The CH_3CN filtrate from the first recrystallization (2.7 L) was evaporated at a water pump to leave a mixture of oil and solid. This was triturated with ether (50 mL), cooled in ice, and then filtered to give a white solid (3.0 g): mp 146–158 °C, consisting of a mixture of **5** and **6**. The solid was heated in boiling ether (200 mL), cooled to room temperature, and filtered to give crude **6** (1.05 g): mp 170–173 °C. Recrystallization twice from ethyl acetate–isopropyl ether gave pure **6**: mp 174–175 °C; ^1H NMR (CD_2Cl_2) δ 7.74–6.78 (m, 52 H), 5.02 (s, 2 H, CHC=N), 4.47–3.36 (m, 26 H). Anal. Calcd for $C_{80}H_{80}N_{10}$: C, 81.31; H, 6.83; N, 11.86. Found: C, 80.93; H, 6.84; N, 11.77.

Quantitative FTIR Analysis. Throughout the IR spectral regions for compounds **5** and **6**, numerous differences were observed. These differences consisted of mostly overlapping absorbances; however, a sharp individual imine band at 1669 cm^{-1} was present for **6**. Other major distinguishable peaks for **6** occur at 3320 (w), 2847 (s), 2772 (w), 1735 (w), 1437 (s), 1247 (w), 1158 (s), 967 (s), 885 (w), 865 (w), and 610 cm^{-1} (w). Analytical standards were prepared with known weight percentages of pure **6** to pure **5** (0–15% by weight of **6**). Standards and samples were ground with KBr and loaded into the PPM-DRA cell. Quantitative analyses were determined on the recorded IR spectra (200 summed scans at 2 cm^{-1} resolution) utilizing the Nicolet partial least-squares (PLS) program version 2.1. Samples of the crude product and the once-recrystallized product from typical synthetic runs, as described above, were found to contain 5–6% and 2.5–3% of **6**, respectively.

HPLC Analysis. The crude reaction product from a typical run was analyzed on a Waters Model 990 HPLC system using a photodiode array detector (254 nm), a 712 WISP automatic injector, and a Model 510 pump. The adsorption column was a Varian MicroPak SI-10 (silica; 30 cm × 4 mm). Mobil phase: 90:10 $CHCl_3/CH_3CN$; flow rate: 1.0 mL/min; injection volume: 5.0 μL; run time: 10 min; sample size: 0.01 g/10 mL dissolved in mobil phase. Compounds **5** and **6** had retention times of 3.43 and 2.83 min, respectively. Minor impurities (*ca.* 1% total) were observed at retention times of 2.42, 4.39, and 6.74 min.

Single-Crystal X-ray Diffraction Analysis of Compound 6. $C_{80}H_{80}N_{10}$, FW = 1181.5, triclinic space group, $P\bar{1}$, a = 11.464 (2) Å, b = 12.172 (2) Å, c = 13.267 (3) Å, α = 114.57 (2)°, β = 95.30 (2)°, γ = 97.47 (2)°, V = 1647.2 (6) Å^3, Z = 1 ($^1/_2$ molecule per asymmetric unit), ρ_{calc} = 1.191 mg/mm^3, λ (MoKα) = 0.710 73 Å, μ = 0.066 mm^{-1}, $F(000)$ = 630, T = 293 K.

A clear colorless 0.22- × 0.36-mm crystal, in the shape of a prism, was used for data collection on an automated Siemens R3m/V diffractometer equipped with an incident beam monochromator. Lattice parameters were determined from 28 centered reflections within $24.3 \le 2\theta \le 33.4°$. The data collection range of hkl was $-12 \le h \le 12$, $-12 \le k \le 13$, $-14 \le l \le 1$, with $[(\sin\theta/\lambda]_{max}$ = 0.54. Three standards, monitored after every 97 reflections, exhibited random variations with deviations up to +2.5% during the data collection. A set of 4922 reflections was collected in the $\theta/2$ scan mode, with scan width $[2\theta(K_{\alpha1}) - 1.0]$ to $[2\theta(K_{\alpha2}) + 1.0]°$ and ω scan rate (a function of count rate) from 6.0°/min to 29.3°/min. There was 4326 unique reflections, and 3198 were observed with $F_o > 3\sigma(F_o)$. The structure was solved and refined with the aid of the SHELXTL system of programs.[11] The full-matrix least-squares refinement varied 462 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms and coordinates and isotropic thermal parameters for the hydrogen atoms bonded to the fused rings. Remaining H atoms were included by using a riding model [coordinate shifts of C applied to attached H atoms, C–H distance set to 0.96 Å, H angles idealized]. Final residuals were R = 0.058 and wR = 0.055 with final difference Fourier excursions of 0.28 and −0.23 eÅ^{-3}.

