Reactions of Trifluoromethyl Ketones. VIII.[1] Investigation of Steric Effect of a Trifluoromethyl Group through Ene Reaction of Trifluoromethyl Ketones[2]

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In the course of our study on the ene reaction of trifluoromethyl ketones, a trifluoromethyl group has been observed to behave as a larger substituent than commonly believed in the biomedicinal field. To estimate the steric effect of a trifluoromethyl group, we synthesized several trifluoromethyl ketones ($RCOCF_3$) and examined in detail their ene reaction with cyclohexene, a 1,2-disubstituted ene having the least steric requirement. In this reaction, a trifluoromethyl group was found to behave as if it were a much larger substituent than a phenyl or isobutyl group and as large as a *sec*-butyl group.

Keywords trifluoromethyl; steric effect; ene reaction; ketone; cyclohexene; homoallyl alcohol; enophile; steric requirement

There are many biologically active organofluorine compounds[3] and their activities are believed to be explicable on the basis that, in terms of steric requirement, a fluorine atom is nearly as small as a hydrogen atom, while a carbon–fluorine bond is much stronger than a carbon–hydrogen bond.[4] The hypothesis generally accepted in the biomedicinal field implies that an organism cannot distinguish a fluorine derivative of a biologically active compound from the unfluorinated one, and the fluorine compound is taken up in the metabolic path of the original compound. This is called the "mimic effect" of fluorine compounds. Similar examples are known where a methyl group is replaced by a trifluoromethyl group. For example, trifluoromethyldeoxyuridine derivatives show antiviral activity, since they are taken up in place of thymidine derivatives due to the similarity of the molecular shapes of both compounds. This "mimic effect" is common in the medicinal field and a trifluoromethyl group is considered to be as small as a methyl group.

On the other hand, the steric effect of a trifluoromethyl group has been reported to be much larger than that estimated in the biomedicinal field. Taft has proposed a scale of steric effect, Es,[5] based on a consideration of the hydrolysis of esters. Dubois' group critically revised the Es scale and proposed the Es' scale.[6] The Es value of a phenyl group is not mentioned, but the Es' value of a phenyl group is much larger than that of a trifluoromethyl group.

Sternhell *et al.* reported effective van der Waals radii based on the rotational barrier of biphenyl derivatives.[7] Here, a phenyl group shows a much smaller value than a *tert*-butyl group and a trifluoromethyl group shows a similar value, 2.2 Å, to an isopropyl group. This value of a *tert*-butyl group is much larger than that of a trimethylsilyl group, and that of a dimethylamino group is smaller than that of an amino group. These data show that the order of the effective values differs from that of the actual volumes of substituents. Della studied the conformation of 4-substituted trifluoromethylcyclohexanes by infrared (IR)[8a] and nuclear magnetic resonance (NMR)[8b] spectroscopy and showed that a trifluoromethyl group is larger than a methyl group. A similar analysis of cyclohexanes using ^1H-, ^{13}C- and ^{19}F-NMR showed that a trimethylsilyl group is as large as a trifluoromethyl group.[8c]

In the course of our study of the ene reaction of trifluoromethyl ketones,[9] we also noticed that a trifluoromethyl group could behave as a much larger substituent than expected from the mimic effect generally accepted in the biomedicinal field. Thus, the reaction of trifluoroacetone (**2**) with 2-octene (**1**) gave an *l*-isomer (**3**), based on Seebach–Prelog's notation,[10] regio- and stereoselectively.[9b] In the ene reaction with non-fluorinated enophiles, a proton of the methyl group is preferentially abstracted,[11] while a methylene proton was abstracted in our reaction. This difference in the regioselectivity can be explained by a comparison of the transition states (I and II in Chart 1). Namely, the transition state is presumed to be a chair form, and the steric repulsion between the trifluoromethyl group and the butyl group in II is much larger than that between the methyl group of **1** and the trifluoromethyl group of **2** in I. In I and II, the catalyst is shown as A, which is supposed to coordinate to the oxygen in an equatorial position of the cyclohexane form. This coordination is shown by a wedge. The stereoselectivity is explained as follows: repulsion between a hydrogen at the 1,3-diaxial position of **1** and the trifluoromethyl group of **2** in the transition state (III) is much larger than that between the methyl group of **2** and a hydrogen of **1** in the transition state (I). In the transition state III, the catalyst is not shown to avoid confusion. Thus, the *l*-isomer (**3**) is formed regio- and stereoselectively through the transition state I.

Steric effects reported so far have mainly been studied in terms of the conformational equilibria of substituted biphenyls or cyclohexanes, and few studies have been reported where regio- or stereoselectivity was controlled by the steric effect of a trifluoromethyl group. Therefore, we examined the ene reaction of other trifluoromethyl ketones, 1,1,1-trifluoro-2-hexanone (**4**) and α,α,α-trifluoroacetophenone (**5**), from the viewpoint of the steric effect. Interestingly, both ketones gave products of the same stereochemistry as in the case of **2** (Chart 2). The reaction of **4** with **1** gave 6-methyl-5-(trifluoromethyl)-7-dodecen-5-ol (**6**, a colorless oil, 63%), the ^{19}F-NMR spectrum of which

