Registry No. 4-$NH_2C_6H_4SH$, 1193-02-8; 2-$MeOC_6H_4SH$, 7217-59-6; 4-$MeOC_6H_4SH$, 696-63-9; 4-MeC_6H_4SH, 106-45-6; 2-MeC_6H_4SH, 137-06-4; 3-MeC_6H_4SH, 108-40-7; PhSH, 108-98-5; 4-BrC_6H_4SH, 106-53-6; 3-ClC_6H_4SH, 2037-31-2; 2-ClC_6H_4SH, 6320-03-2; 3-$CF_3C_6H_4SH$, 937-00-8; 2-OHC_6H_4SH, 1121-24-0; 2,4,5-$Cl_3C_6H_2SH$, 3773-14-6; 4-$NO_2C_6H_4SH$, 1849-36-1; 2,3,4,5,6-Cl_5C_6SH, 133-49-3; MeO_2CCH_2SH, 2365-48-2; 3-$NO_2C_6H_4CH_2SH$, 77472-39-0; $PhCH_2SH$, 100-53-8; BuSH, 109-79-5; *t*-BuSH, 75-66-1; BuCl, 109-69-3; 4-$NH_2C_6H_4S^-$, 35337-61-2; 2-$MeOC_6H_4S^-$, 82044-19-7; 4-$MeOC_6H_4S^-$, 26971-83-5; 2-$MeC_6H_4S^-$, 24309-25-9; PhS^-, 13133-62-5; 4-$BrC_6H_4S^-$, 26972-20-3; 2-$ClC_6H_4S^-$, 82044-20-0; 2-$CF_3C_4H_4S^-$, 78232-02-7; 2-$OHC_6H_4S^-$, 58728-63-5; 2,4,5-$Cl_3C_6H_2S^-$, 78232-01-6; 4-$NO_2C_6H_4S^-$, 45797-13-5; 2,3,4,5,6-$Cl_5C_6S^-$, 46012-16-2; 2-naphthylS$^-$, 29869-27-0; *t*-BuS^-, 20733-19-1; *n*-BuS^-, 20733-16-8; $PhCH_2S^-$, 1492-49-5; 3-$NO_2C_6H_4CH_2S^-$, 82044-21-1; $MeO_2CCH_2S^-$, 64743-45-9; 9-$PhCH_2$-9-PhFl, 35377-96-9; $CH_3S(O)CH_2^-$, 13810-16-7; $PhCH_2SPh$, 831-91-4; 9-MeFl$^-$, 31468-21-0; $PhCH_2SC_6Cl_5$, 82044-22-2; 2,7-Br_2-9-MeFl$^-$, 73872-46-5.

Studies on Organic Fluorine Compounds. 38.[1] Ring-Opening Reactions of *gem*-Difluorocyclopropyl Ketones with Nucleophiles

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Received July 15, 1981

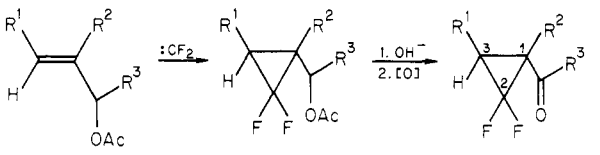
Syntheses of *gem*-difluorocyclopropyl ketones (**3a–d**) and their reactions with nucleophiles are described. Ring-opening reaction of **3a,c,d** having a hydrogen substituent at C_1 adjacent to the carbonyl group with a methanolate anion gave carboxylic acid derivatives derived from C_1–C_2 bond scission (between the carbon atom with an acyl group and the carbon atom with fluorine substituents). On the other hand, reaction of **3a–c** with a thiolate anion resulted in the C_1–C_3 bond cleavage (carbon–carbon bond opposite to the difluoromethylene group).

Introduction

Ring-opening reactions of dihalocyclopropanes, formed by the addition of dihalocarbene to carbon–carbon double bonds, are useful methods for homologation of carbon chain and ring enlargement in synthetic chemistry.[2] Although dichloro- and dibromocyclopropanes have been well investigated, a limited number of reports on the difluoro analogues, which would be expected to have unique features compared with those of dichloro or dibromo analogues due to the characteristic properties of carbon–fluorine bonds, have appeared.[3]

We have already reported our results on the ring-opening reaction of acetoxydifluorocyclopropanes with various nucleophiles[2] and its application to a synthesis of 24,24-difluoro-25-hydroxyvitamin D_3.[4] In our preliminary paper we have demonstrated that the ring-opening reaction of *gem*-difluorocyclopropyl ketones possessing a hydrogen substituent at the carbon atom adjacent to the carbonyl group with a methanolate anion and a thiolate anion occurred by a different course.[5] In this paper we will describe in detail the ring-opening reaction of *gem*-difluorocyclopropyl ketones with nucleophiles and its application to the construction of heterocyclic compounds by the reaction of *gem*-difluorocyclopropanes with two functional nucleophiles.

