylhydrazone with LDA followed by epoxidation of the resulting olefin **22** with MCPBA. In the presence of a strong acid and weak nucleophile, such as trichloroacetic acid, epoxide **23** rearranged in dry acetone to the tertiary cation **24**, which provided 8-methylene-2-*exo*-noradamantanol-*4-d* (**25**) in 30% yield. The ^{13}C NMR, ^1H NMR, IR, and mass spectra of its protio analogue, which was obtained by this route, were identical with those of 8-methylene-2-*exo*-noradamantanol prepared by the route shown in Scheme I. Methylene alcohol **25** was then oxidized by the Jones reagent to 8-methylene-2-noradamantanone-*4-d* (**9a**). The deuterium content of **9a** was found to be 70% (by MS); its ^2H NMR spectrum showed only one signal, while the ^{13}C NMR spectrum exhibited seven singlets, two "isotopic doublets" [δ 57.3 ($^2\Delta$ = −82 ppb), 35.7 ($^2\Delta$ = −83 ppb)], and a weak 1:1:1 triplet shifted upfield by 362 ppb[14] from a low-intensity (10th) singlet (δ

(8) The azines probably arise from the attack of carbene **5** on the intermediary 8-methylene-2-diazonoradamantane.

(9) Szeimies reported thermal retro carbene ring opening of a [3.1.1]- and a [4.1.1]propellane: Szeimies-Seebach, U.; Szeimies, G.; Van Meerssche, M.; Germain, G.; Declercg, J.-P. *Nouv. J. Chim.* **1979**, *3*, 357–358. Baumgart, K.-D.; Harnisch, H.; Szeimies-Seebach, U.; Szeimies, G. *Chem. Ber.* **1985**, *118*, 2883–2916. Szeimies-Seebach, U.; Szeimies, G. *J. Am. Chem. Soc.* **1978**, *100*, 3966–3967.

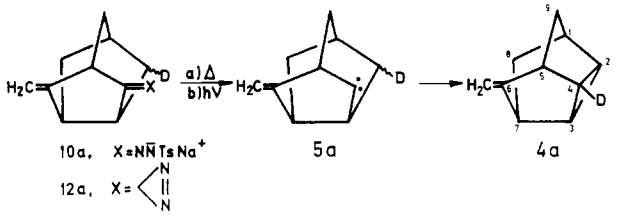
(10) Epoxide **14** was obtained in 54% overall yield from the nonmethylated analogue[7] of tetracyclic ketone **20** by hydrogenolysis with deuterium gas followed by the reactions shown in Scheme IV.

(11) Moriarty, R. M.; Chien, C. C.; Adams, T. B. *J. Org. Chem.* **1979**, *44*, 2206–2210.

(12) Similar approaches were used by Nickon[13] and by us[7] in the preparation of 4-brendanone and 2,8-disubstituted noradamantanes, respectively.

(13) Nickon, A.; Kwasnik, H. R.; Mathew, C. T.; Swartz, T. D.; Williams, R. O.; DiGiorgo, J. B. *J. Org. Chem.* **1978**, *43*, 3904–3916.

Scheme V



41.6) corresponding to one of the saturated methylene carbons. Methylene ketone **9a** was, therefore, specifically deuteriated at only one position, and consequently, the acid-catalyzed rearrangement of methyl epoxide **23** to methylene alcohol **25** was not accompanied by deuterium scrambling.

8-Methylene-2-noradamantanone-*4-d* (**9a**) was converted to the corresponding tosylhydrazone salt **10a** and to the diazirine **12a** as outlined in Scheme I. Pyrolysis of **10a** as well as photolysis of **12a** produced exclusively 6-methylene-2,4-didehydronoradamantane-*4-d*, **4a** (Schemes III, V). No deuterium was detected at position 8 (**4b**). The deuterium content of **4a** was 68% (by MS); its ^{2}H NMR spectrum exhibited only one signal,[16] while the ^{13}C NMR spectrum showed four singlets (C-6, C-10, C-8,9, C-1), three "isotopic doublets" (C-5,7, $^2\Delta$ = −95 ppb; C-2, $^2\Delta$ = −107 ppb; C-3,4, $^2\Delta$ = −110 ppb), and a weak 1:1:1 triplet (J = 26.2 Hz) shifted upfield from the C-3,4 signal by 290 ppb ($^1\Delta$ effect).[14,18]