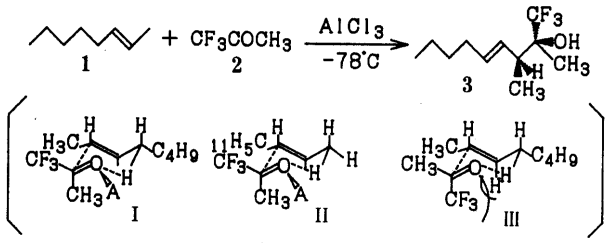


Chart 1

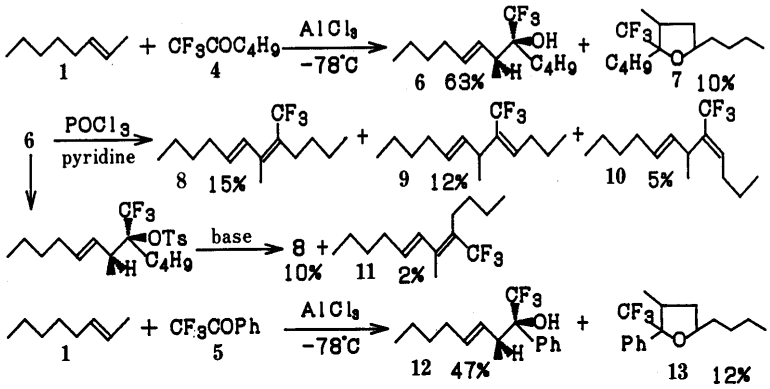


Chart 2

showed a signal at 11.97 ppm (from benzotrifluoride), together with two cyclized products (**7**) in 10% yield (total), but no stereo isomer of the alcohol (**6**) was detected. This alcohol (**6**) was dehydrated by the use of phosphoryl chloride and pyridine to give (5*Z*,7*E*)-6-methyl-5-(trifluoromethyl)-5,7-dodecadiene (**8**) with smaller amounts of (4*Z*,7*E*)- (**9**) and (4*E*,7*E*)-4,7-dienes (**10**), but (5*E*,7*E*)-diene (**11**) was not obtained.[12] The structure of **8** was determined by the fact that nuclear Overhauser effect (NOE) interaction between 7-H and the 4-methylene protons was not observed, while **11**, which was obtained by the reaction of the tosylate of **6** with potassium *tert*-butoxide in a smaller amount along with **8**, showed the NOE interaction. The ^{19}F-NMR chemical shift of a trifluoromethyl group *cis* to a double bond in dienes is lower than that of a trifluoromethyl group *trans* to a double bond. The chemical shifts, -7.49 ppm (**8**) and -5.92 ppm (**11**), support the above structures. This result shows that the stereochemistry of the homoallyl alcohol (**6**) is *l*. Trifluoroacetophenone (**5**) gave only the *u*-isomer (**12**) in Seebach–Prelog's notation. These results may suggest that a trifluoromethyl group behaves as a larger substituent than an *n*-butyl or a phenyl group in this reaction. This is far from the expectation based on the Es' values and roughly in accordance with the effective radii shown above.

Therefore, we planned to study the steric effect of the trifluoromethyl group in detail. For this purpose, we synthesized a number of trifluoromethyl ketones. Most of them were synthesized by the reaction of the corresponding Grignard reagent with trifluoroacetic acid, but *tert*-butyl trifluoromethyl ketone could not be synthesized by this method. Therefore, we chose thexyl trifluoromethyl ketone as a tertiary alkyl trifluoromethyl ketone and synthesized it using the ene reaction of trifluoroacetaldehyde as shown in Chart 3. Treatment of 2,3-dimethyl-2-butene with trifluoroacetaldehyde in the presence of $AlCl_3$ gave 1,1,1-trifluoro-3,3,4-trimethyl-4-penten-2-ol, which was hydrogenated and oxidized with Dess–Martin reagent to give thexyl trifluoromethyl ketone (**19**).

As reported before,[9] the ene reaction of trifluoromethyl ketones suffers from the steric effect of ene compounds. The reactivity of a 1,2-disubstituted ene compound is very low. Thus, for reinvestigation of the steric effect of the ene reaction, we chose cyclohexene (**20**), the 1,2-disubstituted alkene having the least steric hindrance, as an ene compound. The results are summarized in Table I, and determination of the structures is shown in Chart 4.

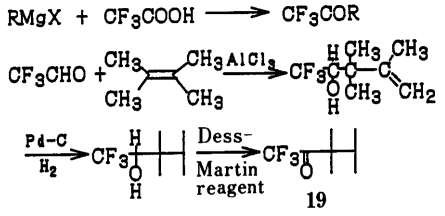


Chart 3

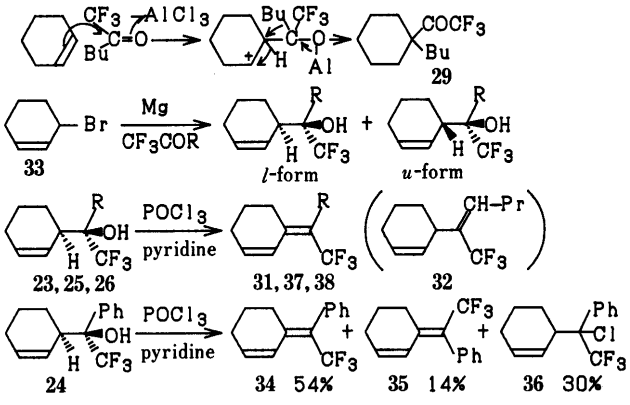
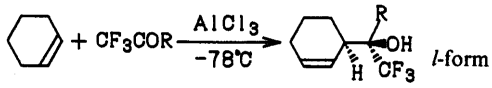


Chart 4

Trifluoroacetaldehyde (**14**) and the ketones from **2** to cyclohexyl trifluoromethyl ketone (**16**) reacted with an equimolar amount of **20** at $-78\,^{\circ}C$ to give ene reaction products of the same stereochemistry. *sec*-Butyl trifluoromethyl ketone (**17**) did not react under the above conditions, but it gave a small amount of the ene reaction product when four equivalents of **20** were used. The thexyl ketone (**19**) did not react at all, even when ten equivalents of **20** were used. Hexafluoroacetone (**18**) reacted without a catalyst but at $160\,^{\circ}C$ to afford a small amount of the product. The structures of the products were determined as follows. The structure of the ene product (**21**) from trifluoroacetaldehyde (**14**) was discussed in the previous paper.[1] The structure of the homoallyl alcohol (**22**) from trifluoroacetone (**2**) was established by X-ray analysis in connection with derivatization of **22** to trifluoro analogs of terpenes.[13] Concerning the ene reaction products from other trifluoromethyl ketones, both isomers of the homoallyl alcohols were synthesized by Grignard reaction of 3-bromocyclohexene (**33**) and the trifluoromethyl ketones. Examination of the spectral data of both isomers established that the ene reaction gave one isomer stereoselectively. Dehydration[12] of the ene reaction products (**23**, **25** and