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Registry No. **5**, 124782-15-6; **6**, 141663-57-2; glyoxal, 107-22-2; benzylamine, 100-46-9.

(11) Sheldrick, G. M. *SHELXDTL80. An Integrated System for Solving, Refining, and Displaying Crystal Structures from Diffraction Data*; Univ. of Gottingen, Germany, 1980.

Supplementary Material Available: Tables of atomic coordinates, bond distances and angles, and anisotropic thermal parameters (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis and Nucleophilic and Photochemical Reactions of *F*-Adamantanone

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Introduction

The successful synthesis of perfluorinated diamondoids has been a synthetic challenge most successfully met by direct fluorination.[1-5] However, the high stability of C–F bonds has made such compounds difficult to functionalize or derivatize. This prompted us to search for a more direct route to functionalized perfluorodiamondoid derivatives. Adamantanone was synthesized many years ago,[6] is commercially available, and has been widely used as a starting material for preparing numerous adamantane derivatives;[7,8] therefore, we sought to synthesize *F*-adamantanone and study some of its reactions. In this paper, we report the synthesis, solution equilibria, and photochemical reactions of *F*-adamantanone.

Results and Discussion

With the help of spectroscopic techniques (vide infra), the major product (98% by weight) collected from the aerosol direct fluorination of adamantanone was identified as the analogous perfluoro ketone. Based on input of adamantanone, the yield of *F*-adamantanone was in the range of 50–73% which varied with the number of hours the product trap was pumped with the vacuum line. The longer the trap was pumped, the higher was the yield. This implies that there exists some kind of interaction between the carbonyl group of *F*-adamantanone and the NaF pellets in the product trap. Although direct fluorination of hydrocarbons into their perfluoro analogues with little carbon framework rearrangement or fragmentation has been achieved by other techniques, these synthesis methods have met with diminished success with diamondoid compounds because of the sensitivity of the compounds to HF generated during the fluorination.[2] In our case possible photolysis of the carbonyl group during photochemical finishing of the fluorination was a concern.[9] The successful synthesis of *F*-adamantanone with almost no fragmentation suggests that photolysis of the perfluoro ketone occurs too slowly to be important on the reactor time scale of about 1 min.

(1) Maraschin, N. J.; Catsikis, B. D.; Davis, L. H.; Jarvinen, G.; Lagow, R. J. *J. Am. Chem. Soc.* **1975**, *97*, 513.
(2) Robertson, G.; Liu, E. K. S.; Lagow, R. J. *J. Org. Chem.* **1978**, *43*, 4981.
(3) Adcock, J. L.; Robin, M. L. *J. Org. Chem.* **1983**, *48*, 3128.
(4) Adcock, J. L.; Luo, H. *J. Org. Chem.* **1992**, *57*, 2162.
(5) Huang, S.; Klein, D. H.; Adcock, J. L. *Rapid Commun. Mass Spectr.* **1988**, *2*, 204.
(6) Schleyer, P. v. R.; Nicholas, R. D. *J. Am. Chem. Soc.* **1961**, *83*, 182.
(7) Cuddy, B. D.; Grant, D.; Karim, A.; McKervey, M. A.; Rea, E. J. F. *J. Chem. Soc., Perkin Trans I* **1972**, 2701.
(8) Faulkner, D.; McKervey, M. A. *J. Chem. Soc.* **1971**, 3906.
(9) Giacometti, G.; Okabe, H.; Price, S. J.; Steacie, E. W. R. *Can. J. Chem.* **1960**, *38*, 104.