These results clearly show that 8-methylene-2-noradamantylidene (**5**) reacts exclusively by intramolecular γ-C,H insertion. No olefin-cycloaddition product **6** is formed even as an unstable intermediate. In contrast, 4-methylene-2-adamantylidene (**2**), the higher homologue of **5**, reacts exclusively by intramolecular olefin cycloaddition to produce 70% of 2,4-methano-2,4-didehydroadamantane, a [3.1.1]propellane (**3**).[4] Inspection of molecular models of carbenes **2** and **5** indicates that the carbenic center in **5** is closer to the olefinic bond and at least as favorably oriented for olefin cycloaddition as is the carbenic center in **2**. Yet, carbene **5** reacts exclusively by γ-C,H insertion and carbene **2** by olefin cycloaddition. This result suggests a relatively late and high activation energy transition state between carbene **5** and the resultant intramolecular olefin cycloaddition product **6**, a highly strained [2.1.1]propellane.

Experimental Section

The purity of all compounds was determined by GC and/or ^{13}C NMR. ^{13}C NMR and ^{1}H NMR spectra were acquired with a JEOL FX90Q spectrometer, IR spectra were recorded with a Perkin-Elmer 297 spectrophotometer, and mass spectra were obtained on a Varian CH-7 spectrometer. The quantitative analyses with ^{13}C NMR were performed by a combination of long pulse intervals (100 s) to assure complete relaxation of all ^{13}C nuclei and a gated decoupling, which eliminated the nuclear Overhauser enhancement. GC analyses were carried out on a Varian Aerograph 1800 gas chromatograph. Melting points were determined, in sealed capillary tubes completely immersed in oil, by using a Thiele apparatus and were uncorrected. MCPBA (*m*-chloroperbenzoic acid) was of technical grade and contained 85% of the active material. All other chemicals were of commercial reagent grade and were used without purification.

8-Methylene-2-noradamantanone (9). A solution of methyl iodide (2.85 g, 20.1 mmol) in dry ether (20 mL) was added dropwise to a stirred suspension of magnesium turnings (550 mg, 22.6 mmol) in dry ether (5 mL). The reaction mixture was stirred under reflux for an additional hour and then allowed to cool. To the resulting solution of methyl-Grignard reagent was added dropwise a solution of 8-*exo*-hydroxy-2-noradamantanone,[7] **7** (1.22 g, 8.0 mmol), in dry ether (50 mL). The reaction mixture was stirred under reflux for 4 h and cooled to room temperature. A saturated aqueous solution of ammonium chloride (30 mL) was added, the layers were separated, and the aqueous one was extracted with ether (3 × 50 mL). The extracts were combined, washed with saturated aqueous NaCl solution (30 mL), and dried. Removal of the solvent left 2-methyl-2,8-noradamantanediol, **8** (1.28 g, 95%), which was used without further purification in the next step. A solution of diol **8** (750 mg, 4.46 mmol) in benzene (40 mL) was stirred with iodine (~150 mg) under reflux with a Dean–Stark apparatus. The reaction was monitored by GC (DEGS, 170 °C). When no starting diol was present, the mixture was cooled, washed with an aqueous $NaHSO_3$ solution (1–2 mL) followed by water, and dried. The solvent was evaporated, and the crude product was purified by column chromatography on neutral alumina (activity II/III[19]). Elution with pentane–ether (2:1) yielded **8-methylene-2-*exo*-noradamantanol** (335 mg, 50%; ≥98% pure by GC, DEGS, 170 °C): mp 100–102 °C; ^{13}C NMR ($CDCl_3$) δ 160.5 (s), 102.2 (t), 80.4 (d), 51.6 (d), 47.3 (d), 45.3 (t), 42.5 (d), 40.1 (t), 36.5 (t), 34.8 (d); ^{1}H NMR ($CDCl_3$) δ 4.76 (s, 2 H), 3.72 (s, 1 H), 2.8–1.4 (m, 11 H); IR (neat) 3270 (s), 3075 (w), 2920 (s), 2865 (s), 1675 (m), 1445 (m), 1352 (m), 1090 (m), 870 (m) cm^{-1}; MS, *m/z* (relative intensity) 150 (M^+, 13), 132 (5), 122 (14), 106 (13), 94 (25), 93 (100), 92 (44), 91 (48), 80 (40), 79 (46), 77 (39). Anal. Calcd for $C_{10}H_{14}O$ (150.21): C, 79.95; H, 9.39. Found: C, 80.06; H, 9.44.