TABLE I. Ene Reaction of $RCOCF_3$ with Cyclohexene



l-form

R	H	Me	*n*-Bu	Ph	iso-Bu	c-Hex	*sec*-Bu	CF_3	Thexyl
No.	**14**	**2**	**4**	**5**	**15**	**16**	**17**	**18**	**19**
Product	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	—
Yield (%)	43	53	41	21	9	6	6.7	7	0

26) gave only *Z*-isomers (**31**, **37** and **38**) of (trifluoromethyl)methylenecyclohexenes, the structures of which were established by NMR. The dehydration of **23** gave an unconjugated diene (**32**), but no stereoisomer of **31** was observed, while dehydration of the phenyl-substituted alcohol (**24**) gave a smaller amount of an *E*-isomer (**35**) together with a chlorinated compound (**36**). Compounds **35** and **36** seemed to be formed through a cation stabilized by the phenyl group. These results also support the proposed structures of the ene reaction products. The fact that all the ketones except thexyl trifluoromethyl ketone (**19**), which did not react at all, gave products of the same stereochemistry shows that a trifluoromethyl group has a larger steric effect than these alkyl groups, including a *sec*-butyl or phenyl group, in this reaction.

In the reaction of 1,1,1-trifluoro-2-hexanone (**4**), 1-butyl-1-(trifluoroacetyl)cyclohexane (**29**) was isolated. This may be formed through a cationic intermediate by migration of a hydride ion and a butyl group, as shown in Chart 4. The reaction of trifluoroacetophenone (**5**) gave a by-product, 7-phenyl-7-(trifluoromethyl)-6-oxabicyclo-[3.2.1]octane (**30**), which might be formed by the cyclization of **24** by the same mechanism as reported before for tetrahydrofuran formation.[14]

In conclusion, as proposed by several groups,[5-8] a trifluoromethyl group behaves as a much larger substituent in the transition states of the ene reaction described here than is commonly accepted in the biomedicinal field, in which the trifluoromethyl group is regarded as mimicking the methyl group in terms of effect on biological activities. In other words, a rigid, spherical trifluoromethyl group might show a larger steric effect in some transition states than a thin and flexible *n*-butyl group or a flat phenyl group, even though its total volume is much smaller than those of the latter groups.

Experimental

General Procedure ^{1}H-NMR spectra were obtained on JNM-FX90Q and JNM-GX400 spectrometers. ^{19}F-NMR spectra were recorded on the JNM-FX90Q spectrometer, using benzotrifluoride as an internal standard (upper field taken as plus).

Ene Reaction of 1,1,1-Trifluoro-2-hexanone (4) with 2-Octene (1) A solution of **1** (1.12 g, 10 mmol), the ketone **4** (1.54 g, 10 mmol) and $AlCl_3$ (1.32 g, 10 mmol) in anhydrous CH_2Cl_2 (20 ml) was stirred at −78 °C for 4 h. After usual workup, the products were separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 2 : 1) to give 2,5-dibutyl-3-methyl-2-(trifluoromethyl)tetrahydrofuran (**7**, 257 mg, 10%) and *l*-6-methyl-5-(trifluoromethyl)-7-dodecen-5-ol (**6**, 1.68 g, 63%). **6**: A colorless oil. MS *m/z*: 266 (M^+). HRMS Calcd for $C_{14}H_{25}F_3O$: 266.186. Found: 266.186. ^{1}H-NMR ($CDCl_3$) δ: 0.74—1.80 (16H, m), 1.10 (3H, d, J=7.2 Hz), 1.80—2.14 (2H, m), 2.10 (1H, s), 2.64 (1H, qd, J=7.2, 7.2 Hz), 5.17—5.74 (2H, m). ^{19}F-NMR ($CDCl_3$) ppm: 11.97 (s). **7**: A colorless oil. MS *m/z*: 266 (M^+). HRMS Calcd for $C_{14}H_{25}F_3O$: 266.186. Found: 266.184. ^{1}H-NMR ($CDCl_3$) δ: 0.60—2.00 (23H, m), 2.31—2.63 (1H, m), 3.66—4.20 (1H, m). ^{19}F-NMR ($CDCl_3$) ppm: 9.92 (s), 15.17 (s) (peak area ratio 2 : 3).

Ene Reaction of α,α,α-Trifluoroacetophenone (5) with 1 A solution of **1** (2.24 g, 20 mmol), the ketone (**5**, 3.48 g, 20 mmol) and $AlCl_3$ (2.64 g, 20 mmol) in anhydrous CH_2Cl_2 (15 ml) was stirred at −78 °C for 8.5 h. After usual workup, the products were separated by column chromatography (SiO_2, hexane–EtOAc, 20 : 1) to give 5-butyl-3-methyl-2-phenyl-2-(trifluoromethyl)tetrahydrofuran (**13**, 696 mg, 12%) and *u*-1,1,1-trifluoro-3-methyl-2-phenyl-4-nonen-2-ol (**12**, 2.70 g, 47%). **12**: A colorless oil, bp 100 °C/2.5 mmHg (bulb to bulb distillation). *Anal.* Calcd for $C_{16}H_{21}F_3O$: C, 67.11; H, 7.39. Found: C, 67.00; H, 7.53. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, d, J=7.0 Hz), 0.91 (3H, t, J=5.9 Hz), 1.06—1.63 (4H, m), 1.89—2.25 (2H, m), 2.62 (1H, s), 3.07 (1H, qd, J=7.0, 6.8 Hz), 5.41—5.91 (2H, m), 7.23—7.68 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 10.89 (s). **13**: A colorless oil, bp 90 °C/3 mmHg (bulb to bulb distillation). *Anal.* Calcd for $C_{16}H_{21}F_3O$: C, 67.11; H, 7.39. Found: C, 67.21; H, 7.57. ^{1}H-NMR ($CDCl_3$) δ: 0.58—2.38 (11H, m), 0.77 (3H, d, J=7.0 Hz), 2.64—3.14 (1H, m), 3.96—4.55 (1H, m), 7.06—7.74 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 13.03 (s), 13.08 (s) (peak area ratio 1 : 3).