0022-3263/92/1957-4297$03.00/0

Table I. Concentration and Steric Effects on the Position of Equilibrium between *F*-Adamantanone and Its Hemiketals

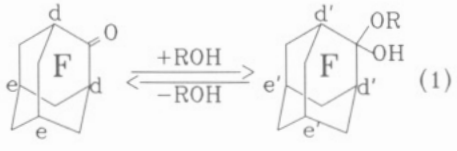
	R =					
	CH_3				$CH(CH_3)_2$	$C(CH_3)_3$
[ROH]/[*F*-ADM]	0	1.4	3.6	5.0	5.0	9.0
hemiketals (%)	0	31.5	66.6	100	42.8	5.7
$\phi_{d'}$ (ppm)			−220.60		−221.07	−222.27
$\phi_{e'}$ (ppm)			−224.26		−224.37	−224.55

Table II. Determination of *F*-Adamantanone/Hemiketal Equilibrium Constants by ^{19}F NMR

temp (°C)	rel peak intensities: ketone (ϕ_d)	rel peak intensities: hemiketal ($\phi_{d'}$)	K^a
Concentration (mmol): ketone, 0.2216; methanol, 0.8063			
$\Delta H^b = -37.02$ kJ·mol^{-1}; $\Delta S^b = -108.8$ J·mol^{-1}·K^{-1}			
25.3	1	4.23	6.35
27.8	1	3.48	5.16
30.1	1	3.37	5.00
32.7	1	3.07	4.53
35.2	1	2.57	3.75
37.7	1	2.55	3.71
40.2	1	2.19	3.15
42.7	1	1.84	2.62
45.2	1	1.74	2.46
47.7	1	1.49	2.08
50.2	1	1.41	1.97
52.7	1	1.25	1.72
55.2	1	1.24	1.70

[a] Equilibrium constant for hemiketal formation: dimensions are M^{-1}. [b] A straight line was obtained by plotting ln K vs $1/T$. ΔH and ΔS can be calculated from its slope and intercept, respectively.

Fluoro ketones have long been known as highly reactive, electrophilic carbonyl compounds which are readily susceptible to nucleophilic attack. Indeed, fluorination greatly enhances the tendency of a carbonyl group to add water and other nucleophiles[10] so that fluoro ketones exist predominantly as the hydrate in aqueous solution.[11-13] The carbonyl polarization has been presumed to be responsible for the enhanced electrophilicity of fluoro ketones relative to ketones. Recently Linderman and Jamois have argued against this explanation and provided a rationale based on the relative energy of the acceptor (LUMO) orbitals for fluoro ketones and ketones by results of MNDO and 6-31G** calculations.[14] Surprisingly, *F*-adamantanone is not hygroscopic and does not dissolve in or react with water to any detectible extent. However, *F*-adamantanone, dissolved in $CFCl_3$, reversibly forms hemiketals with alcohols (eq 1). These equilibria can be easily monitored



(1)

R=CH_3,$CH(CH_3)_2$,$C(CH_3)_3$

by ^{19}F NMR because the chemical shift of the bridgehead, tertiary fluorine atoms adjacent to the carbonyl group change significantly in chemical shift on substitution of the carbonyl. When the alcohol is methanol, a 1.4:1 ratio of alcohol to *F*-adamantanone produces a mixture which is about 32% in the hemiketal form. The expected concentration effect is observed; see Table I. Increasing the