Scheme I



1a, 2a, 3a, R^1 = Ph; R^2 = H; R^3 = CH_3
1b, 2b, 3b, R^1 = Ph; R^2 = CH_3; R^3 = CH_3
1c, 2c, 3c, R^1 = H; R^2 = H; R^3 = *n*-Bu
1d, 2d, R^1 = Ph; R^2 = H; R^3 = H; **3d** R^1 = Ph; R^2 = H; R^3 = OCH_3

Results and Discussion

Syntheses of *gem*-Difluorocyclopropyl Ketones. It is known that the addition reaction of difluorocarbene generated by pyrolysis of sodium chlorodifluoroacetate to α,β-unsaturated carbonyl compounds usually proceeds in low yields due to the low reactivity of the electron-deficient carbon–carbon double bond toward electrophilic difluorocarbene and causes the formation of the side reaction products.[6] Therefore, we synthesized *gem*-difluorocyclopropyl ketones (**3**) by the following three-step procedure: (1) addition of difluorocarbene to the allyl acetate (**1**), (2) alkaline hydrolysis, and (3) Jones oxidation. Compound **3d** was prepared by treatment of the resulting carboxylic

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(4) Y. Kobayashi, T. Taguchi, T. Terada, J. Oshida, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, 2023 (1979).
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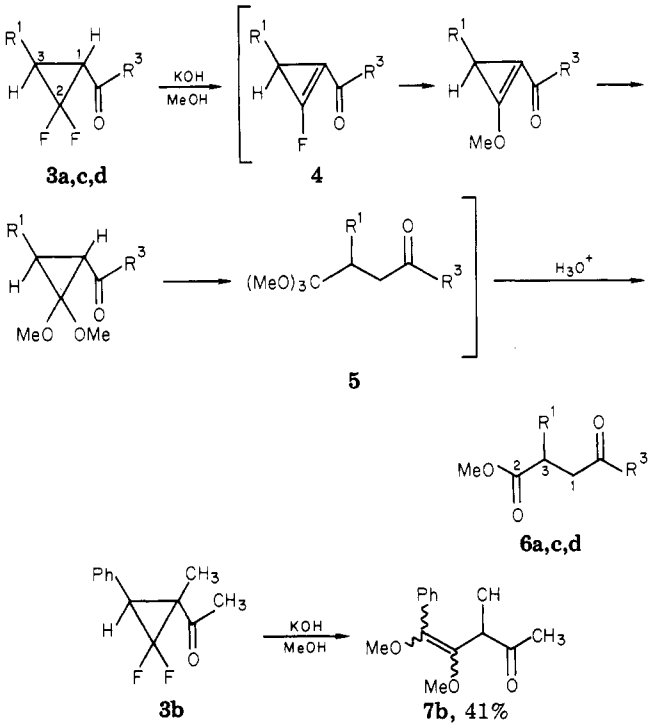
Scheme II



acid formed by these sequences with diazomethane (Scheme I).

When the starting allyl acetate (1) remained in the reaction of 1 with difluorocarbene, the unreacted 1 was converted to the more polar bromohydrin by treatment of the reaction mixture with *N*-bromosuccinimide in a mixture of dimethoxyethane and water, which caused the desired difluorocyclopropane (2) to be readily separated by silica gel column chromatography.

Reactions of **1a** and **1b**, which are of the *E* form, with difluorocarbene afforded the cyclopropanes (**2a** and **2b**) as a mixture of two racemic diastereoisomers, separable by column chromatography (SiO_2). By the subsequent hydrolysis and oxidation of **2a** and **2b**, both diastereoisomers were converted to the *gem*-difluorocyclopropyl ketones (**3a** and **3b**) as an identical single isomer from the data of their NMR spectrum and GLC assay. Because the addition of $:CF_2$ to carbon–carbon double bond proceeds in a stereospecific cis manner,[7] these results may indicate that the stereochemical relationship between the phenyl (R^1 = Ph) and the acetyl (R^3 = CH_3) groups of **3a** and **3b** is trans, as in the case of the starting allyl acetates (**1a** and **1b**).

Reactions of *gem*-Difluorocyclopropyl Ketones (3) with Methanolate Anion. First, we investigated the ring-opening reaction of *gem*-difluorocyclopropyl ketone (**3**) with a methanolate anion as a nucleophile. Reactions of **3a,c,d**, which have a hydrogen substituent at the C_1 adjacent to the carbonyl group, with a methanolate anion were found to afford the corresponding γ-keto esters or a succinic acid derivative via C_1–C_2 bond cleavage. On the other hand, the reaction of **3b**, which has a methyl substituent at C_1, with a methanolate anion gave a ring-opening product (**7b**) via C_1–C_3 bond cleavage (Scheme II).

For example, treatment of **3a** with 6 equiv of KOH in methanol and tetrahydrofuran (THF) for 12 h under reflux, followed by acidic workup, gave the γ-keto ester (**6a**) in 85% yield. Similarly, **3c** and **3d** afforded **6c** and **6d** in 33 and 13% yields, respectively, in both cases with recovery of the starting cyclopropanes. In these experiments, products derived from C_1–C_3 bond cleavage could not be detected.