General Procedure for Synthesis of Trifluoromethyl Ketones A solution of trifluoroacetic acid in Et_2O was added dropwise at room temperature to a solution of Grignard reagent, which was formed by treatment of Mg with alkyl halide in dry Et_2O. The mixture was stirred for 12 h, then poured into concentrated HCl–ice and extracted with Et_2O. The Et_2O layer was washed with saturated $NaHCO_3$ and saturated NaCl, and dried over $MgSO_4$. Distillation of the mixture gave the corresponding trifluoromethyl ketone.

Isobutyl Trifluoromethyl Ketone (**15**): Mg (9.6 g, 0.4 mol), isobutyl bromide (49.2 g, 0.4 mol), and trifluoroacetic acid (22.5 g, 0.2 mol) were allowed to react to give isobutyl trifluoromethyl ketone (**15**, 6.89 g, 11%). **15**: A colorless oil, bp 71 °C. IR (film): 1770 (C=O) cm^{-1}. MS *m/z*: 154 (M^+) (EI-MS); 155 (M+1) (CI-MS). HRMS Calcd for $C_5H_6F_3O$ (M−CH_3): 139.037. Found: 139.036. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (6H, d, J=6.9 Hz), 2.24 (1H, heptet-t, J=6.9, 6.9 Hz), 2.59 (2H, d, J=6.9 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 17.53 (s).

Cyclohexyl Trifluoromethyl Ketone (16) This ketone was formed as in the case of isobutyl trifluoromethyl ketone by Grignard reaction of cyclohexyl bromide. **16**: Yield 15%. A colorless oil, bp 123 °C. IR (film): 1758 (C=O) cm^{-1}. MS *m/z*: 179 (M−H) (EI-MS); 181 (M+1) (CI-MS). HRMS Calcd for $C_8H_{11}F_3O$: 180.076. Found: 180.076. ^{1}H-NMR ($CDCl_3$) δ: 1.13—2.19 (12H, m), 2.59—2.99 (1H, m). ^{19}F-NMR ($CDCl_3$) ppm: 15.34 (s).

***sec*-Butyl Trifluoromethyl Ketone (17)** This ketone was formed as above through Grignard reagent. **17**: Yield 10%. A colorless oil, bp 82 °C. IR (film): 1762 (C=O) cm^{-1}. MS *m/z*: 154 (M^+). HRMS Calcd for $C_6H_9F_3O$: 154.061. Found: 154.060. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t, J=7.4 Hz), 1.13 (3H, d, J=7.2 Hz), 1.66 (2H, qd, J=7.4, 7.2 Hz), 3.14 (1H, qt, J=7.2, 7.2 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 15.96 (s).

Thexyl Trifluoromethyl Ketone (1,1,2-Trimethylpropyl Trifluoromethyl Ketone) (19). Ene Reaction of 2,3-Dimethyl-2-butene with Trifluoroacetaldehyde (Synthesis of 1,1,1-Trifluoro-3,3,4-trimethyl-4-penten-2-ol) $AlCl_3$ (2.64 g, 20 mmol) was added portionwise at −78 °C to a solution of trifluoroacetaldehyde, which was obtained by treating trifluoroacetaldehyde ethyl hemiacetal (16 ml) with concentrated H_2SO_4 (24 ml), and 2,3-dimethyl-2-butene (3.25 g, 39 mmol) in anhydrous CH_2Cl_2 (50 ml). The mixture was stirred at −78 °C for 2 h, then poured into ice–concentrated HCl and extracted with Et_2O. The Et_2O layer was washed with dilute HCl, saturated $NaHCO_3$ and saturated NaCl, and dried over $MgSO_4$. After evaporation of the solvent under atmospheric pressure, the residue was distilled under vacuum to give 1,1,1-trifluoro-3,3,4-trimethyl-4-penten-2-ol (4.92 g, 69%). 1,1,1-Trifluoro-3,3,4-trimethyl-4-penten-2-ol: A colorless oil, bp 95 °C/95 mmHg. MS *m/z*: 182 (M^+). HRMS Calcd for $C_8H_{13}F_3O$: 182.092. Found: 182.092. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (6H, br s),

1.80 (3H, br s), 2.27 (1H, d, J=5.3 Hz), 3.92 (1H, dq, J=5.3, 7.6 Hz), 4.80—5.17 (2H, m). ^{19}F-NMR ($CDCl_3$) ppm: 8.56 (d, J=7.6 Hz).

1,1,1-Trifluoro-3,3,4-trimethyl-2-pentanol (Reduction of 1,1,1-Trifluoro-3,3,4-trimethyl-4-penten-2-ol) A solution of 1,1,1-trifluoro-3,3,4-trimethyl-4-penten-2-ol (4.78 g, 26.3 mmol) in MeOH (100 ml) was shaken with 5% Pd–C (200 mg) in an atmosphere of hydrogen at room temperature. After filtration to remove the catalyst, the solution was concentrated and the residue was distilled under vacuum to give 1,1,1-trifluoro-3,3,4-trimethyl-2-pentanol (3.35 g, 69%). 1,1,1-Trifluoro-3,3,4-trimethyl-2-pentanol: A colorless oil, bp 80 °C/33 mmHg (bulb to bulb distillation). MS m/z: 151 ($M-CH_3-H_2O$). HRMS (Calcd for $C_7H_{10}F_3$: 151.073. Found: 151.074. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (6H, d, J=7.0 Hz), 0.92 (3H, br s), 0.98 (3H, s), 1.89 (1H, heptet, J=7.0 Hz), 2.14 (1H, d, J=8.0 Hz), 3.89 (1H, dq, J=6.6, 8.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 8.27 (d, J=8.0 Hz).