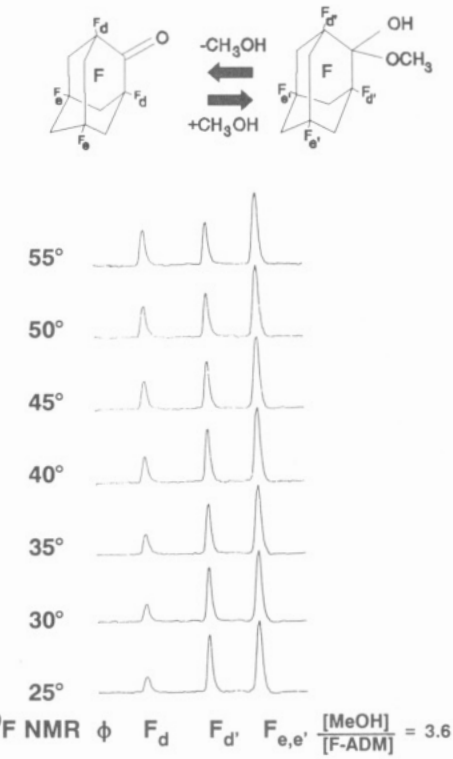


Figure 1. Temperature effect on the methanol/*F*-adamantanone hemiketal equilibrium.

Table III. Determination of *F*-Adamantanone/Hemiketal Equilibrium Constants by ^{19}F NMR

temp (°C)	rel peak intensities: ketone (ϕ_d)	rel peak intensities: hemiketal ($\phi_{d'}$)	K^a
Concentration (mmol): ketone, 0.2219; methanol, 0.3125			
$\Delta H^b = -35.34$ kJ·mol^{-1}; $\Delta S^b = -109.9$ J·mol^{-1}·K^{-1}			
25.2	1	0.733	2.63
27.7	1	0.663	2.32
30.2	1	0.633	2.19
32.8	1	0.599	2.05
35.2	1	0.526	1.75
37.8	1	0.489	1.60
40.3	1	0.453	1.46
42.7	1	0.410	1.29
45.3	1	0.394	1.24
47.7	1	0.350	1.07
50.3	1	0.296	0.89
52.7	1	0.264	0.78
55.2	1	0.243	0.71

[a] Equilibrium constant for hemiketal fromation: dimensions are M^{-1}. [b] A straight line was obtained by plotting ln K vs $1/T$. ΔH and ΔS can be calculated from its slope and intercept, respectively.

alcohol/ketone ratio to 5:1 results in disappearance of the ketone signals. The steric effect of the alkyl group of the alcohol is also apparent from Table I. At a given alcohol:ketone ratio the larger alkyl groups give lower percentages of hemiketal. Temperature effects on the position of equilibrium are also observed by ^{19}F NMR (Figure 1). The equilibrium shifts toward the ketone when the temperature is increased. This is consistent with an entropy effect. Equilibrium constants (K), enthalpy (ΔH), free energy (ΔG), and entropy (ΔS) can be derived from these NMR data (Tables II and III).[15] In all of these cases when

(10) Chambers, R. D. *Fluorine in Organic Chemistry*; John Wiley and Sons: New York, 1973; pp 219–25.
(11) Stewart, R.; Van der Linden, R. *Can. J. Chem.* **1960**, *38*, 399.
(12) Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898.
(13) Hine, J.; Flachskam, N. W. *J. Org. Chem.* **1977**, *42*, 1979.
(14) Linderman, R. J.; Jamois, E. A. *J. Fluorine Chem.* **1991**, *53*, 79.

(15) A detailed study on the nucleophilic reactions of *F*-adamantanone will be reported separately. For a comprehensive study of nucleophilic additions to a fluoro ketone, see: Ritchie, C. D. *J. Am. Chem. Soc.* **1984**, *106*, 7187. A linear free energy relation for the addition of nucleophiles to carbonyl compounds has been proposed: Sander, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154.

