Reactions of trifluoromethyl ketones. IX.* Investigation of the steric effect of a trifluoromethyl group based on the stereochemistry on the dehydration of trifluoromethyl homoallyl alcohols**

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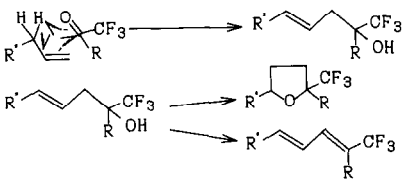
Abstract

In a previous paper we reported that a trifluoromethyl group behaves as a larger substituent than a butyl or a phenyl group and slightly larger than a *sec*-butyl group in ene reactions of trifluoromethyl carbonyl compounds. Dehydration of trifluoromethyl homoallyl alcohols, which are obtained by the ene reaction of trifluoromethyl ketones, has now been extensively investigated to compare further the steric effect of a trifluoromethyl group with those of other substituents. A trifluoromethyl group behaves as a substituent as large as a cyclohexyl group and a little smaller than a *sec*-butyl group Differences between steric effects in the ene reaction and in the dehydration are discussed

Introduction

In previous papers, we reported the ene reaction of trifluoromethyl ketones [3] and the derivatization of reaction products to various kinds of trifluoromethyl compounds [4], as shown in Scheme 1.



Scheme 1

*For Part VIII, see ref 1

**Part of this work was presented at the 200th Meeting of the American Chemical Society, August 1990, Washington DC, for a preliminary report, see ref 2

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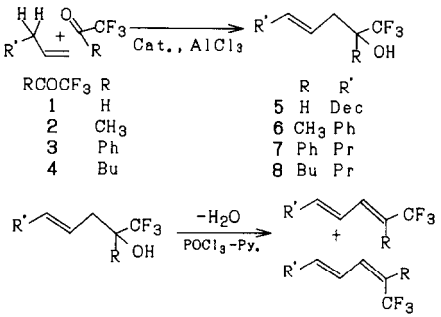
In this work, the trifluoromethyl group was found to behave as a larger substituent than expected from the small size it is commonly believed to have in the biomedicinal field [5], although a few reports have demonstrated that it shows as large a steric effect as a *sec*-butyl group [6]. Systematic study of the steric effect of a trifluoromethyl group on the ene reaction of trifluoromethyl ketones with cyclohexene showed that its steric effect is much larger than those of a phenyl or a butyl group and a little larger than that of a *sec*-butyl group [1]. To examine whether this large steric effect of a trifluoromethyl group is general or not, we examined the dehydration of the homoallyl alcohols which are the ene reaction products of trifluoromethyl ketones. This examination also showed that the steric effect of a trifluoromethyl group is fairly large, although the order of the steric effects of various substituents is slightly different from that in the above ene reaction.

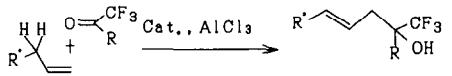
Results and discussion

Scheme 2 shows the previous results of the ene reaction of several trifluoromethyl ketones (CF_3COR) and the general dehydration of the reaction products, trifluoromethyl homoallyl alcohols, with phosphoryl chloride and pyridine.



Scheme 2.

We have already reported the ene reaction of trifluoroacetaldehyde (**1**) [3d], trifluoroacetone (**2**) [3b], α,α,α-trifluoroacetophenone (**3**) and 1,1,1-trifluoro-2-hexanone (**4**) [3c], and the dehydration of the ene reaction products (**5**–**8**) [4b]. For an extended study of the steric effects in dehydration, it was necessary to obtain some new homoallyl alcohols by the ene reaction of other trifluoromethyl ketones (**9**–**12**). We have reported the syntheses of these ketones [1], and their ene reactions are now examined (Scheme 3).

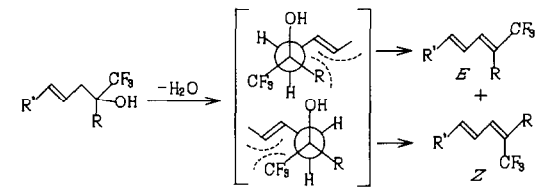


Ketone	R: iso-Bu, cyclo-Hex, sec-Bu, thexyl			
No:	9	10	11	12
Product R':	Pr	Pr	Pr	TMS
No:	13	14	15	16
%:	54	65	56	(22)

Scheme 3.