1,1,2-Trimethylpropyl Trifluoromethyl Ketone (19) (Oxidation of 1,1,1-Trifluoro-3,3,4-trimethyl-2-pentanol) A solution of 1,1,1-trifluoro-3,3,4-trimethyl-2-pentanol (8.75 g, 47.5 mmol) in anhydrous CH_2Cl_2 (200 ml) was added dropwise to a solution of Dess–Martin reagent (41 g, 96.7 mmol) in anhydrous CH_2Cl_2 (400 ml), at room temperature, and the mixture was stirred at this temperature for 1 h. Then 1.3 M NaOH (500 ml) was added, stirring was continued for 15 min, and the CH_2Cl_2 layer was separated. The CH_2Cl_2 layer was washed twice with 1.3 M NaOH (250 ml) and H_2O (100 ml), and dried over $MgSO_4$. Distillation of the extract gave **19** (7.01 g, 81%). **19**: A colorless oil, bp 123 °C. IR (film): 1746 (C=O) cm^{-1}. MS m/z: 167 ($M-CH_3$). HRMS Calcd for $C_7H_{10}F_3O$: 167.068. Found: 167.068. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (6H, d, J=6.8 Hz), 1.18 (6H, q, J=1.0 Hz), 2.24 (1H, heptet, J=6.8 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 9.65 (s).

A Typical Ene Reaction of Trifluoromethyl Ketones with Cyclohexene (20). Ene Reaction of 1,1,1-Trifluoro-2-hexanone (4) A solution of **20** (820 mg, 10 mmol), **4** (1.54 g, 10 mmol) and $AlCl_3$ (1.32 g, 10 mmol) in anhydrous CH_2Cl_2 (15 ml) was stirred at −78 °C for 4 h. The mixture was poured into dilute HCl and extracted with Et_2O. The Et_2O layer was washed with saturated $NaHCO_3$ and saturated NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was separated on a column chromatography (SiO_2, hexane–CH_2Cl_2, 4:1) to give 1-butyl-1-(trifluoroacetyl)cyclohexane (**29**, 902 mg, 38%) and *l*-3-[1-(trifluoromethyl)-1-hydroxypentyl]cyclohexene (**23**, 958 mg, 41%). **29**: A colorless oil. MS m/z: 236 (M^+). HRMS Calcd for $C_{12}H_{19}F_3O$: 236.139. Found: 236.139. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.8 Hz), 0.97—1.82 (14H, m), 1.90—2.32 (2H, m). ^{19}F-NMR ($CDCl_3$) ppm: 9.56 (s). IR (film): 1740 cm^{-1}. **23**: A colorless oil. MS m/z: 236 (M^+). HRMS Calcd for $C_{12}H_{19}F_3O$: 236.139. Found: 236.138. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=6.2 Hz), 1.10—2.16 (13H, m), 2.52—2.82 (1H, m), 5.59—6.06 (2H, m). ^{19}F-NMR ($CDCl_3$) ppm: 11.88 (s).

Ene Reaction of α,α,α-Trifluoroacetophenone (5) A solution of **20** (820 mg, 10 mmol), **5** (1.74 g, 10 mmol) and $AlCl_3$ (1.32 g, 10 mmol) in anhydrous CH_2Cl_2 (15 ml) was treated at −78 °C for 8 h. After workup as above, the residue was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 4:1) to give 7-phenyl-7-(trifluoromethyl)-6-oxabicyclo[3.2.1]octane (**30**, 725 mg, 28%) and *l*-3-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)cyclohexene (**24**, 527 mg, 21%). **30**: A colorless oil. MS m/z: 256 (M^+). HRMS Calcd for $C_{14}H_{15}F_3O$: 256.107. Found: 256.107. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.21 (2H, m), 1.37—1.66 (4H, m), 1.79—1.87 (1H, m), 2.56—2.69 (1H, m), 2.94—3.00 (1H, m), 4.68—4.74 (1H, m), 7.24—7.43 (3H, m), 7.91 (2H, d, J=7.6 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 12.71 (s). **24**: A colorless oil. MS m/z: 256 (M^+). HRMS Calcd for $C_{14}H_{15}F_3O$: 256.107. Found: 256.107. ^{1}H-NMR ($CDCl_3$) δ: 1.06—1.85 (4H, m), 1.86—2.14 (2H, m), 2.62 (1H, s), 2.93—3.26 (1H, m), 5.77—6.05 (1H, m), 6.05—6.31 (1H, m), 7.22—7.69 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 10.57 (d, J=1.5 Hz).

Ene Reaction of Isobutyl Trifluoromethyl Ketone (15) Reaction of **20** (820 mg, 10 mmol), **15** (1.40 g, 9 mmol) and $AlCl_3$ (1.32 g, 10 mmol) in anhydrous CH_2Cl_2 (5 ml) at −78 °C for 2.5 h, followed by column chromatography (SiO_2, hexane–CH_2Cl_2, 2:1) and preparative GLC twice (column, 15% DEGS 2 m × 4 mm; temperature, 100 °C; He, 30 ml/min; and AGL 2 m × 4 mm, 100 °C, 30 ml/min), gave *l*-3-[1-(trifluoromethyl)-1-hydroxy-3-methylbutyl]cyclohexene (**25**, 191 mg, 9%). **25**: A colorless oil. MS m/z: 236 (M^+). HRMS Calcd for $C_{12}H_{19}F_3O$: 236.139. Found: 236.139. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J=6.7 Hz), 1.00 (3H, d, J=6.7 Hz), 1.31—1.43 (1H, m), 1.45—1.64 (3H, m), 1.78—2.03 (5H, m), 2.09 (1H, br s), 2.58—2.66 (1H, m), 5.74 (1H, br d, J=10.4 Hz), 5.84—5.90 (1H, m). ^{19}F-NMR ($CDCl_3$) ppm: 12.89 (s).

Ene Reaction of Cyclohexyl Trifluoromethyl Ketone (16) Reaction of **20** (900 mg, 5 mmol), **16** (490 mg, 6 mmol) and $AlCl_3$ (0.66 g, 5 mmol) in anhydrous CH_2Cl_2 (5 ml) at −78 °C for 3 h, followed by column chromatography gave *l*-3-(1-cyclohexyl-1-hydroxy-2,2,2-trifluoroethyl)cyclohexene (**26**, 745 mg, 5.2%). **26**: A colorless oil. MS m/z: 262 (M^+). HRMS Calcd for $C_{14}H_{21}F_3O$: 262.154. Found: 262.154. ^{1}H-NMR ($CDCl_3$) δ: 1.11—1.36 (5H, m), 1.47—1.71 (3H, m), 1.71—1.90 (6H, m), 1.97—2.06 (3H, m), 2.13 (1H, s), 2.72—2.81 (1H, m), 5.78 (1H, br d J=10.4 Hz), 5.92—6.00 (1H, dddd, J=10.4, 3.5, 3.5, 2.5 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 6.87 (s).