Since the γ-keto esters (**6a,c,d**) thus obtained were readily hydrolyzed by KOH in methanol to the corresponding acids, the above results may indicate that the ring-opening products in the reactions of **3a,c,d** with a methanolate anion should be the ortho esters (**5**), which readily converted to the esters (**6**) by acidic workup. Parham and his co-workers reported that the ring-opening reaction of 1,1-dialkoxy-2-(phenylsulfonyl)cyclopropane with sodium alkoxide afforded the corresponding ortho ester.[8]

In contrast to the above-mentioned reactions, reaction of **3b** with KOH in a mixture of methanol and THF for 24 h under reflux proceeded rather slowly to afford **7b**, derived from C_1–C_3 bond cleavage, as a stereoisomeric mixture in 41% yield (**3b** was recovered in 15% yield).

Formation of **6** by the reactions of *gem*-difluorocyclopropyl ketones having a hydrogen substituent at C_1 (e.g., **3a,c,d**) with a methanolate anion may be explained as one of the possible pathways via the intermediary cyclopropene compound (**4**). Direct nucleophilic attack of the methanolate anion on C_2 may be excluded as a possible pathway, since **3b** reacts with the methanolate anion from initial attack of the methanolate anion at C_3 to cleave the C_1–C_3 bond of **3b**. Similar C_3 attack is observed in the reactions of the difluorocyclopropanes (**3a–c**) with the thiolate anion (vide infra).

Reaction with the Thiolate Anion. Reaction of **3** with the benzenethiolate anion easily proceeded to afford the products derived from C_1–C_3 bond cleavage of the difluorocyclopropyl ketones, exclusively. Thus, treatment of **3a** with 2.5 equiv of benzenethiol and 2.5 equiv of KOH in a mixture of methanol and THF at room temperature for 3 h gave 5-phenyl-4,5-bis(phenylthio)-3-penten-2-one (**9a**) and the corresponding β,γ-unsaturated ketone (**10a**) in 69 and 11% yields, respectively, while the products derived from C_1–C_2 bond cleavage of **3a**, such as thiol ester, thio ortho ester, or γ-keto acid, could not be detected. Longer reaction time (room temperature, 6h) reversed the ratio of **9a** (3% yield) and **10a** (80% yield), the latter being also formed by the treatment of **9a** with methanolic KOH quantitatively. These reactions may proceed via the intermediary β-fluoro enone (**8**) as follows: in the first stage, the C_1–C_3 bond of the cyclopropane ring is cleaved by nucleophilic attack of the thiolate anion on C_3 followed by the elimination of a fluorine atom to afford the intermediary β-fluoro enone (**8**). In the next stage, nucleophilic attack of the second thiolate anion on the β-carbon atom of **8** and elimination of a fluorine atom lead to the formation of α,β-unsaturated ketone (**9**), which easily isomerizes to β,γ-unsaturated ketone (**10**) under basic conditions (Scheme III). Similar results were obtained by the reactions of **3a–c** with benzenethiol or toluene-3,4-dithiol as summarized in Table I.

Reaction of **3a–c** with *o*-aminobenzenethiol and KOH in methanol or triethylamine in DMF gave the 1-thia-4-aza-2,3-dihydronaphthalene derivative (**13**), which was derived via C_1–C_3 bond cleavage of the cyclopropanes by initial nucleophilic attack of a thiolate anion on C_3 following the attack of an amino function on C_2 (Table I). The facts that the NH proton of **13** was observed around 12–13 ppm in the NMR spectrum and that the IR band ($\nu_{C=O}$) was observed about 1600 cm^{-1} indicate the presence

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Table I. Reaction of Difluorocyclopropanes (3a-c) with Benzenethiol, Toluene-3,4-dithiol, and o-Aminobenzenethiol

F_2-c-Pr	R^1	R^2	R^3	thiol	method[a]	time, h	products (yield, %)
3a	Ph	H	Me	14	A	3	9a (69), 10a (11)
3a	Ph	H	Me	14	A	6	9a (3), 10a (80)
3b	Ph	Me	Me	14	A	4	10b (72)
3c	H	H	n-Bu	14	A	5.5	10c (27)
3a	Ph	H	Me	15	A	3	11a (76)
3b	Ph	Me	Me	15	A	3	11b (90)
3c	H	H	n-Bu	15	A	6	12c (59)
3a	Ph	H	Me	16	B	5	13a (35)
3b	Ph	Me	Me	16	A	4.5	13b (73)
3c	H	H	n-Bu	16	B	5	13c (23)

[a] Method A = KOH/MeOH-THF, room temperature. Method B = Et_3N/DMF, 100 °C.