To a solution of 8-methylene-2-*exo*-noradamantanol (335 mg, 2.23 mmol) in acetone (15 mL), which was stirred at room temperature, was added the Jones reagent dropwise until a permanent red color appeared. The reaction mixture was stirred for an additional 10 min, then diluted with water (20 mL), and extracted with chloroform (3 × 50 mL). The extracts were dried, and the solvent was evaporated to give the crude product, which was purified by column chromatography on neutral alumina (activity II/III). Elution with pentane–ether (10:1) yielded **8-methylene-2-noradamantanone**, **9** (220 mg, 67%; ≥98% pure by GC, DEGS, 170 °C): mp 43–45 °C; ^{13}C NMR ($CDCl_3$) δ 213.1 (s), 152.6 (s), 102.1 (t), 57.3 (d), 50.8 (d), 45.4 (t), 44.3 (t), 43.8 (d), 41.6 (t), 35.7 (d); ^{1}H NMR ($CDCl_3$) δ 4.70 (d, J = 2.2 Hz, 2 H), 3.2–2.95 (m, 1 H), 2.95–2.6 (m, 2 H), 2.5–2.25 (m, 1 H), 2.25–1.8 (m, 6 H); IR (neat) 3075 (w), 2950 (s), 2870 (s), 1755 (s), 1665 (m), 1445 (m), 1170 (m), 1058 (m), 885 (m), 640 (m) cm^{-1}; MS, *m/z* (relative intensity) 148 (M^+, 45), 120 (35), 105 (33), 92 (100), 91 (78), 79 (43), 71 (28), 66 (36). Anal. Calcd for $C_{10}H_{12}O$ (148.20): C, 81.04; H, 8.16. Found: C, 81.01; H, 8.11.

Tosylhydrazone Sodium Salt of 8-Methylene-2-noradamantanone (10). A mixture of ketone **9** (160 mg, 1.08 mmol), *p*-tosylhydrazine (220 mg, 1.18 mmol), and absolute ethanol (3–4 mL) was stirred for 5 h at 40–50 °C and then poured into water (50 mL). The product was extracted with chloroform (3 × 20 mL). The extracts were dried, and the solvent was evaporated to afford the tosylhydrazone of ketone **9** (324 mg, 95%). The crude tosylhydrazone was dissolved in dry tetrahydrofuran (3–4 mL), sodium hydride (50% suspension in mineral oil; 52 mg, 1.08 mmol) was added, and the resulting thick suspension was stirred for 1 h. The solvent was evaporated, and the tosylhydrazone salt **10** was dried at 50 °C and 5 Pa for 2 h in a round-bottomed flask.

(14) These values are typical for $^1\Delta$ and $^2\Delta$ deuterium isotope effects on ^{13}C NMR chemical shifts.[15]

(15) Majerski, Z.; Žuanić, M.; Metelko, B. *J. Am. Chem. Soc.* **1985**, *107*, 1721–1726. Aydin, R.; Frankmölle, W.; Schmalz, D.; Günther, H. *Magn. Reson. Chem.* **1988**, *26*, 408–411.

(16) To exclude the possibility of overlap of the C_4-D and C_8-D signals, we recorded a ^{2}H NMR spectrum of an isotopomer mixture of 4 deuteriated at positions 4, 8-endo, 9-syn, and 9-anti.[17] Owing to the symmetry of the molecular skeleton, the 8-endo and 9-syn deuterium atoms are equivalent. The spectrum showed three well-separated signals in a ratio of 1:1:2.