As mentioned before, steric hindrance is rather small for the ene reaction of terminal olefins [3b]. Thus, 1-hexene reacts with isobutyl (**9**), cyclohexyl (**10**) or *sec*-butyl trifluoromethyl ketone (**11**) to give a moderate yield of the corresponding trifluoromethylated homallyl alcohol (**13**, **14** or **15**). On the other hand, the ene reaction of thexyl trifluoromethyl ketone (**12**) with 1-hexene gave too poor a yield to obtain an appreciable amount of dehydration product. To obtain a larger amount of α-thexyl-α-(trifluoromethyl)alcohol, a lithium salt of allyltrimethylsilane was treated with **12** to give 5,5,6-trimethyl-4-(trifluoromethyl)-1-trimethylsilyl-1-hepten-4-ol (**16**) in 22% yield, the structure of which is that expected from the ene reaction.

Next, we examined the dehydration of these homoallyl alcohols with phosphoryl chloride in the presence of pyridine. This dehydration was established to proceed through an *anti*-elimination mechanism [4b]. Thus, if an alkyl group (R) is smaller than a trifluoromethyl group, this reaction will give an *E*-isomer preferentially and, if larger, a *Z*-isomer. Therefore, the smaller the *E*/*Z* ratio, the larger the steric effect of alkyl group of the ketones will have. The results of dehydration are summarized in Scheme 4 in the decreasing order of *E*/*Z* ratio, namely increasing order of the steric effect of the alkyl group. (See Scheme 4.)



Alcohol	5	6	7	8	13	14	15	16
R	H	Me	Ph	n-Bu	iso-Bu	c-Hex	sec-Bu	thexyl
E/*Z*	13/2	9/2	3/1	2/1	5/2	7/8	2/3	1/10

Scheme 4.

This order shows that a cyclohexyl group has about the same steric effect as a trifluoromethyl group and that a *sec*-butyl group is a little larger than a trifluoromethyl group. This order is slightly different from that observed in the ene reaction of these trifluoromethyl ketones with cyclohexene [1], where a trifluoromethyl group behaved as a larger substituent than a cyclohexyl group and slightly larger than a *sec*-butyl-

group. This difference may be due to the difference in the reaction temperatures, −78 °C for the ene reaction and 110 °C for the dehydration. Thus, a rapid rotation around the C–C bond at 110 °C makes the difference between *n*-butyl and isobutyl groups much smaller than that at −78 °C. The C–H part of the *sec*-butyl group is almost fixed near to the reaction center at −78 °C and it behaves as a smaller substituent than a trifluoromethyl group; at 110 °C, the rotation around the C–C bond becomes faster and the *sec*-butyl group behaves as a larger substituent than a trifluoromethyl group.

In conclusion, a trifluoromethyl group behaves as a much larger substituent in the dehydration of α-trifluoromethyl alcohols than expected from the commonly believed small size in the biomedicinal field [5], while its steric effect is a little smaller than that observed in the ene reaction of trifluoromethyl ketones with cyclohexene. These results show that, even though the total volume of a trifluoromethyl group may be similar to that of a methyl group in a mimic effect of a trifluoromethyl analog of a biologically active compound, a trifluoromethyl group behaves as a much larger substituent than a butyl or phenyl group. A symmetrical and hard trifluoromethyl group has a larger steric effect than a thin and flexible *n*-butyl group or a flat phenyl group in the transition state of some reactions, even though its total volume is much smaller.

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 and R-1500 spectrometers, using benzotrifluoride as an internal standard (upper field taken as plus).

Ene reaction of 1-hexene with isobutyl trifluoromethyl ketone (9)

A solution of 1-hexene (1.48 g, 17.6 mmol), **9** (1.20 g, 7.8 mmol) and $AlCl_3$ (1.04 g, 7.8 mmol) in anhydrous CH_2Cl_2 (15 ml) was stirred at −78 °C for 2 h, poured into a mixture of ice and 10% HCl then extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O and dried over $MgSO_4$. After evaporation of the solvent, the product was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 10:1–4:1) to give 2-(2-methylpropyl)-5-propyl-2-(trifluoromethyl)tetrahydrofuran (**17**, 62 mg, 3%), 6-chloro-2-methyl-4-(trifluoromethyl)-4-decanol (**18**, 153 mg, 7%) and 2-methyl-4-(trifluoromethyl)-6-decen-4-ol (**13**, 1.004 g, 54%).