Table II. Spectral Data of the Compounds Obtained by the Reaction of 3a-c with Benzenethiol, Toluene-3,4-dithiol, and o-Aminobenzenethiol

compd[a]	IR $\nu_{C=O}$, cm^{-1}	NMR δ ($CDCl_3$)	formula	MS[b]
9a	1665 (neat)	2.28 (3 H, s), 4.97 (1 H, s), 6.90-7.38 (16 H, m)	$C_{23}H_{20}OS_2$	376.0955 (376.0958)
10a (l)[c]	1730 (CCl_4)	2.00 (3 H, s), 3.81 (2 H, s), 6.81-7.47 (15 H, m)	$C_{23}H_{20}OS_2$	376.0955 (376.0958)
10a (m)[c]	1730 (CCl_4)	1.69 (3 H, s), 3.26 (2 H, s), 6.90-7.53 (15 H, m)		
10b (l)[c]	1715 (neat)	1.47 (3 H, d, 7 Hz), 2.27 (3 H, s), 4.30 (1 H, q, 7 Hz), 6.90-7.37 (15 H, m)	$C_{24}H_{22}OS_2$	390.1112 (390.1118)
10b (m)[c]	1720-1700 (neat)	1.15 (3 H, d, 7 Hz), 1.97 (3 H, s), 3.48 (1 H, q, 7 Hz), 6.78-7.58 (15 H, m)		
10c (l)[c]	1720 (neat)	0.60-2.58 (9 H, m), 3.50 (2 H, s), 6.63 (1 H, s), 6.91-7.78 (10 H, m)	$C_{20}H_{22}OS_2$	342.1112 (342.1110)
10c (m)[c]	1720 (neat)	0.60-2.47 (9 H, m), 3.27 (2 H, s), 6.63 (1 H, s), 6.87-7.77 (10 H, m)		
11a[d]	1715 (KBr)	2.05 (3 H, s), 2.33 (3 H, s), 3.48 (2 H, s), 6.90-7.50 (8 H, m)	$C_{18}H_{16}OS_2$	312.0642 (312.0661)
11b	1720-1700 (neat)	1.32 (3 H, d, 7 Hz), 1.84 (3 H, s), 2.34 (3 H, s), 3.05 (1 H, q, 7 Hz), 7.00-7.40 (8 H, m)	$C_{19}H_{18}OS_2$	326.0799 (326.0799)
12c[e]	1665 (CCl_4)	0.80-2.50 (9 H, m), 2.32 (3 H, s), 3.52 (2 H, s), 6.24 (1 H, s), 6.80-7.30 (3 H, m)	$C_{15}H_{18}OS_2$	
13a	1620, 1590, 1560 ($CHCl_3$)	2.00 (3 H, s), 4.56 (1 H, s), 5.01 (1 H, s), 6.72-7.30 (9 H, m), 12.70 (1 H, br s)	$C_{17}H_{15}NOS$	281.0874 (281.0899)
13b[f]	1600, 1580, 1545 (KBr)	1.92 (3 H, s), 2.26 (3 H, s), 5.00 (1 H, s), 6.70-7.30 (9 H, m), 13.83 (1 H, br s)	$C_{18}H_{17}NOS$	
13c	1620, 1590, 1560 ($CHCl_3$)	0.80-2.48 (9 H, m), 3.18 (2 H, s), 5.10 (1 H, s), 6.76-7.24 (4 H, m), 12.36 (1 H, br s)	$C_{14}H_{17}NOS$	247.1031 (247.1033)

[a] All compounds, except 11a, 12c, and 13b were obtained as oil. [b] The observed values of high-resolution MS are shown in the parentheses. Compounds 12c (C, H, and S) and 13b (C, H, and N) gave satisfactory combustion analyses. [c] An abbreviation of "l" is used for the less polar compound and "m" for the more polar one on thin-layer chromatography (SiO_2). The ratio of the stereoisomers are as follows: 10a (l)/10a (m), 1.1:1; 10b (l)/10b (m), 1:2; 10c (l)/10c (m), 1.7:1. [d] mp 114-117 °C (from a mixture of n-hexane and ethyl acetate). [e] mp 113-117 °C (from cyclohexane). [f] mp 186-187 °C (from cyclohexane).