(17) This mixture was obtained from 4,5-*exo*-epoxybrendane-*2-d* (**14**) by the route shown in Scheme I.

(18) The fact that the C-1 NMR signal of **4a** is a singlet rather than an "isotopic doublet" strongly indicates that only a small amount (if any) of the deuterium is attached to the adjacent carbon C-2. Consequently, the deuterium in both ketones **9a** and **21** is preferably (or exclusively) in the endo orientation. This is in good agreement with only one signal in the ^{2}H NMR spectra of **4a**, **9a**, and **21**.

(19) Alumina of activity II/III was prepared by the addition of 4.5% water to alumina of activity I.

Pyrolysis of the Tosylhydrazone Salt 10. The flask containing the dry salt **10** was connected to a high-vacuum pump via a "U" trap cooled by liquid nitrogen, evacuated (5 Pa), and then immersed in a hot-oil bath (200 °C). An oily liquid, which was shown to be ≥98% pure (by ^{13}C NMR) 6-methylene-2,4-didehydronoradamantane (**4**), distilled into the trap. After 15 min, the oil bath was removed, dry N_2 gas was allowed to fill the apparatus, and the trap was disconnected and weighed to determine the yield of **4** (125 mg, 92%). The ^{13}C NMR and ^1H NMR spectral data are given in the text with the results; IR (film) 3070 (m sh), 3050 (m), 2950 (s), 2860 (s), 1670 (s), 1450 (m), 1318 (m), 874 (s), 858 (m), 785 (m), 774 (m), 728 (m), 670 (m) cm^{-1}; MS, *m/z* (relative intensity) 132 (M^+, 70), 131 (26), 117 (100), 115 (24), 104 (26), 91 (97), 79 (21), 78 (50), 77 (23), 66 (20), 65 (19), 50 (18). Anal. Calcd for $C_{10}H_{12}$ (132.20): C, 90.85; H, 9.15. Found: C, 90.99; H, 9.23.

8-Methylenenoradamantane-2-spiro-3′-diazirine (12). A solution of ketone **9** (250 mg, 1.7 mmol) in methanol (10 mL) was cooled to −78 °C. Liquefied ammonia (~20 mL) was added, and the resulting mixture was stirred for 1 h at reflux of ammonia (−31 °C). A solution of *freshly prepared* hydroxylamine-*O*-sulfonic acid (500 mg, 4.42 mmol) in methanol (2 mL) was added in four portions over 30 min. The reaction mixture was stirred for an additional 3 h at −31 °C and overnight at room temperature to remove excess ammonia. Water (30 mL) was added, and the product was extracted with methylene chloride (3 × 20 mL). The extracts were combined and dried. Evaporation of the solvent yielded 8-methylenenoradamantane-2-spiro-3′-diaziridine, **11** (240 mg). A solution of the above crude diaziridine in methanol (15 mL) was added dropwise to a stirred mixture of a 1 N aqueous solution of $AgNO_3$ (2.5 mL) and a 2.5 N aqueous solution of NaOH (1 mL). Stirring was continued for an additional 10 min. The mixture was filtered, and the precipitate was washed with methanol (2 × 10 mL). Water (150 mL) was added to the combined filtrate, and the product was extracted with methylene chloride (3 × 25 mL). The extracts were dried, and the solvent was evaporated to give the crude product, which was purified by column chromatography on neutral alumina (activity II/III). Elution with pentane yielded oily 8-methylenenoradamantane-2-spiro-3′-diazirine, **12** (120 mg, 44%; ≥95% pure by ^{13}C NMR): ^{13}C NMR (C_6D_6) δ 99.3 (t), 47.2 (d), 45.4 (d), 45.0 (t), 43.3 (s), 42.6 (d), 38.5 (t), 36.7 (d), 36.2 (t); ^1H NMR (C_6D_6) δ 4.55 (d, *J* = 7.8 Hz, 2 H), 2.9–2.6 (br s, 1 H), 2.2–1.9 (m, 2 H), 1.9–1.0 (m, 7 H); IR (neat) 3075 (m), 2950 (s), 2870 (s), 1670 (m), 1570 (m), 1450 (m), 1440 (m), 878 (m) cm^{-1}; MS, *m/z* (relative intensity) 132 ($M^+ - N_2$, 15), 131 (24), 117 (69), 104 (32), 91 (100), 79 (24), 78 (27), 77 (21), 67 (28), 66 (45), 65 (22). Anal. Calcd for $C_{10}H_{12}N_2$ (160.22): C, 74.96; H, 7.55; N, 17.49. Found: C, 74.70; H, 7.84; N, 17.66.