*Compound **17***

Colorless oil: MS *m/z*: 237 (M–H), 195 (M–C_3H_7); HRMS Calcd. for $C_9H_{14}F_3O$ (M–C_3H_7), 195.100; Found: 195.100. ^{1}H NMR ($CDCl_3$) δ: 0.65–1.11 (3H, m), 0.97 (6H, d, J = 6.1 Hz), 1.11–2.37 (11H, m), 3.83–4.23 (1H, m). ^{19}F NMR ($CDCl_3$) ppm: 16.90 (s), 17.27 (s). 2:11.

Compound ***18***

Colorless oil: MS *m/z*: 239 (M–Cl), 205 (M–CF_3). HRMS Calcd. for $C_{11}H_{22}ClO$ (M–CF_3): 205.136; Found: 205.137. ^1H NMR ($CDCl_3$) δ: 0.77–1.14 (3H, m), 0.99 (3H, d, $J = 6.4$ Hz), 1.03 (3H, d, $J = 6.4$ Hz), 1.14–2.06 (10H, m), 2.06–2.30 (2H, m), 4.10–4.42 (1H, m). ^{19}F NMR ($CDCl_3$) ppm: 16.54 (s), 19.70 (s). 22:1.

Compound ***13***

Colorless oil: MS *m/z*: 238 (M^+). HRMS Calcd. for $C_{12}H_{21}F_3O$: 238.154; Found: 238.154. ^1H NMR ($CDCl_3$) δ: 0.90 (3H, t, $J = 7.7$ Hz), 0.98 (3H, d, $J = 6.4$ Hz), 1.00 (3H, d, $J = 6.4$ Hz), 1.06–1.63 (3H, m), 1.57 (2H, d, $J = 5.9$ Hz), 1.63–2.20 (4H, m), 2.40 (1H, bs), 5.19–5.83 (2H, m). ^{19}F NMR ($CDCl_3$) ppm: 16.73 (s), 17.10 (s), 6:1 (*E*/*Z* isomerism).

Ene reaction of 1-hexene with cyclohexyl trifluoromethyl ketone ***(10)***

A solution of 1-hexene (5.5 g, 65 mmol), **10** (1.80 g, 10 mmol) and $AlCl_3$ (1.40 g, 10 mmol) in anhydrous CH_2Cl_2 (5 ml) was stirred at −78 °C for 2 h. After work-up as above, the product was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 4:1) to give 2-cyclohexyl-5-propyl-2-(trifluoromethyl)tetrahydrofuran (**19**; 247 mg, 9%), 4-chloro-2-cyclohexyl-1,1,1-trifluoro-2-octanol (**20**; 291 mg, 10%) and 2-cyclohexyl-1,1,1-trifluoro-4-octen-2-ol (**14**; 1.728 g, 65%).

Compound ***19***

Colorless oil: MS *m/z*: 221 (M–C_3H_7). HRMS Calcd. for $C_{11}H_{16}F_3O$: 221.115; Found: 221.116. ^1H NMR ($CDCl_3$) δ: 0.66–2.14 (22H, m), 3.66–4.14 (1H, m). ^{19}F NMR ($CDCl_3$) ppm: 12.58 (s), 12.75 (s), 1:7.

Compound ***20***

Colorless oil: MS *m/z*: 282 (M–H_2O), 265 (M–Cl), 231 (M–CF_3). HRMS Calcd. for $C_{13}H_{24}ClO$: 231.151; Found: 231.154. ^1H NMR ($CDCl_3$) δ: 0.76–2.44 (22H, m), 4.02–4.38 (1H, m). ^{19}F NMR ($CDCl_3$) ppm: 11.57 (s), 11.71 (s). 1:5.

Compound ***14***

Colorless oil: MS *m/z*: 264 (M^+). HRMS Calcd. for $C_{14}H_{23}F_3O$: 264.170; Found: 264.170. ^1H NMR ($CDCl_3$) δ: 0.90 (3H, t, $J = 7.1$ Hz), 1.04–2.67 (18H, m), 5.19–5.55 (1H, m), 5.63 (1H, d–t, $J = 15.4$, 5.9 Hz). ^{19}F NMR ($CDCl_3$) ppm: 11.32 (s), 11.74 (s), 5:1 (due to *E*/*Z* isomers).