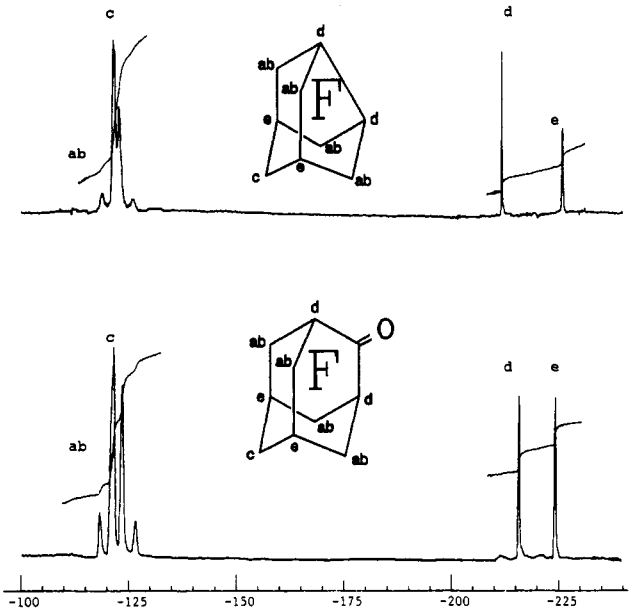
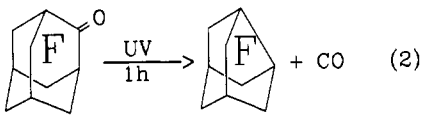


Figure 2. ^{19}F NMR spectra of *F*-noradamantane (top) and *F*-adamantanone (bottom).

a certain amount of water was added, the alcohol was extracted into the water layer and the equilibrium shifts back to the ketone. This clearly shows that the *gem*-diol is not stable and that its lack of reactivity with water is not simply due to the insolubility of the perfluorinated ketone in water. There is to our knowledge no available literature concerning the reversible addition of nucleophiles to nonfluorinated adamantanone and partially fluorinated adamantanones.

It was very interesting that the UV irradiation of *F*-adamantanone in either gas-phase or $CFCl_3$ (R-11) solution for as little as 10 min resulted in the formation of a new compound as suggested by monitoring changes in ^{19}F NMR. The signals corresponding to *F*-adamantanone disappeared gradually during irradiation. After 1 h of irradiation, *F*-adamantanone signals were no longer observed and a new set of signals with different chemical shifts appeared. Although the chemical shifts of the two compounds are different, the spectrum patterns were almost unchanged (Figure 2). This implied that the photochemical product had retained the C_{2v} symmetry of the parent compound, perhaps via the extrusion of CO followed by radical recombination to form a C–C bond (eq 2). This assertion was confirmed by mass spectrometry



(2)

and elemental analysis of the photochemical product. In addition, the released carbon monoxide was identified by FT-IR. The photochemical reaction of *F*-adamantanone was very clean and almost quantitative. In order to better understand the photochemical reaction, we conducted the irradiation of *F*-adamantanone in the presence of H_2, Cl_2, Br_2, or I_2. Only *F*-noradamantane was obtained in all cases. This is in contrast with the photolysis of hexafluoroacetone where radicals ($CF_3\dot{C}O$ or $^{\bullet}CF_3$) can be easily trapped by hydrogen and halogen.[16-18] This failure to capture intermediate radicals may be due to the fact that the two carbon radical centers formed from *F*-adamantanone are rigidly held in space and are unable to diffuse away so that the chance of recombination between them is enhanced. However a concerted reaction cannot be discounted.

The ^{19}F NMR spectra of *F*-adamantanone and *F*-noradamantane were very similar (Figure 2). Both compounds belong to the C_{2v} point group. In the case of *F*-adamantanone, while the four CF_2 groups nearest the carbonyl group are identical, the two fluorines comprising these CF_2 groups are not chemically equivalent. Since their chemical shift difference (355.5 Hz) is not much greater than their coupling constant (276.7 Hz), they gave a clear AB spectral pattern. The unique CF_2 group labeled F_c has two fluorine nuclei which are not only chemically but also magnetically equivalent, since a plane of symmetry bisects them. F_c is observed as a singlet (ϕ = −121.16 ppm) which overlaps the AB pattern. Signals d and e were assigned by comparing the methine fluorine region in the ^{19}F NMR spectra of *F*-adamantanone and its hemiketals. Signals d are very sensitive to the substituents of the carbonyl group and signals e are almost unchanged (see Table I); therefore, signals d were assigned to the bridgehead, tertiary fluorine atoms nearest to the carbonyl group. The ^{19}F NMR spectrum of *F*-noradamantane may be analyzed in a similar fashion.