8-Methylenenoradamantane-2-spiro-3′-diaziridine-*4-d* and 8-methylenenoradamantane-2-spiro-3′-diazirine-*4-d* (**12a**) were prepared from deuteriated ketone **9a** in the same manner as were the protio analogues.

Photolysis of 8-Methylenenoradamantane-2-spiro-3′-diazirine (12). Diazirine **12** (43 mg, 0.27 mmol) was dissolved in toluene-d_8 (0.3 mL) in an NMR tube. The NMR tube was cooled by a stream of dry, cold (~−70 °C) nitrogen gas and irradiated through a Pyrex filter by UV light (Hanau, TQ 150) for 24 h. The ^{13}C NMR spectrum indicated the presence of 6-methylene-2,4-didehydronoradamantane (**4**) and considerable amounts of byproducts. The products were separated by column chromatography on neutral alumina (activity II/III) with pentane and ether as the eluents. The combined pentane fractions provided 6-methylene-2,4-didehydronoradamantane, **4** (17 mg, 48%), while the ether fractions gave mainly 8-methylene-2-noradamantanone azines. Photolysis of the deuteriated diazirine **12a** was conducted analogously.

3-Methyl-5,9-didehydro-4-brendanone (20). A mixture of 2-*exo*-methyl-5-norbornene-2-*endo*-carboxylic acid[11] (**18**; 7.0 g, 46 mmol) and thionyl chloride (8 mL, 13 g, 110 mmol) was stirred for 5 h at room temperature. The excess of thionyl chloride was evaporated, and the crude acid chloride was dissolved in dry ether (50 mL) and added dropwise over a period of 30 min to an ethereal diazomethane solution (300 mL; prepared from 30 g, 290 mmol, of *N*-nitrosomethylurea), which was stirred at 0 °C. The mixture was stirred for an additional 30 min at 0 °C and then left overnight at room temperature. Evaporation left oily diazomethyl ketone **19**. A solution of crude **19** in toluene (100 mL) was added dropwise for 2 h to a suspension of copper-bronze powder (10 g) in boiling toluene (500 mL). The mixture was refluxed for an additional 2 h, cooled to room temperature, and filtered. The solvent was removed in vacuo, and the residue was triturated with ether (100 mL). The solid was removed, ether was evaporated, and the residue was chromatographed on neutral alumina (activity II/III). Elution with pentane through pentane–ether (4:1) gave preliminary impure fractions followed by pure fractions. The elution was monitored by GC (DEGS, 170 °C). The pure fractions provided the tetracyclic ketone **20** (2.48 g, 36%; ≥98% pure by GC, DEGS, 170 °C). For spectral analyses, **20** was purified by Kugelrohr distillation [106–108 °C (1.8 kPa)]: ^{13}C NMR ($CDCl_3$) δ 214.2 (s), 50.0 (t), 49.0 (t), 47.2 (s), 45.4 (d), 38.2 (d), 36.7 (d), 35.5 (d), 34.6 (d), 15.7 (q); ^1H NMR ($CDCl_3$) δ 2.7–1.9 (m, 6 H), 1.8–1.2 (m, 3 H), 1.03 (s, 3 H); IR (neat) 3050 (m), 2960 (s), 2870 (m), 1727 (s), 1447 (m), 1337 (m), 1305 (m), 1280 (m) cm^{-1}; MS, *m/z* (relative intensity) 148 (M^+, 23), 133 (13), 120 (19), 105 (38), 91 (33), 79 (100), 78 (70), 69 (79). Anal. Calcd for $C_{10}H_{12}O$ (148.20): C, 81.04; H, 8.16. Found: C, 81.29; H, 8.21.