Ene Reaction of *sec*-Butyl Trifluoromethyl Ketone (17) With an Equimolar Amount of **20**: Reaction of **20** (345 mg, 4.2 mmol), **17** (645 mg, 4.2 mmol) and $AlCl_3$ (600 mg, 4.5 mmol) in anhydrous CH_2Cl_2 (10 ml) at −78 °C for 2 h did not give any detectable ene reaction products on ^{1}H-NMR, ^{19}F-NMR, or GLC.

With Four-fold Molar Excess of **20**: Reaction of **20** (2.48 g, 30 mmol), **17** (1.2 g, 7.5 mmol) and $AlCl_3$ (1.3 g, 10 mmol) in anhydrous CH_2Cl_2 (20 ml) at −78 °C for 2 h, followed by column chromatography (SiO_2, hexane–CH_2Cl_2, 4:1) gave *l*-3-[1-(trifluoromethyl)-1-hydroxy-2-methylbutyl)]cyclohexene (**27**, 120 mg, 6.7%). **27**: A colorless oil. MS m/z: 236 (M^+). HRMS Calcd for $C_{12}H_{19}F_3O$: 236.139. Found: 236.139. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3/2H, t, J=7.5 Hz), 0.95 (3/2H, t, J=7.3 Hz), 1.00 (3/2H, dq, J=7.2, 1.7 Hz), 1.10 (3/2H, dq, J=6.9, 1.7 Hz), 1.47—1.69 (3H, m), 1.71—1.93 (3H, m), 1.93—2.04 (3H, m), 2.14 (1H, br s), 2.75—2.84 (1H, m), 5.74 (1H, br d, J=10.5 Hz), 5.97—6.04 (1H, m). ^{19}F-NMR ($CDCl_3$) ppm: 6.06 (s), 6.45 (s) (peak area ratio 6:5). This is a mixture of diastereoisomers at the *sec*-butyl carbon and the carbinol carbon.

Ene Reaction of 1 and Hexafluoroacetone (18) A solution of **20** (1.64 g, 20 mmol) and **18** (2 ml) in benzene (10 ml) was sealed in a stainless steel tube and heated at 160 °C for 24 h. The tube was cooled and opened, and the product was purified by vacuum distillation to give 3-[2,2,2-trifluoro-1-(trifluoromethyl)-1-hydroxyethyl]cyclohexene (**28**, 358 mg, 7%). **28**: A colorless oil. MS m/z: 248 (M^+). HRMS Calcd for $C_9H_{10}F_6O$: 248.063. Found: 248.062. ^{1}H-NMR ($CDCl_3$) δ: 1.48—1.62 (1H, m), 1.68 (1H, ddd, J=12.2, 12.2, 12.2 Hz), 1.84—1.94 (1H, m), 1.94—2.12 (3H, m), 2.84—3.01 (1H, m), 3.38 (1H, br s), 5.74—5.84 (1H, m), 5.84—5.94 (1H, m). ^{19}F-NMR ($CDCl_3$) ppm: 9.76 (q, J=9.4 Hz), 10.91 (q, J=9.4 Hz).

Ene Reaction of 1,1,2-Trimethylpropyl Trifluoromethyl Ketone (19) Reaction of **20** (8.2 g, 100 mmol), **19** (1.75 g, 9.6 mmol) and $AlCl_3$ (1.32 g, 10 mmol) in anhydrous CH_2Cl_2 (100 ml) at −78 °C for 5 h did not give any ene reaction products observable on ^{1}H-NMR, ^{19}F-NMR, TLC, or GLC.

Dehydration of *l*-3-(1,1,1-Trifluoro-2-hydroxy-2-hexyl)cyclohexene (23) A solution of **23** (236 mg, 1 mmol) and $SOCl_2$ (178 mg, 1.5 mmol) in pyridine (0.5 ml) was stirred at room temperature for 24 h. After usual workup, products were separated by column chromatography (SiO_2, hexane) to give a nonpolar oil (64 mg, 29%). Analysis of the ^{19}F-NMR spectrum showed that the oil consists of 3-[1-(trifluoromethyl)pentylidene]cyclohexene (**31**) and 3-[1-(trifluoromethyl)-1-hexenyl]cyclohexene (**32**, two isomers) in a ratio of 8:6:1. Compounds **31** and **32** were separated by preparative GLC (15% DEGS 2 m × 4 mm; 90 °C; He, 30 ml/min). **31**: A colorless oil. MS m/z: 218 (M^+). HRMS Calcd for $C_{12}H_{17}F_3$: 218.128. Found: 218.128. ^{1}H-NMR ($CDCl_3$) δ: 0.78—1.07 (3H, m), 1.07—1.58 (4H, m), 1.58—1.94 (2H, m), 2.01—2.54 (6H, m), 6.02 (1H, dt, J=10.3, 4.0 Hz), 6.54 (1H, dq, J=10.3, 2.6 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 7.02 (d, J=2.6 Hz). The stereochemistry of the new double bond was determined to be *Z* by comparison of the coupling constant between 2-H and F with those of other compounds. Therefore, the stereochemistry of **23** was assigned to be (*R**,*R**) or *l*. **32**: A colorless oil. MS m/z: 218 (M^+). HRMS Calcd for $C_{12}H_{17}F_3$: 218.128. Found: 218.128. ^{1}H-NMR ($CDCl_3$) (assigned to *Z*-isomer) δ: 0.91 (3H, t, J=7.3 Hz), 1.37—1.51 (1H, m), 1.43 (2H, q, J=7.3 Hz), 1.51—1.65 (2H, m), 1.82—1.92 (1H, m), 1.97—2.03 (2H, m), 2.20—2.29 (2H, m), 3.05 (1H, br s), 5.46 (1H, ddt, J=10.2, 3.4, 2.3 Hz), 5.70 (1H, t, J=7.0 Hz), 5.85 (1H, dtd, J=10.2, 3.7, 2.5 Hz). Other olefinic protons assigned to the *E*-isomer are: 5.54 (1/6H, br d, J=10.0 Hz), 5.75 (1/6H, m), 6.11 (1/6H, tq, J=5.9, 2.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −3.75 (s), 3.29 (d, J=2.0 Hz) (peak ratio *Z*:*E*=6:1).