Experimental Section

The perfluorination was carried out on an improved reactor and detailed operating procedures have been described elsewhere.[19] The products were characterized by vapor-phase infrared spectra recorded on a Bio-Rad Spc 3200 spectrometer. The negative chemical ionization (electron attachment) mass spectrum was recorded on a VG.ZAB-EQ mass spectrometer. Samples were introduced into the source via the reference inlet to a pressure of 10^{-6} Torr and diluted with nitrogen gas to 10^{-5} to 10^{-4} Torr and bombarded with 70-eV electrons. ^{19}F NMR spectra were determined on a JEOL FX90Q FTNMR spectrometer (using the omniprobe and NM-PVTS1 programmable VT system) in $CFCl_3$ as both solvent and internal standard. Elemental analyses were performed by E+R Microanalytical Laboratory, Inc., Corona, NY. Photolyses were carried out using a 550-W medium-pressure mercury lamp (Ace-Hanovia) in a water-cooled quartz immersion well.

Aerosol Direct Fluorination of Adamantanone. Adamantanone (99%) was used as received from Aldrich Chemical Co. without further purification. With reference to components in the citation[19] (Figure 1, aerosol fluorinator), the following fluorination conditions were used: preaerosol furnace (>1050 °C); main carrier, 500 mL/min He; hydrocarbon evaporator (110 °C), primary hydrocarbon carrier, 170 mL/min He, secondary hydrocarbon carrier, 500 mL/min He; module 1 (−18 °C), inlet 1-1, 170 mL/min He, 8 mL/min F_2; inlet 1-2, 170 mL/min He, 50 mL/min F_2; module 2 (−10 °C), inlet 2-1, 170 mL/min He, 36 mL/min F_2; inlet 2-2, 170 mL/min He, 6 mL/min F_2. In a typical run, adamantanone (1.5 g, 10 mmol) was first loaded into the evaporator. All helium carrier gas flows were started except the primary hydrocarbon carrier. When the thermocouple positioned above the crucible of the preaerosol furnace containing NaF powder reached 1050 °C, fluorine gas flows were started. When all gas flows were stable and required temperatures were reached, the dewar around the product trap was filled with liquid N_2. The valve controlling the primary hydrocarbon carrier was opened and the evaporator heated gradually until 110 °C at which temperature 2-adamantanone can be sublimed slowly. After 4.5 h, the reaction was stopped. The product trap was connected to the vacuum line and pumped for over 50 h to effect maximum transfer. Following trap to trap fractionation, 2.7 g of product was collected as a white solid in the −22 °C trap. Gas chromatographic separation on a Fluorosilicone QF-1 column (7 m × $^3/_8$ in.) showed only one peak

(16) Tucker, B. G.; Whittle, E. *Trans. Faraday Soc.* **1965**, *61*, 484.
(17) McIntosh, J. S. E.; Porter, G. B. *Trans. Faraday Soc.* **1968**, *64*, 119.
(18) Kibby, C. L.; Weston, R. E., Jr. *J. Chem. Phys.* **1968**, *49*, 4825.
(19) Adcock, J. L.; Cherry, M. L. *Ind. Eng. Chem. Res.* **1987**, *26*, 208.

other than the solvent (R-113) peak. The column temperature was 140 °C and retention time was 17.8 min. Anal. Calcd for $C_{10}F_{14}O$: C, 29.87; F, 66.15; H, 0.00. Found: C, 29.91; F, 65.80; H, 0.00. The prominent peaks in the mass spectrum were [m/z (formula, int.)] 403 ($^{13}CC_9F_{14}O$, 9.5), 402 ($C_{10}F_{14}O$, 100), 374 (C_9F_{14}, 4.1), 337 ($^{13}CC_8F_{12}$, 5.1), and 336 (C_9F_{12}, 45.0). The ^{19}F NMR spectrum consisted of an AB pattern (-120.47, -124.44 ppm) overlapped with a singlet (-121.16 ppm) in the CF_2 region and two unresolved peaks (-215.82, -224.26 ppm) in the CF region. The infrared spectrum contained a C=O absorption (1815.2 cm^{-1}).