Ene reaction of 1-hexene with sec*-butyl trifluoromethyl ketone* ***(11)***

A solution of 1-hexene (2.52 g, 30 mmol), **11** (1.54 g, 10 mmol) and $AlCl_3$ (1.34 g, 10 mmol) in anhydrous CH_2Cl_2 (20 ml) was stirred at −78 °C for 2 h. After work-up as above, the product was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 10:1–2:1) to give 3-methyl-4-(trifluoromethyl)-6-decen-4-ol (**15**; 1.339 g, 56%).

Compound ***15***

Colorless oil. MS *m/z*: 238 (M^+). HRMS Calcd. for $C_{12}H_{21}F_3O$: 238.154; Found: 238.154. ^1H NMR ($CDCl_3$) δ: 0.65–2.80 (19H, m), 5.07–6.00 (2H, m). ^{19}F NMR ($CDCl_3$) ppm: 11.41 (s), 11.86 (s), 12.29 (s), 13.53 (s). 3:4:1:1. The first two isomers are tentatively assigned as *E*- and the last two as *Z*-isomers about the double bond. Isomerism at the *sec*-butyl carbon gave pairs of diastereoisomers.

Ene reaction of 1-hexene and trifluoromethyl 1,1,2-trimethylpropyl ketone (thexyl trifluoromethyl ketone, ***12****)*

A solution of 1-hexene (3.36 g, 40 mmol), **12** (1.82 g, 10 mmol) and $AlCl_3$ (1.32 g, 10 mmol) in anhydrous CH_2Cl_2 (50 ml) was stirred at −78 °C for 3.5 h. After work-up as above, the product was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 10:1–2:1) to give 2,3,3-trimethyl-4-(trifluoromethyl)-6-decen-4-ol (**21**; 118 mg, 4%).

Compound ***21***

Colorless oil: MS *m/z*: 266 (M^+). HRMS Calcd. for $C_{14}H_{25}F_3O$: 266.186; Found: 266.185. ^1H NMR ($CDCl_3$) δ: 0.45–2.40 (23H, m), 5.20–5.70 (2H, m). ^{19}F NMR ($CDCl_3$) ppm: 16.91 (s), 17.49 (s). 1:3

5,5,6,-Trimethyl-4-(trifluoromethyl)-1-trimethylsilyl-1-hepten-4-ol ***(16)***

To a solution of allyltrimethylsilane (342 mg, 3 mmol) and TMEDA (348 mg, 3 mmol) in THF (6 ml), a solution of BuLi (hexane, 3 ml) was added at 0 °C and stirred at this temperature for 4 h. To this mixture, a solution of **12** in THF (1 ml) at 0 °C was added and stirred for 3.5 h. After addition of aq NH_4Cl, the mixture was extracted with Et_2O, and the Et_2O layer was washed with sat. $NaHCO_3$ and then sat. NaCl, then dried over $MgSO_4$. After evaporation of the solvent, the residue was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 10:1–4:1) to give **16** (176 mg, 22%).

Compound ***16***

Colorless oil: MS *m/z*: 281 ($M-CH_3$), 227 ($M-CF_3$), 211 ($M-C_6H_{13}$). HRMS Calcd. for $C_{13}H_{24}F_3OSi$ ($M-CH_3$): 281.155; Found: 281.155. ^1H NMR ($CDCl_3$) δ: 0.08 (9H, s), 0.97 (6H, d, $J = 6.9$ Hz), 1.01 (6H, s), 2.00 (1H, hept, $J = 6.9$ Hz), 2.37 (1H, s), 2.41–2.87 (2H, m), 5.95 (1H, d, $J = 17.4$ Hz), 5.95–6.35 (1H, m). ^{19}F NMR ($CDCl_3$) ppm: 6.86 (s).