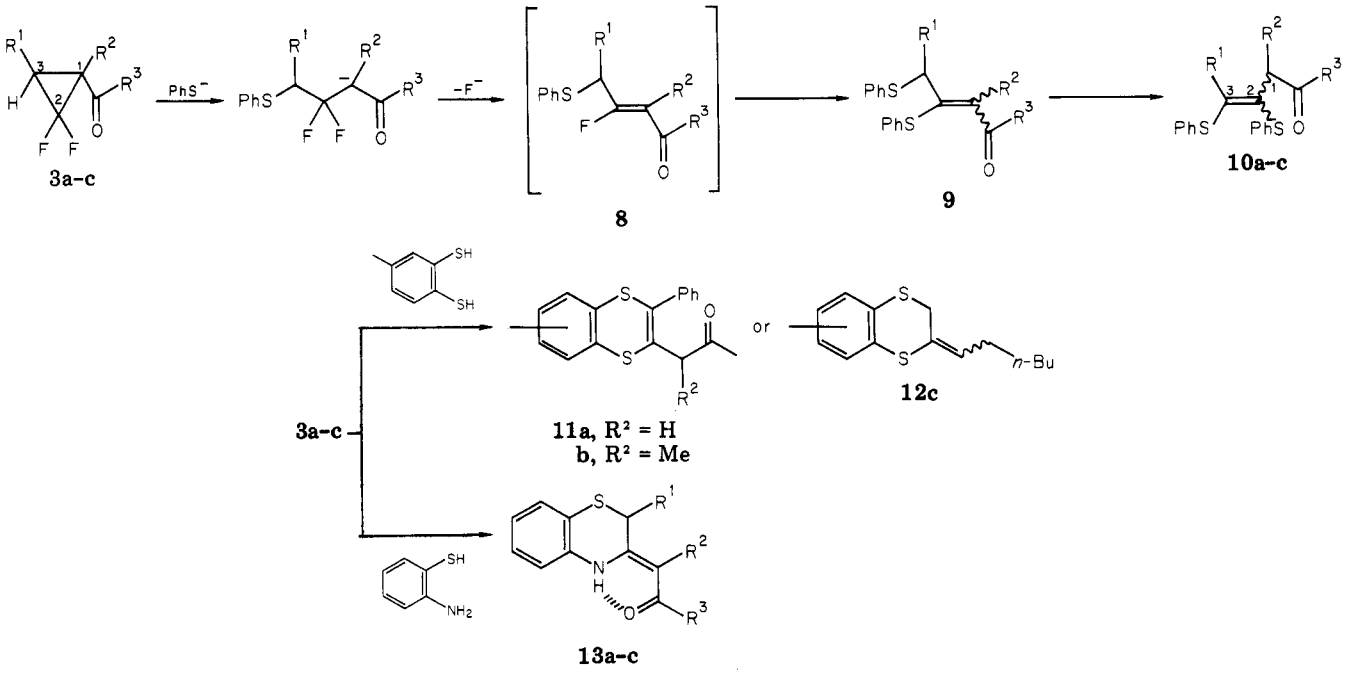
of an intramolecular hydrogen bond between the NH and carbonyl group and an α,β-unsaturated carbonyl structure (Scheme III).

These reactions show the high selectivity of the bond cleavage of the difluorocyclopropanes with the methanolate anion and the thiolate anion due to the presence of the fluorine atom. One possible explanation would be given by consideration of the basicity and the nucleophilicity of the methanolate anion and the thiolate anion and also of the stability of the intermediary carbanion. As mentioned before, reaction of the difluorocyclopropyl ketone, containing a hydrogen atom adjacent to the carbonyl group, with the methanolate anion is initiated by abstruction of the hydrogen atom on C_1 adjacent to both the carbonyl and difluoromethylene groups to form a dimethoxycyclopropane derivative, which further reacts with the methanolate anion to give the products derived from the C_1–C_2 bond cleavage. In the case of the thiolate anion, a stronger nucleophile, direct nucleophilic attack resulted in cleavage of the ring bond. Attack by thiolate anion at C_3 leads to the formation of the anion stabilized by both the carbonyl and β-difluoromethylene groups (C_1–C_3 bond cleavage), while attack at C_2 leads to the formation of the anion stabilized by a carbonyl group (C_1–C_2 bond cleavage). These results clearly show the difference between the substituent effect of fluorine and the alkoxy group on the cyclopropane ring in the nucleophilic ring-opening reactions.

Experimental Section

Melting points were taken on a hot-stage microscope (Yanagimoto) and are uncorrected. GLC analyses were run on a

Scheme III



Shimazu gas chromatograph, Model GC-3AF, equipped with a flame-ionization detector with a stainless-steel column (1 m) packed with 5% SE-30. Infrared spectra were recorded using a JEOL A-1 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian Associates Model T-60 or JEOL JNH-PS-100 spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale relative to tetramethylsilane internal standard. Fluorine magnetic resonance spectra were recorded on a Varian Associates Model T-60 spectrometer. Chemical shifts are reported in parts per million relative to benzotrifluoride internal standard, and a plus sign indicates high field.

1-(1-Acetoxyethyl)-2,2-difluoro-3-phenylcyclopropane (2a). After a solution of 24 g (158 mmol) of sodium chlorodifluoroacetate in 65 mL of diglyme was added dropwise during 1 h to a refluxing solution of 4 g (21 mmol) of **1a** in 12 mL of diglyme, the reaction mixture was refluxed for 20 min. The reaction mixture was cooled to room temperature, poured into 200 mL of ice–water, and extracted with 300 mL of *n*-hexane. The organic layer was washed with water three times and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was chromatographed on silica gel to give 2.25 g (45%) of the less polar isomer of **2a** and 2.18 g (43%) of the more polar isomer of **2a**. Less polar isomer of **2a**: bp 129 °C (5 mmHg) (bath temperature); IR (CCl_4) $\nu_{C=O}$ 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (3 H, d, J = 6 Hz), 2.0 (3 H, s, acetyl), 1.8–2.16 (1 H, m), 2.8 (1 H, ddd, J = 16, 8, and 5 Hz), 4.75–5.10 (1 H, m), 7.04–7.40 (5 H, m); ^{19}F NMR ($CDCl_3$) +68.4 (m); MS, m/e 240 (M^+), 180, 165. Anal. Calcd for $C_{13}H_{14}F_2O_2$: C, 64.99; H, 5.87; F, 15.82. Found: C, 64.93; H, 5.85; F, 15.93. More polar isomer of **2a**: bp 127–129 °C (5 mmHg) (bath temperature); IR (CCl_4) $\nu_{C=O}$ 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (3 H, d, J = 7 Hz), 2.3 (3 H, s, acetyl), 2.0–2.44 (1 H, m), 2.42–2.66 (1 H, m), 4.64–5.0 (1 H, m), 7.0–7.4 (5 H, m); ^{19}F NMR ($CDCl_3$) +68.6 (dd, J = 6 and 6 Hz) ppm; MS, m/e 240 (M^+), 180, 165. Anal. Calcd for $C_{13}H_{14}F_2O_2$: C, 64.99; H, 5.87; F, 15.82. Found: C, 65.14; H, 5.87; F, 15.91.