3-Methyl-4-brendanone-*9-d* (21). A suspension of the tetracyclic ketone **20** (2.3 g, 15.5 mmol) and 10% Pd/C (0.2 g) in ethyl acetate (7 mL) was stirred at room temperature for 24 h in a deuterium atmosphere at 400 kPa. The mixture was filtered through a short neutral alumina column (activity II/III). Evaporation of the solvent left 3-methyl-4-brendanone-*5,9-d_2*, **21a** (2.17 g, 92%; ≥98% pure by GC, DEGS, 170 °C). The analytical and spectral data of the protio analogue were as follows: mp 66–68 °C; ^{13}C NMR ($CDCl_3$) δ 223.0 (s), 51.7 (s), 51.1 (d), 45.0 (t), 44.5 (t), 38.9 (t), 38.4 (t), 38.1 (d), 33.0 (d), 20.0 (q); ^1H NMR ($CDCl_3$) δ 2.4–2.2 (m, 5 H), 1.64 (br s, 2 H), 1.41 (br s, 2 H), 1.01 (s, 3 H), 1.0–0.7 (m, 2 H); IR (neat) 2950 (s), 2860 (s), 1735 (s), 1445 (m), 1325 (m), 1058 (m) cm^{-1}; MS, *m/z* (relative intensity) 150 (M^+, 15), 122 (6), 93 (20), 91 (9), 81 (23), 80 (100), 79 (25), 77 (14). Anal. Calcd for $C_{10}H_{14}O$ (150.21): C, 79.95; H, 9.39. Found: C, 80.19; H, 9.57. A solution of the dideuteriated ketone **21a** (4.0 g, 26 mmol) and KOH (0.2 g, 3.5 mmol) in 50% aqueous dioxane (60 mL) was stirred under reflux for 4 h and then cooled and diluted with water (80 mL). The ketone was extracted with ether (3 × 100 mL). The extracts were combined, and the solvent was evaporated. The resulting ketone was subjected to the above procedure once again to give the monodeuteriated ketone, 3-methyl-4-brendanone-*9-d*, **21** (3.65 g, 93%; deuterium content: 70% d_1, 30% d_0 by MS).

3-Methyl-4-brendene-*9-d* (22). To a solution of ketone **21** (2.16 g, 14.3 mmol) in methanol (20 mL) were added (*p*-tolylsulfonyl)hydrazine (3.0 g, 16.1 mmol) and *p*-toluenesulfonic acid (~10 mg), and the mixture was stirred at 50 °C until all the (*p*-tolylsulfonyl)hydrazine was dissolved. The reaction mixture was then left overnight at −10 °C. The precipitated tosylhydrazone was collected by filtration (4.32 g, 95%). To a solution of diisopropylamine (11 mL, 7.9 g, 78 mmol) in dry tetrahydrofuran (30 mL), which was stirred at −78 °C, was added dropwise a 1.6 M hexane solution of *n*-butyllithium (35 mL, 56 mmol). Stirring was continued at this temperature for an additional 30 min. To the resulting lithium diisopropylamide solution stirred at −78 °C was then added dropwise a solution of the tosylhydrazone derived from ketone **21** (1.5 g, 4.7 mmol) in dry tetrahydrofuran (30 mL). Stirring was continued for 90 min at −78 °C and for an additional 4 h at room temperature. The mixture was diluted with pentane (100 mL), and a saturated aqueous solution of ammonium chloride (50 mL) was added dropwise. The layers were separated, and the organic one was washed successively with water (3 × 100 mL), 1 N hydrochloric acid (100 mL), and saturated aqueous $NaHCO_3$ solution (100 mL) and dried. Removal of the solvent in vacuo at room temperature left the crude olefin **22** (400 mg, 63%), which was purified for analyses by column chromatography on neutral alumina (activity I) with pentane as eluent followed by Kugelrohr distillation [90–92 °C (1.8 kPa)]. The analytical and spectral data for the protio analogue were as follows: ^{13}C NMR ($CDCl_3$) δ 143.8 (d), 137.2 (d), 59.4 (d), 48.7 (s), 43.96 (t or d), 43.87 (d or t), 42.6 (d), 37.4 (t), 34.4 (t), 24.1 (q); ^1H NMR ($CDCl_3$) δ 6.0–5.6 (m), 2.6–2.2 (m), 1.8–0.9 (m, sharp s at δ 1.02); IR (neat) 3040 (m), 2940 (s), 2860 (s), 1450 (m), 720 (m) cm^{-1}; MS, *m/z* (relative intensity) 134 (M^+, 27), 119 (17), 105 (16), 93 (100), 92 (26), 91 (65), 80 (14), 79 (31), 77 (49). Anal. Calcd for $C_{10}H_{14}$ (134.21): C, 89.49; H,