Dehydration of 2-methyl-4-(trifluoromethyl)-6-decene-4-ol ***(13)***

A solution of 13 (902 mg, 3.8 mmol) and $POCl_3$ (870 mg, 5.7 mmol) in pyridine (1.5 ml) was stirred at 110 °C for 67 h. The mixture was poured into ice-water and extracted with Et_2O, and the Et_2O layer was washed with dilute HCl, sat. $NaHCO_3$ and sat. NaCl, then dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane) to give a mixture of dienes (528.7 mg,

63.2%): (4*E*,6*E*)-2-methyl-4-(trifluoromethyl)-4,6-decadiene; (4*Z*,6*E*)-2-methyl-4-(trifluoromethyl)-4,6-decadiene; (3*E*,6*E*)-2-methyl-4-(trifluoromethyl)-3,6-decadiene; (3*Z*,6*E*)-2-methyl-4-(trifluoromethyl)-3,6-decadiene (ratio 5:2:1:1). The ratio was estimated from the peak area ratio on ^{19}F NMR. The stereochemistries were estimated from a comparison of chemical shifts and coupling constants in 400 MHz ^{1}H NMR and ^{19}F NMR with those of already reported dienes [4a], and GC–MS.

Mixture

^{1}H NMR ($CDCl_3$) δ: 0.86–1.02 (9H, m), 1.34–1.50 (2H, m), 1.70–2.25 (41/9H, m), 2.81 (2/9H, d, J = 6.5 Hz), 2.88 (2/9H, d, J = 6.0 Hz), 5.30–5.52 (4/9H, m), 5.75–5.80 (1/9H, m), 5.85 (2/9H, d–t, J = 15.0, 7.0 Hz), 5.97 (5/9H, d, J = 15.0, 7.0 Hz), 6.14 (2/9H, d, J = 11.5 Hz), 6.24 (5/9H, d–d, J = 15.0, 11.0 Hz), 6.43 (2/9H, d–d, J = 15.0, 11.5 Hz), 6.60 (5/9H, d, J = 11.0 Hz), 6.93 (1/9H, d, J = 11.5 Hz).

2-Methyl-4-(trifluoromethyl)-3,6-decadiene

GC–MS m/z: 220 (M^+). HRMS Calcd. for $C_{12}H_{19}F_3$: 220.144; Found: 220.144. ^{19}F NMR ($CDCl_3$) ppm: −3.08 (s), 4.47 (s), 1:1.

2-methyl-4-(trifluoromethyl)-4,6-decadiene

GC–MS m/z: 220 (M^+). HRMS Calcd. for $C_{12}H_{19}F_3$: 220.144; Found: 220.143. ^{19}F NMR ($CDCl_3$) ppm: 2.87 (s), −3.95 (d, J = 1.5 Hz), 5:2. The ratio estimated by GC–MS is approximately same as that based on ^{19}F NMR.

*Dehydration of 2-cyclohexyl-1,1,1-trifluoro-4-octen-2-ol (**14**)*

A solution of **14** (1.728 g, 6.5 mmol) and $POCl_3$ (1.50 g, 9.8 mmol) in pyridine (2 ml) was stirred at 110 °C for 85 h. After work-up as above, the product was purified by column chromatography (SiO_2, hexane) to give a mixture of dienes (918 mg, 57%). MS m/z: 246 (M^+). HRMS Calcd. for $C_{14}H_{21}F_3$: 246.160; Found: 246.160. ^{1}H NMR ($CDCl_3$) δ: 0.85–0.96 (3H, m), 1.10–1.90 (12H, m), 2.10–2.25 (3/5H, m), 2.48–2.60 (2/5H, m), 5.30–5.47 (7/20H, m), 5.68 (1/10H, d–t, J = 11.0, 7.5 Hz), 5.78 (1/10H, d–t, J = 11.0, 7.0 Hz), 5.86 (2/5H, d–t, J = 15.0, 7.0 Hz), 5.95 (7/20H, d–t, J = 15.0, 7.0 Hz), 6.16 (2/5H, d, J = 11.5 Hz), 6.34 (7/20H, d–d, J = 15.0, 11.0 Hz), 6.46 (2/5H, d–d, J = 15.0, 11.5 Hz), 6.48 (7/20H, d, J = 11.0 Hz), 6.80 (1/10H, d, J = 11.5 Hz). (Other olefinic protons were not identified.) ^{19}F NMR showed that the mixture contained five components (chemical shifts: −6.56, −4.27, −4.09, 0.25, 11.32; 2:2:8:7:1).

Based on comparison of their GC–MS, 400 MHz ^{1}H NMR, and ^{19}F NMR with those of other dienes, the component which showed a peak at 0.25 ppm on ^{19}F NMR was identified as (2*E*,4*E*)-2-cyclohexyl-1,1,1-trifluoro-2,4-octadiene, and that at −4.09 ppm to be its (2*Z*,4*E*)-isomer.