1-(1-Acetoxyethyl)-2,2-difluoro-1-methyl-3-phenylcyclopropane (2b) (Diastereoisomeric Mixture): yield 64%; bp 107–114 °C (4 mmHg); ^1H NMR ($CDCl_3$) δ 0.90–1.04 (3 H, m), 1.37 and 1.43 (3 H, 2 d, J = 6 and 6 Hz), 2.04 and 2.10 (3H, 2 s, acetyl), 2.52 and 2.88 (1 H, 2 d, J = 16 Hz), 4.76–5.12 (1 H, m), 7.08–7.44 (5 H, m); ^{19}F NMR ($CDCl_3$) +66.6 ppm for one isomer and +76.0 ppm for another isomer. MS, m/e 254 (M^+). Anal. Calcd for $C_{14}H_{16}F_2O_2$: C, 66.13; H, 6.34; F, 14.94. Found: C, 65.95; H, 6.61; F, 14.92.

1-(Acetoxymethyl)-2,2-difluoro-3-phenylcyclopropane (2d): yield 90%; bp 138–141 °C (22 mmHg); IR (CCl_4) $\nu_{C=O}$ 1750 cm^{-1}; ^1H NMR (CCl_4) δ 2.02 (3 H, s, acetyl), 2.1–2.41 (1 H, m), 2.64 (1 H, ddd, J = 14, 8, and 4 Hz), 4.08–4.44 (2 H, m), 7.05–7.40 (5 H, m); ^{19}F NMR (CCl_4) +69.8 (m) ppm; MS, m/e 226 (M^+), 147, 134. Anal. Calcd for $C_{12}H_{12}O_2F_2$: C, 63.71; H, 5.35; F, 16.80. Found: C, 63.60; H, 5.35; F, 16.67.

1-Acetyl-2,2-difluoro-3-phenylcyclopropane (3a). A solution of 5.32 g (95 mmol) of KOH and 8.88 g (37 mmol) of **2a** in methanol (150 mL) and THF (50 mL) was stirred for 2 h at room temperature. After the solvent was removed in vacuo, the residue was acidified with dilute HCl and extracted with ether. The organic layer was successively washed with $NaHCO_3$ solution and water and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was used for next step without purification. Thus, the crude alcohol was dissolved in acetone (100 mL), and to this solution was added Jones reagent at 0 °C until the characteristic orange color of the reaction mixture persisted for 20 min. To destroy the excess chromic acid, isopropyl alcohol was added to the reaction mixture, and then the reaction mixture was neutralized by the addition of solid $NaHCO_3$. After the precipitate was filtered off and washed with acetone, the combined filtrate was concentrated in vacuo. To the residue was added water, and the reaction mixture was extracted with ether, dried over $MgSO_4$, and chromatographed on silica gel to give 5.90 g (81%) of **3a**: bp 110–113 °C (8 mmHg); IR (CCl_4) $\nu_{C=O}$ 1720 cm^{-1}; ^1H NMR (CCl_4) δ 2.26 (3 H, s), 2.68–3.0 (1 H, m), 3.29–3.61 (1 H, m), 7.45–7.50 (5 H, m); ^{19}F NMR (CCl_4) +65.6 (m) ppm; MS, m/e 196 (M^+), 176, 153. Anal. Calcd for $C_{11}H_{10}F_2O$: C, 67.34; H, 5.14; F, 19.37. Found: C, 67.40; H, 5.07; F, 19.27.

1-Acetyl-2,2-difluoro-1-methyl-3-phenylcyclopropane (3b): yield 73%; bp 92–93 °C (7 mmHg); IR (neat) $\nu_{C=O}$ 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (3 H, dd, J = 2 and 2 Hz, 1-methyl), 2.03 (3 H, s, acetyl), 3.72 (1 H, dd, J = 16 and 2 Hz, methyne), 7.08–7.44 (5 H, m); ^{19}F NMR ($CDCl_3$) +62.4 (d, J_{F-F} = 151 Hz), +72.4 (d, J_{F-F} = 151 Hz) ppm; MS, m/e 210 (M^+), 195, 190, 167. Anal. Calcd for $C_{12}H_{12}F_2O$; C, 68.56; H, 5.75; F, 18.08. Found: C, 68.47; H, 5.60; F, 17.83.