Grignard Reaction of α,α,α-Trifluoroacetophenone (5) with 3-Bromocyclohexene (33) A solution of **33** (800 mg, 5 mmol) and **5** (174 mg, 1 mmol) in Et_2O (10 ml) was added dropwise at 0 °C to a suspension of Mg (120 mg, 5 mmol) in Et_2O. The solution was refluxed for 1 h, then poured into ice water containing NH_4Cl and extracted with Et_2O. The Et_2O layer was washed with saturated NH_4Cl and dried over $MgSO_4$. After evaporation of the solvent, the *u*-isomer (**24**, 134 mg) and the *l*-isomer of **24** (68 mg) were obtained by column chromatography. The *u*- and *l*-isomers showed *Rf* values of 0.40 and 0.27, respectively, on TLC analysis (SiO_2, hexane–CH_2Cl_2, 4:1). This analysis of the ene reaction product showed

that it did not contain any *l*-isomer. The *l*-isomer: MS *m/z*: 256 (M^+). HRMS Calcd for $C_{14}H_{15}F_3O$: 256.107. Found: 256.107. ^{1}H-NMR ($CDCl_3$) δ: 1.00—2.23 (6H, m), 2.37 (1H, s), 2.88—3.24 (1H, m), 4.96 (1H, br d, J=10.8 Hz), 5.64—5.91 (1H, m), 7.17—7.63 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 10.73 (d, J=1.5 Hz).

Dehydration of 24 A solution of **24** (1.024 g, 4 mmol) and $POCl_3$ (918 mg, 6 mmol) in pyridine (1 ml) was stirred at 110 °C for 48 h. After usual workup, the mixture was separated by column chromatography (SiO_2, hexane) to give a nonpolar oil (251 mg) and the starting material (359 mg, 35%). Analysis of the nonpolar oil by GLC (15% DEGS 2 m × 4 mm, 150 °C, N_2 at 30 ml/min) showed it contained 14% *E*-3-(2,2,2-trifluoro-1-phenylethylidene)cyclohexene (**34**), 54% *Z*-3-(2,2,2-trifluoro-1-phenylethylidene)cyclohexene (**35**), and 30% 3-(1-chloro-2,2,2-trifluoro-1-phenylethyl)cyclohexene (**36**). This oil was separated by preparative GLC (15% DEGS 2 m × 4 mm, 120 °C, He at 30 ml/min). **36** (the 3rd fraction): A colorless oil. MS *m/z*: 274 (M^+). HRMS Calcd for $C_{14}H_{14}ClF_3$: 274.074. Found: 274.073. ^{1}H-NMR ($CDCl_3$) δ: 1.09—2.29 (6H, m), 3.14—3.57 (1H, m), 4.97 (4/7H, d, J=11.0 Hz), 5.29—6.11 (10/7H, m), 7.14—7.85 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 5.37 (s), 6.16 (s) (peak area ratio 3 : 5). **34**: A colorless oil. MS *m/z*: 238 (M^+). HRMS Calcd for $C_{14}H_{13}F_3$: 238.097. Found: 238.097. ^{1}H-NMR ($CDCl_3$) δ: 1.81 (2H, tt, J=6.3, 6.3 Hz), 2.14—2.21 (2H, m), 2.68—2.76 (2H, m), 5.86 (1H, d, J=10.1 Hz), 5.99 (1H, dt, J=10.1, 4.3 Hz), 7.14—7.18 (2H, m), 7.30—7.39 (3H, m). ^{19}F-NMR ($CDCl_3$) ppm: −7.74 (s). The stereochemistry of the new double bond was determined to be *E* based on an NOE interaction (3.1%) between C2-H and phenyl protons. **35**: A colorless oil. MS *m/z*: 238 (M^+). HRMS Calcd for $C_{14}H_{13}F_3$: 238.097. Found: 238.096. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (2H, tt, J=6.3, 6.3 Hz), 2.09—2.11 (4H, m), 6.19 (1H, dt, J=10.4, 4.3 Hz), 6.76 (1H, dq, J=10.4, 2.3 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −8.71 (d, J=2.3 Hz), Since a two-dimensional-NMR (2D-NMR) analysis showed an NOE interaction between the phenyl protons and 4-CH_2 protons, the stereochemistry of the new double bond is considered to be *Z*. Therefore, the stereochemistry of **24** is estimated to be *u* or (*R*,S**).

Grignard Reaction of Isobutyl Trifluoromethyl Ketone (15) and 33 A solution of **33** (800 mg, 5 mmol) and **15** (280 mg, 1.8 mmol) in Et_2O (10 ml) was added slowly to a suspension of Mg (120 mg, 5 mmol) in Et_2O at 0 °C, and the mixture was refluxed for 1 h. After usual workup, the product was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 4 : 1) to give two fractions, crude *l*-isomer (**25**, 117 mg) and crude *u*-isomer of **25** (28 mg), each of which was further purified by preparative GLC (15% DEGS 2 m × 4 mm, 100 °C, He at 30 ml/min). The *Rf* values of the isomers on TLC (SiO_2, hexane–CH_2Cl_2, 4 : 1) were 0.29 and 0.19 (*l*- and *u*-): retention time on GLC (5% SE-30, 2 m × 4 mm; 110 °C; N_2, 30 ml/min) were 18.7 and 23.0 min. Thus, separations in TLC and GLC were good enough to rule out the possible formation of the *u*-isomer in the ene reaction. *u*-Isomer: A colorless oil. MS *m/z*: 236 (M^+). HRMS Calcd for $C_{12}H_{19}F_3O$: 236.139. Found: 236.138. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (6H, d, J=6.4 Hz), 1.30—2.27 (10 H, m), 2.52—2.85 (1H, m), 5.59—5.99 (2H, m). ^{19}F-NMR ($CDCl_3$) ppm: 12.93 (s).