Reaction of *F*-Adamantanone with ROH. *F*-Adamantanone (0.089 g, 0.22 mmol) was first dissolved in $CFCl_3$ contained in a 5-mm borosilicate NMR tube, and then a known amount of alcohol was added and the tube sealed. After up to 24 h for equilibration, ^{19}F NMR spectra were recorded. In temperature effect experiments, the NMR tube was sealed on the vacuum line and the spectrum was taken every 2.5 °C.

Synthesis of *F*-Noradamantane. *F*-Adamantanone (0.059 g, 0.146 mmol) was dissolved in $CFCl_3$ (R-11, 0.726 g) in a 5-mm borosilicate NMR tube. The NMR tube was sealed on the vacuum line and irradiated using a mercury lamp for 1 h. During irradiation, the atmospheric temperature increased to about 120 °C. After irradiation, the NMR tube was connected to the vacuum line. Following trap-to-trap fractionation, *F*-noradamantane (0.050 g, yield 91%) was obtained as a white solid in the -22 °C trap. Gas chromatographic separation on a Fluorosilicone QF-1 column (7 m × 3/8 in.) showed only one peak. The column temperature was 90 °C and the retention time was 12.8 min. Anal. Calcd for C_9F_{14}: C, 28.90; F, 71.10; H, 0.00. Found: C, 28.83; F, 71.42; H, 0.00. The prominent peaks in the mass spectrum were [m/z (formula, int.)] 375 ($^{13}CC_8F_{14}$, 9.0), 374 (C_9F_{14}, 100), 355 (C_9F_{13}, 7.4), and 336 (C_9F_{12}, 4.7). The ^{19}F NMR spectrum consisted of an AB pattern (-120.69, -123.88 ppm) overlapped with a singlet (-121.85 ppm) in the CF_2 region and two unresolved peaks (-211.91, -225.99 ppm) in the CF region. The infrared spectrum contained no C=O absorption.

Registry No. ADM, 700-58-3; F-ADM, 141635-73-6; F_2, 7782-41-4; CH_3OH, 67-56-1; $HOCH(CH_3)_2$, 67-63-0; $HOC(CH_3)_3$, 75-65-0; *F*-noradamantane, 141635-77-0; F-ADM (isopropyl hemiketal, 141635-75-8; F-ADM (*tert*-butyl hemiketal), 141635-76-9; F-ADM (methyl hemiketal), 141635-74-7.

Enantio- and Diastereoselective Synthesis of β-Substituted Cycloalkanecarboxylates

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Conjugate addition is a useful reaction for carbon-carbon formation. Asymmetric conjugate addition has been widely studied for the synthesis of optically active β-substituted or α,β-disubstituted carbonyl compounds.[1] In a previous paper,[2] we reported the utility of (*R*,*R*)-1,2-cyclohexanediol as a chiral auxiliary for asymmetric conjugate addition. 1,4-Addition of Ph_2CuLi to (*R*,*R*)-2-hydroxycyclohexyl (*E*)-2-pentenoate showed high diastereoselectivity. In this paper, we wish to report the enantio- and diastereoselective synthesis of β-substituted five- or six-membered cycloalkanecarboxylates using (*R*,*R*)-1,2-cyclohexanediol as a chiral auxiliary.

In pursuing the above synthesis, two types of reactions were planned. One was based on asymmetric conjugate addition and subsequent diastereoselective cyclization of the resulting enolate using substrates **1** and **2** (Table I, entries 1-5).[2a] The other was based on asymmetric conjugated addition to cycloalkenyl substrates **3** and **4** (Table I, entries 6-9) and following diastereoselective protonation.

Substrate **1** was synthesized by monoacylation of (*R*,*R*)-1,2-cyclohexanediol[3] with (*E*)-6-chloro-2-hexenoyl chloride in 60% yield. Compound **2** was synthesized from the corresponding chloride by treatment with NaI in 79% yield. Substrates **3** and **4** were also prepared by similar monoacylation with cycloalkene-1-carboxylic acid chlorides in 68% and 74% yields, respectively.