1-Pentanoyl-2,2-difluorocyclopropane (3c): yield 73%; bp 70–73 °C (20 mmHg); IR (neat) $\nu_{C=O}$ 1720–1700 cm^{-1}; ^{19}F NMR ($CDCl_3$) +59.6 (d, J_{F-F} = 144 Hz), +75.8 (d, J_{F-F} = 144 Hz) ppm; MS, m/e 162 (M^+), 133, 126. High-resolution MS Calcd for $C_8H_{12}F_2O$: 162.0854. Found: 162.0853.

2,2-Difluoro-3-phenylcyclopropane-1-carboxylic acid: yield 53%; mp 92–94 °C; IR (KBr) $\nu_{C=O}$ 1710–1695 cm^{-1}; ^1H NMR (CCl_4) δ 2.68 (1 H, ddd, J = 10, 8, and 4 Hz), 3.47 (1 H, ddd, J = 10, 8, and 6 Hz), 7.08–7.64 (5 H, m), 10.2 (1 H, s); ^{19}F NMR (CCl_4) +65.6 (m) ppm; MS, m/e 198 (M^+), 178, 153, 133. High-resolution MS Calcd for $C_{10}H_8O_2F_2$: 198.0492. Found: 198.0481.

Methyl 2,2-Difluoro-3-phenylcyclopropane-1-carboxylate (3d). Treatment of the acid with diazomethane gave the methyl ester (**3d**) in quantitative yield: bp 70–75 °C (6 mmHg) (bath temperature); IR (CCl_4) $\nu_{C=O}$ 1750 cm^{-1}; ^1H NMR (CCl_4) δ 2.43–2.96 (1 H, m), 3.0–3.53 (1 H, m), 3.72 (3 H, s), 7.23 (5 H, m); ^{19}F NMR (CCl_4) +67.2 (m) ppm; MS, m/e 212 (M^+), 192, 181, 153, 133.

Methyl 4-Oxo-2-phenylpentanoate (6a). A solution of 183 mg (3.27 mmol) of KOH and 100 mg (0.51 mmol) of **3a** in a mixture of methanol (5 mL) and THF (1 mL) was refluxed for 12 h. The reaction mixture was diluted with dilute HCl and extracted with ether. The organic layer was washed with water, dried over $MgSO_4$, and then submitted to preparative TLC to give 89 mg (85%) of **6a**: mp 68–69 °C (lit.[9] 69.5–70 °C, from *n*-hexane and $CHCl_3$); IR (CCl_4) $\nu_{C=O}$ 1740, 1725 cm^{-1}; ^1H NMR (CCl_4) δ 2.07 (3 H, s), 2.30 (1 H, dd, J = 19 and 4 Hz), 2.83 (1 H, dd, J = 19 and 10 Hz), 3.55 (3 H, s), 3.62 (1 H, dd, J = 10 and 4 Hz), 6.88 (5 H, s). High-resolution MS calcd for $C_{12}H_{14}O_3$: 206.0943. Found: 206.0926.

Methyl 4-Oxooctanoate (6c). Reaction of 562 mg (10 mmol) of KOH and 332 mg (2.05 mmol) of **3c** in a mixture of methanol and THF (2 mL) for 48 h under reflux gave 118 mg (33%) of **6c**: bp 134–142 °C (20 mmHg) (bath temperature); IR (neat) $\nu_{C=O}$ 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–1.80 (7 H, m), 2.32–2.82 (6 H, m), 3.68 (3 H, s); MS, m/e 141 ($M^+ - OCH_3$), 130, 115, 85. Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 63.11; H, 9.45.

Dimethyl 2-Phenylbutanedioate (6d). A solution of sodium methoxide (Na, 150 mg) and **3d** (343 mg, 1.62 mmol) in methanol (15 mL) was refluxed for 18.5 h. The reaction mixture was concentrated in vacuo, the residue was acidified with dilute HCl and extracted with ether, and the extract was dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was treated with diazomethane in dichloromethane at 0 °C. The reaction mixture was submitted to preparative TLC to give 45 mg (13%) of **6d** and 228 mg (63%) of **3d**. **6d**: ^1H NMR (CCl_4) δ 2.50 (1 H, dd, J = 16 and 6 Hz), 3.08 (1 H, dd, J = 16 and 10 Hz), 3.58 (6 H, s, OCH_3), 3.94 (1 H, dd, J = 10 and 6 Hz), 7.16 (5 H, s); MS, m/e 222 (M^+).