Dehydration of 25 A solution of **25** (190 mg, 0.8 mmol) and $POCl_3$ (196 mg, 1.28 mmol) in pyridine (1 ml) was stirred at 110 °C for 48 h. After usual workup, analysis of the product showed it contained the starting material (60%), the dienes 15% and a chloro compound, which was assigned by GC-MS. It was separated by column chromatography (SiO_2, hexane) to give a mixture of the 1,3-diene and the 1,4-diene, from which the major product, the 1,3-diene (**37**), was isolated by preparative GLC (15% DEGS, 2 m × 4 mm; 100 °C; He at 30 ml/min). 3-[1-(Trifluoromethyl)-3-methylbutylidene]cyclohexene (**37**): A colorless oil. MS *m/z*: 218 (M^+). HRMS Calcd for $C_{12}H_{17}F_3$: 218.128. Found: 218.128. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, d, J=6.7 Hz), 1.71—1.83 (3H, m), 2.12—2.20 (4H, m), 2.36—2.44 (2H, m), 6.02 (1H, dt, J=10.4, 4.3 Hz), 6.57 (1H, dq, J=10.4, 2.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −7.78 (d, J=2.0 Hz). A long-range coupling between 2-H and fluorine supports the *Z*-structure. Further, no NOE interaction was observed between the 2-H and isobutyl protons. Formation of the *Z*-olefin shows that the structure of **25** is *l*.

Grignard Reaction of 33 and 16 A solution of **33** (1.6 g, 10 mmol) and **16** (720 mg, 4 mmol) in Et_2O (15 ml) was added slowly to a suspension of Mg (240 mg, 10 mmol) in Et_2O at 0 °C, and the mixture was refluxed for 1 h. After usual workup, the products were separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 4 : 1) to give the *l*-isomer (**26**, 116 mg, 11%) and *u*-isomer of **26** (118 mg, 11%). The *Rf* values of the isomers on TLC (SiO_2, hexane–CH_2Cl_2, 4 : 1) are 0.22 and 0.15, respectively, which eliminated the possibility of contamination of the ene reaction product by the *u*-isomer. *u*-Isomer: A colorless oil. MS *m/z*: 262 (M^+). HRMS Calcd for $C_{14}H_{21}F_3O$: 262.154. Found: 262.155. ^{1}H-NMR ($CDCl_3$) δ: 1.08—1.37 (5H, m), 1.44—1.60 (2H, m), 1.63—1.72 (1H, m), 1.75—1.92 (7H, m), 1.94—2.10 (3H, m), 2.64—2.76 (1H, m), 5.76 (1H, dddd, J=10.0, 3.5, 3.5, 2.8 Hz), 5.83 (1H, br d, J=10.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 6.36 (s).

Dehydration of 26 A solution of **26** (303 mg, 1.1 mmol) and $SOCl_2$ (476 mg, 4.0 mmol) in pyridine (1 ml) was stirred at room temperature for 12 h. After usual workup, the product was separated by column chromatography (SiO_2, hexane) to give a nonpolar oil (16 mg) containing *Z*-3-(1-cyclohexyl-2,2,2-trifluoroethylidene)cyclohexene (**38**, 42% from ^{19}F-NMR). No NOE was observed between 2-H and the methylene protons and only a small coupling was observed between 2-H and F. These results support the *Z*-structure and thus *l*-structure of the ene reaction product. **38**: MS *m/z*: 224 (M^+). HRMS Calcd for $C_{14}H_{19}F_3$: 224.144. Found: 224.143. Olefinic protons in 400 MHz NMR are 6.01 (1H, dt, J=11.0, 4.0 Hz) and 6.54 (1H, dq, J=11.0, 3.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −10.87 (s)

Dehydration of *u*-Isomer of 26 A solution of the *u*-isomer (223 mg, 0.8 mmol) and $SOCl_2$ (357 mg, 3.0 mmol) in pyridine (1 ml) was stirred at room temperature for 12 h. After usual workup, the product was purified by column chromatography (SiO_2, hexane) to give a nonpolar oil (5.8 mg), which contained 3-(1-cyclohexyl-2,2,2-trifluoroethylidene)cyclohexene as the major component. 2D-NMR analysis of this oil by 400 MHz NMR showed NOE between 2-H and the protons of cyclohexane. Therefore, the stereochemistry of the new double bond is *E* and thus that of the original product was *u*. MS *m/z*: 224 (M^+). HRMS Calcd for $C_{14}H_{19}F_3$: 224.144. Found: 224.144. ^{1}H-NMR ($CDCl_3$) δ: 6.10 (1H, dt, J=11.5, 4.0 Hz), 6.46 (1H, d, J=11.5 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −9.83 (s).

Grignard Reaction of 33 and 17 A solution of **33** (2.615 g, 16.2 mmol) and **17** (1.20 g, 8.1 mmol) in Et_2O (15 ml) was added dropwise to a suspension of Mg (390 mg, 16.2 mmol) in Et_2O at 0 °C, and the mixture was stirred at room temperature for 1 h. After usual workup, the products were separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 4 : 1) to give the *l*-isomer (**27**, 382 mg, 20%) and a *u*-isomer of **27** (142 mg, 7.4%). The *Rf* values of these isomers on TLC (SiO_2, hexane–CH_2Cl_2, 2 : 1) were 0.46 and 0.33, with clear separation. The *u*-isomer: A colorless oil. MS *m/z*: 236 (M^+). HRMS Calcd for $C_{12}H_{19}F_3O$: 236.139. Found: 236.137. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3/2H, t, J=7.3 Hz), 0.95 (3/2H, t, J=7.3 Hz), 1.01—1.08 (3H, m), 1.46—1.62 (2H, m), 1.70—2.05 (8H, m), 2.68—2.80 (1H, m), 5.76—5.85 (2H, m). ^{19}F-NMR ($CDCl_3$) ppm: 6.31 (s), 6.36 (s), (peak area ratio 1 : 1), isomers due to *sec*-butyl carbon.

References and Notes

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