10.51. Found: C, 89.46; H, 10.77.

3-Methyl-4,5-*exo*-epoxybrendane-*9-d* (23). Crude 3-methyl-4-brendene-*9-d* (**22**; 400 mg, 2.96 mmol) was dissolved in methylene chloride (30 mL) and stirred at room temperature with a saturated aqueous solution of sodium bicarbonate (10 mL). MCPBA (850 mg, 4.2 mmol of the active substance) was added, and stirring was continued for an additional 4 h at room temperature. The layers were separated, and the organic one was washed with 1 N NaOH (2 × 20 mL) followed by water (2 × 20 mL) and dried. The solvent was evaporated, and the crude product was purified by column chromatography on neutral alumina (activity II/III). Elution with pentane–ether (3:1) gave epoxide **23** (240 mg, 34% based on the tosylhydrazone of ketone **21**; ≥95% pure by ^{13}C NMR). The analytical and spectral data for the protio analogue were as follows: mp 73–76 °C; ^{13}C NMR ($CDCl_3$) δ 63.6 (d), 59.2 (d), 45.6 (s), 45.2 (d), 41.6 (t), 40.6 (d), 36.7 (d), 35.0 (t), 32.7 (t), 21.0 (q); ^1H NMR ($CDCl_3$) δ 3.4–3.0 (m, 2 H), 2.6–2.1 (m, 2 H), 1.9–0.7 (m, 10 H; sharp signal at δ 1.12); IR (neat) 3010 (sh), 2950 (s), 2860 (s), 1445 (m), 1400 (m), 860 (m), 850 (m) cm^{-1}; MS, *m/z* (relative intensity) 150 (M^+, 5), 122 (9), 106 (32), 93 (82), 92 (24), 91 (25), 84 (100), 81 (34), 80 (84), 79 (47). Anal. Calcd for $C_{10}H_{14}O$ (150.21): C, 79.95; H, 9.39. Found: C, 80.17; H, 9.68.

8-Methylene-2-*exo*-noradamantanol-*4-d* (25). A solution of epoxide **23** (160 mg, 1.06 mmol) in dry acetone (2 mL) was stirred with a catalytic amount of trichloroacetic acid (~10 mg) for 30 min at room temperature. Water (30 mL) was added, and the mixture was extracted with chloroform (3 × 20 mL). The extracts were combined and dried. Removal of the solvent afforded the crude product, which was purified by column chromatography on neutral alumina (activity II/III) with pentane–ether (2:1) eluent to give pure 8-methylene-2-*exo*-noradamantanol-*4-d*, **25** (50 mg, 31%). The ^{13}C NMR, ^1H NMR, IR, and mass spectra of the protio analogue of **25**, which was obtained by this route, were identical with those of 8-methylene-2-*exo*-noradamantanol prepared by methyl-Grignard addition to hydroxy ketone **7** followed by dehydration of the resulting methyl diol **8** (Scheme I).

8-Methylene-2-noradamantanone-*4-d* (9a) was obtained in 55% yield by Jones oxidation of **25** through the use of the procedure described for **9**. Deuterium content: 70% d_1, 30% d_0 (by MS).