3-Methyl-4,5-dimethoxy-5-phenylpent-4-en-2-one (7b). A solution of 815 mg (14.6 mmol) of KOH and 598 mg (2.84 mmol) of **3b** in a mixture of methanol (10 mL) and THF (2 mL) was refluxed for 24 h. After extractive workup, the reaction mixture was chromatographed on silica gel [*n*-hexane–AcOEt (5:1), v/v, as eluent] to give 151 mg (23%) of the less polar isomer of **7b**, 117 mg (18%) of the more polar isomer of **7b**, and 92 mg (15%) of **3b**. Further purification of the products by high-performance liquid chromatography gave analytical samples. Less polar isomer of **7b**: IR (CCl_4) $\nu_{C=O}$ 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3 H, d, J = 7 Hz), 2.28 (3 H, s), 3.34 (3 H, s), 3.38 (3 H, s), 3.74 (1 H, q, J = 7 Hz), 7.18–7.60 (5 H, m); MS, m/e 234 (M^+), 191, 159, 144. High-resolution MS Calcd for $C_{14}H_{18}O_3$: 234.1256. Found: 234.1243. More polar isomer of **7b**: IR (CCl_4) $\nu_{C=O}$ 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (3 H, d, J = 7 Hz), 2.08 (3 H, s), 3.12 (1 H, q, J = 7 Hz), 3.40 (3 H, s), 3.83 (3 H, s), 7.35 (5 H, br s); MS, m/e 234 (M^+), 191, 159, 144. High-resolution MS Calcd for $C_{14}H_{18}O_3$: 234.1256. Found: 234.124.

1-Phenyl-1,2-bis(phenylthio)pent-2-en-4-one (9a) and 1-Phenyl-1,2-bis(phenylthio)pent-1-en-4-one (10a). To a solution of 291 mg (2.64 mmol) of benzenethiol and 154 mg (2.75 mmol) of KOH in methanol (2 mL) was added a solution of 202 mg (1.03 mmol) of **3a** in THF (1 mL), and the reaction mixture was stirred for 3 h at room temperature. After extractive workup, the extracts were chromatographed on silica gel [*n*-hexane–AcOEt (10:1), v/v, as eluent] to give 268 mg (69%) of **9a** and 43.3 mg (11%) of **10a**, as a stereoisomeric mixture. The ratio between the less polar isomer and the more polar isomer of **10a** was 1:1.1. In another experiment, reaction of **3a** with benzenethiol and KOH at room temperature for 6 h afforded **9a** and **10a** in 3 and 80% yield, respectively.

Reaction of 3a with Toluene-3,4-dithiol. To a methanol solution (2.5 mL) of 199 mg (1.28 mmol) of toluene-3,4-dithiol and 153 mg (2.73 mmol) of KOH was added a solution of 200 mg (1 mmol) of **3a** in THF (1 mL), and the reaction mixture was stirred for 3 h at room temperature. After extractive workup, the extracts were concentrated in vacuo, and the residue was purified by preparative TLC to give 236 mg (76%) of the 1,4-dithiadihydronaphthalene derivative (**11a**): mp 114–117 °C (from *n*-hexane–AcOEt).

Reaction of 3b with *o*-Aminobenzenethiol. To a solution of 171 mg (1.36 mmol) of *o*-aminobenzenethiol and 152 mg (2.71 mmol) of KOH in methanol (2 mL) was added 222 mg (1.06 mmol) of **3b** in THF (1 mL), and the reaction mixture was stirred for 4.5 h at room temperature. The reaction mixture was diluted by the addition of water and extracted with ether. After the extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo, the residue was chromatographed on silica gel (CH_2Cl_2 as eluent) to give 227 mg (73%) of the 1-thia-4-aza-2,4-dihydronaphthalene derivative (**13b**): mp 186–187 °C (from cyclohexane).

Registry No. (*E*)-(±)-**1a**, 82045-04-3; (*E*)-(±)-**1b**, 82045-05-4; *trans*-(±)-**2a** (isomer 1), 74497-61-3; *trans*-(±)-**2a** (isomer 2), 74457-53-7; *trans*-(±)-**2b** (isomer 1), 74497-62-4; *trans*-(±)-**2b** (isomer 2), 74457-54-8; *trans*-(±)-**2d**, 82045-06-5; *trans*-(±)-**3a**, 82045-07-6; *trans*-(±)-**3b**, 82045-08-7; (±)-**3c**, 82045-09-8; *trans*-(±)-**3d**, 82045-10-1; (±)-**6a**, 82045-11-2; **6c**, 4316-48-7; (±)-**6d**, 82079-51-4; (*E*)-(±)-**7b**, 82056-47-1; (*Z*)-(±)-**7b**, 82045-12-3; (±)-**9a**, 82109-84-0; (*E*)-**10a**, 74457-46-8; (*Z*)-**10a**, 74457-47-9; (*E*-(±)-**10b**, 82045-13-4; (*Z*)-(±)-**10b**, 82045-14-5; (*E*)-**10c**, 74457-50-4; (*Z*)-**10c**, 74457-51-5; **11a**, 74463-97-1; (±)-**11b**, 82109-88-4; **12c**, 82109-87-3; (*Z*)-(±)-**13a**, 82045-15-6; (*Z*)-(±)-**13b**, 82045-16-7; (*Z*)-**13c**, 82045-17-8; **14**, 108-98-5; **15**, 496-74-2; **16**, 137-07-5; *trans*-(±)-2,2-difluoro-3-phenylcyclopropane-1-carboxylic acid, 82045-18-9.

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