*Dehydration of 3-methyl-4-(trifluoromethyl)-6-decen-4-ol (**15**)*

A solution of **15** (1.275 g, 5.36 mmol) and $POCl_3$ (1.24 g, 8.1 mmol) in pyridine (3 ml) was stirred at 110 °C for 85 h. After work-up as above, the products were separated by column chromatography (SiO_2, hexane) to give a mixture of dienes (933 mg, 79%). Colorless oil: MS *m/z*: 220 (M^+). HRMS Calcd. for $C_{12}H_{19}F_3$: 220.144; Found: 220.143. ^1H NMR ($CDCl_3$) δ: 0.84–0.95 (5.4H, m), 1.00–1.07 (0.8H, m), 1.10 (1.3H, d, $J = 7.0$ Hz), 1.18 (0.9H, d, $J = 7.0$ Hz), 1.31–1.69 (3.9H, m), 1.76–1.81 (0.3H, m), 1.86–1.90 (0.3H, m), 1.90–2.00 (0.4H, m), 2.00–2.40 (2.5H, m), 2.55–2.70 (0.3H, m), 2.84–2.95 (0.5H, m), 5.29–5.47 (0.4H, m), 5.66–5.81 (0.1H, m), 5.86 (0.3H, d–t, $J = 15.0$, 7.0 Hz), 5.95 (0.3H, d–t, $J = 15.0$, 7.0 Hz), 6.15 (0.3H, d, $J = 11.5$ Hz), 6.33 (0.3H, d–d, $J = 11.5$, 15.0 Hz), 6.47 (0.3H, d–d, $J = 11.5$, 15.0 Hz), 6.53 (0.3H, d, $J = 11.5$ Hz), 6.87 (0.1H, d, $J = 11.0$ Hz). ^{19}F NMR showed that the mixture contained five isomers (chemical shifts: −5.47, −5.04, −4.31, −4.15, 0.31; 0.6:0.6:0.6:5:3).

Based on comparison of their GC–MS, 400 MHz ^1H NMR, and ^{19}F NMR with those of other dienes, the component which showed a peak at −5.47 ppm and −5.04 ppm was identified as 3-methyl-4-(trifluoromethyl)-3,6-decadiene; that with a peak at −4.31 ppm as (4*Z*,6*Z*)-3-methyl-4-(trifluoromethyl)-4,6-decadiene; that with a peak at −4.15 ppm as (4*Z*,6*E*)-3-methyl-4-(trifluoromethyl)-4.6-decadiene; and that with a peak at 0.31 ppm as (4*E*,6*E*)-3-methyl-4-(trifluoromethyl)-4,6-decadiene.

*Dehydration of 5,5,6-trimethyl-4-(trifluoromethyl)-1-trimethylsilyl-1-hepten-4-ol (**16**)*

To a mixture of **16** (176 mg, 0.59 mmol) and $SOCl_2$ (106 mg, 1.5 eq), pyridine (0.5 ml) was added dropwise at 0 °C and the mixture was stirred at room temperature for 22 h. After work-up as above, the products were separated by column chromatography (SiO_2, hexane) to give 5,5,6-trimethyl-1-trimethylsilyl-4-(trifluoromethyl)-1,3-heptadiene (24 mg, 14.6%) and the starting material (55.8 mg, 31.7%).

5,5,6-Trimethyl-1-trimethylsilyl-4-(trifluoromethyl)-1,3-heptadiene

Colorless oil: MS *m/z*: 278 (M^+). HRMS Calc. $C_{14}H_{25}F_3Si$: 278.168; Found: 278.168. ^1H NMR ($CDCl_3$) δ: 0.13 (9H, s), 0.83 (6H, d, $J = 7.2$ Hz), 1.11 (6H, s), 2.09 (1H, hept, $J = 7.2$ Hz), 6.13 (1H, d, $J = 17.9$ Hz), 6.31 (1H, d, $J = 10.5$ Hz), 6.94 (1H, d–d–q, $J = 17.9$, 10.5, 2.8 Hz). ^{19}F NMR ($CDCl_3$) ppm: −10.58 (s), −3.32 (s). 13:1. The absence of NOE between the 5-CH_3 and 2-H, and the presence between the 5-CH_3 and 3-H suggested that the stereochemistry of the major product was (1*E*,3*Z*).

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