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Registry No. **4**, 102737-51-9; **7**, 88685-73-8; **8**, 116026-32-5; **9**, 102737-54-2; **9** (tosylhydrazone), 116026-34-7; **9a**, 116052-52-9; **10**, 116026-50-7; **11**, 116026-35-8; **11a**, 116026-36-9; **12**, 102737-53-1; **12a**, 116026-37-0; **18**, 32190-81-1; **18** (acid chloride), 33783-95-8; **19**, 116026-38-1; **20**, 116026-39-2; **21**, 116026-42-7; **21** (protio analogue), 116026-40-5; **21** (tosylhydrazone), 116026-44-9; **21** (protio analogue, tosylhydrazone), 116026-43-8; **21a**, 116026-41-6; **22**, 116026-46-1; **22** (protio analogue), 116026-45-0; **23**, 116026-48-3; **23** (protio analogue), 116026-47-2; **25**, 116026-49-4; **25** (protio analogue), 116026-33-6.

The Case Favoring Direct C-Alkylation of Heteroatom-Substituted Enolates

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The alkylation of selenium-stabilized enolates has been shown to proceed by direct alkylation of the enolate carbon atom, rather than by alkylation on selenium and subsequent alkyl group migration to carbon.

Heteroatom-substituted enolates have proven to be useful intermediates for performing many important chemical transformations. For example, depending upon the nature of the hetero group, one can exploit the presence of these heteroatom substituents to (a) enhance reaction regioselectivity, (b) facilitate functional group interconversions, and/or (c) suppress undesired side reactions, such as enolate exchange.[1] This is particularly true when the α-substituent in question is an arylsulfenyl or arylselenenyl group.[2]

From a mechanistic viewpoint these enolates formally belong to that class of anions whose enhanced nucleophilicity has been classified under the general rubric, the "α-effect". Although enolate alkylations with simple carbon-based electrophiles most likely involve straightforward S_N2 reactions, the corresponding processes with allylic electrophiles could proceed via a number of alternative pathways. In this regard, one can postulate three general mechanisms. These include: (a) direct allylation on carbon either by an S_N2 process to give **2** or by an S_N2' process to give **3** (see pathway A, Scheme I),[3] (b) heteroatom allylation of the enolate to form an ylide, **4**, followed by [2,3]-sigmatropic rearrangement of the allyl group to the α-position (see pathway B), or (c) O-allylation, followed by [3,3]-sigmatropic rearrangement (see pathway C).

Perhaps the most definitive mechanistic investigation of the allylation of heteroatom-substituted enolates is the elegant study of Reich and Cohen.[4] These workers have reported that enolates derived from seleno- and thio-substituted acetophenones, **6**, give products consistent with pathway B when alkylated with various allyl bromides and iodides. This hypothesis provides an attractive explanation for their observations for the following reasons: (a) assuming ylide formation is faster than direct C-alkylation, it is reasonable that products derived from [2,3]-sigma-

(1) For some papers dealing with this subject, see the following: (a) Reich, H. J.; Shah, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 3250. (b) Reich, H. J.; Shah, S. K. *J. Am. Chem. Soc.* **1977**, *99*, 263. (c) Reich, H. J. *J. Org. Chem.* **1975**, *40*, 2570. (d) Reich, H. J.; Chow, F. *J. Chem. Soc., Chem. Commun.* **1975**, 790. (e) Reich, J. J.; Shah, S. K. *J. Org. Chem.* **1977**, *42*, 1773. (f) Liotta, D.; Zima, G.; Barnum, C. *J. Org. Chem.* **1980**, *45*, 2737. (g) Liotta, D.; Zima, G.; Barnum, C.; Saindane, M. *Tetrahedron Lett.* **1980**, *21*, 3643. (h) Liotta, D.; Ensley, H. Saindane, M.; Barnum, C.; Balkrishnan, P. *Tetrahedron Lett.* **1981**, *22*, 3043.

(2) For a general description of the synthetic utility of selenium-stabilized enolates, see: *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley-Interscience: New York, 1987.

(3) Note that products derived from S_N2' reactions formally correspond to those obtained from pathway B.

(4) Reich, H. J.; Cohen, M. L. *J. Am. Chem. Soc.* **1979**, *101*, 1307.

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