Reaction of **1** and **2** with R_2CuLi afforded the desireable trans-cyclized products **5-8A** and **5-8B** in the ratio of 7-9 to 1 (entries 1-4), which could be easily separated in an optically pure form by usual silica-gel column chromatography as reported in a previous communication.[2a]

Next, asymmetric conjugate addition to cycloalkenyl substrates (**3** and **4**) was studied. Reaction of the five-membered **3** with R_2CuLi at -30 °C (R = Ph) or at -50 °C (R = Bu) afforded, **5,6C** (49-51%) as a major product accompanied with a small amount of the other possible stereoisomers **5,6A,B,D** (entries 6 and 7). Reaction of the six-membered **4** with R_2CuLi (R = Ph, Bu) afforded two kinds of cis-oriented compounds **8,9C** (49-59%) and **8,9D** (14-29%) (entries 8 and 9). These two products could be easily isolated in an optically pure form by usual silica-gel column chromatography. The diastereomeric ratio of **C** and **D** was 2-3.5 to 1. From the above results, it is concluded that (1*R*,2*R*)-products **A** were predominantly obtained from substrates **1** and **2** and (1*S*,2*R*)-products **C** from substrates **3** and **4**.

The structure of each product was determined by the analysis of spectroscopic data and transformation to known compounds. As a typical example, in the ^1H NMR spectra of entries 1-3, disappearance of the signals attributable to CH_2Cl and olefinic protons in substrate **1** and new appearance of the signals due to H-1 and the alkyl (phenyl, butyl, and methyl) function in cyclized products support the formation of the five-membered ring, in addition to the molecular ion peak (M^+) in mass spectra. The similar ^{13}C NMR spectra of **5A** and **5B** showed that they are diastereomers. The relative configuration of two substituents on the five-membered ring was determined from the chemical shift of H-1 in the ^1H NMR spectra, comparing 1,2-cis and 1,2-trans isomers (Table II). It is generally accepted that a proton α to a vicinal substituent is more shielded when it is cis than when it is trans.[5] These δ values of H-1 suggest that the relative configurations of **5-7A,B** are trans and those of **5-6C,D** are cis (comments and reference ^1H NMR chemical shifts for C-1 H of *cis*- and *trans*-ethyl 2-acetoxy- and 2-hydroxycyclopentanecarboxylates are provided in the supplementary material). In the case of six-membered products (**8A,B**

(1) (a) Ullenius, C.; Christeson, B. *Pure Appl. Chem.* **1988**, *60*, 57. (b) Taylor, R. J. K. *Synthesis* **1985**, 364. (c) Wilheim, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. (d) Tomioka, K.; Koga, K. In *Asymmetric Synthesis*, Vol. 2; Morroson, J. D., Ed.; Academic Press: New York, 1983; p 219. (e) Somfai, P.; Tanner, D.; Alsson, T. *Tetrahedron* **1985**, *41*, 5973. (f) Cardani, S.; Poli, G.; Scolastico, C.; Villa, R. *Tetrahedron* **1988**, *44*, 5929. (g) Bermardi, A.; Cardani, S.; Pilati, T.; Poli, G.; Scolastico, C.; Villa, R. *J. Org. Chem.* **1988**, *53*, 1600. (h) Oppolzer, W.; Kingma, A. J.; Poli, G. *Tetrahedron* **1989**, *45*, 479.

(2) (a) Fang, C.-L.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1990**, *31*, 4751. (b) Fang, C.-L.; Ogawa, T.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry* **1991**, *2*, 389.

(3) (a) Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1987**, 838. (b) Xie, Z.-F.; Nakamura, I.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 966.

(4) This complex mixture was assumed to consists of **9B**, 1,4-adduct, and a dialkylated product by 1,4-addition and subsequent substitution of iodine with a butyl group.

(5) Kagan, H. B. *Stereochemistry*, Vol. 1; Georg Thieme Publishers: Stuttgart, 1977; p 92.

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