ELSEVIER

Journal of Fluorine Chemistry 86 (1997) 81–87

JOURNAL OF FLUORINE CHEMISTRY

Stereoselective synthesis of trifluoromethylated compounds via Johnson–Claisen and Eshenmoser–Claisen rearrangements

Tsutomu Konno, Hirofumi Nakano, Tomoya Kitazume *

Department of Bioengineering, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226, Japan

Received 18 October 1996; accepted 6 May 1997

Abstract

Johnson–Claisen and Eshenmoser–Claisen rearrangements of chiral γ-trifluoromethylated allylic alcohols, which were prepared via effective enzymatic resolution of the corresponding propargylic alcohols, are demonstrated. As a result, it is shown that both reactions could become important methods for the preparation of highly functionalized chiral trifluoromethylated materials. © 1997 Elsevier Science S.A.

Keywords: Trifluoromethyl derivatives; Johnson–Claisen rearrangement; Eshenmoser–Claisen rearrangement

1. Introduction

Trifluoromethylated organic materials are becoming very important in the development of more effective medicines, agricultural chemicals, and ferroelectric liquid crystals because of electronegativity, lipophilicity, and stability derived from a CF_3 group [1]. Therefore, considerable efforts have been made to establish efficient and reliable as well as stereoselective preparations for CF3-containing molecules thus far [2].

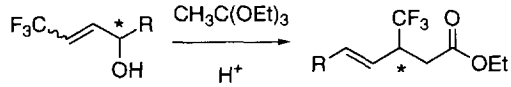
Johnson–Claisen or Eshenmoser–Claisen rearrangements have been well known as one of the most valuable stereoselective pathways in non-fluorinated systems, and they have been applied for various natural products syntheses [3]. Despite this, very little has been reported on their applications to chiral trifluoromethylated compounds thus far [4].

Recently, we have reported efficient as well as convenient synthetic methods for chiral γ-trifluoromethylated propargylic and allylic alcohols via effective enzymatic kinetic resolution [5]. Therefore, as an extension of our study on the utility of such materials, we have attempted Johnson–Claisen and Eshenmoser–Claisen rearrangements. In this paper we describe their scope and limitations in detail.

2. Results and discussion

2.1. Johnson–Claisen rearrangement

First of all, we have attempted a Johnson–Claisen rearrangement (Eq. (1)) of the chiral substrate, **(*R*)-(*E*)-1a** ($R = n\text{-}C_5H_{11}$, 87% enantiomeric excess (ee)) [5] under the same reaction conditions as described in the literature [4a].



(*E*)- or (*Z*)-1 **2**

a : R = *n*-C_5H_{11}
b : R = CH_2OBn
c : R = *c*-C_6H_{11}

Thus, a mixture of the allylic alcohol and a large amount of ethyl ortho acetate in the presence of a catalytic amount of propionic acid was stirred under a nitrogen atmosphere at 130°C overnight; however, surprisingly, the rearranged product was obtained in a moderate yield (46% yield). In the case of **(*R*)-(*Z*)-1a**, the same phenomenon was observed, and it was reproducible. Thus, **(*R*)-(*Z*)-1a** gave the rearranged product in 49% yield. On the other hand, the rearrangement of **(*R*)-(*E*)-1b** or **(*R*)-(*Z*)-1b** proceeded sluggishly to afford the desired compounds in a low yield. Unfortunately, this phenomenon remains unsolvable at present.

The reaction of **(*R*)-(*E*)-1a** was then performed at 130°C in a sealed tube for 12 h, the reaction mixture was cooled to room temperature, and evaporated in vacuo. Chromatography of the crude materials gave the rearranged products **(*R*)-2a** in 96% yield as a single isomer, which was turned out to be the *E*-isomer by careful ^{1}H-NMR analysis (Table 1, Entry 1). In

* Corresponding author.

PII S0022-1139(97)00049-3

Table 1
Preparation of compounds 2

Entry	Substrate	R	Product [a]	$[\alpha]_D$ [b]	Yield (%) [b,c]
1	**(*R*)-(*E*)-1a** (87% ee)	*n*-C_5H_{11}	**(*R*)-2a** (90% ee)	−14.7°	96 (46)
2	**(*R*)-(*Z*)-1a** (81% ee)	*n*-C_5H_{11}	**(*S*)-2a** (81% ee)	+13.2°	88 (49)
3	**(*R*)-(*E*)-1b** (96% ee)	CH_2OBn	**(*S*)-2b**	+18.2°	79
4	**(*R*)-(*Z*)-1b** (96% ee)	CH_2OBn	**(*R*)-2b**	−16.2°	77
5	***rac*-(*E*)-1c**	*c*-C_6H_{11}	**2c**		62
6	***rac*-(*Z*)-1c**	*c*-C_6H_{11}	**2c**		66

[a] High *E* stereoselection was observed at the newly created olefinic bond.
[b] The values of the rearranged products are shown. The temperature and the concentration are described in the experimental section.
[c] Isolated yield.
[d] The yield in parentheses was obtained when the sealed tube was not employed.

order to investigate its optical purity, **(*R*)-2a** was treated with $LiAlH_4$ to give the corresponding alcohol, which was esterified by MTPA-Cl. However, ^{1}H- and ^{19}F-NMR analysis of the obtained ester did not lead to a satisfactory result. In addition, chiral GC analysis as well as shift reagent were fruitless. Therefore, the enantiomeric excess (ee) was determined by comparison with the authentic optical rotation value [1]. As a result, it was shown that **(*R*)-2a** possessed optical purity of 90% ee. Considering that the ee of the substrate was 87% ee, the transmission of the chirality had occurred completely within an observational error. In a similar way, the other substrates were subjected to the rearrangement under the same condition to afford the desired materials in a high to excellent yield. The results are summarized in Table 1.

As shown in Table 1, a little dependence on the side chain R was observed for the yield. Thus, yield was influenced by the difference of the bulkiness of R, and a lower yield was obtained as R became bulkier. In addition, high *E*-isomer selection was shown at the newly created olefinic bond and then it was clarified that the substrate possessing the same stereoconfiguration in essence (not in the nomenclature) gave the rearranged products with the same stereoselective sense, independent of the difference of R. Thus, the chirality of **(*R*)-(*E*)-1a** is essentially reverse to that of **(*R*)-(*E*)-1b**, although the chirality of both substrates is *R* in the nomenclature. Therefore, these substrates afford **(*R*)-2a** or **(*S*)-2b**, respectively, in which the chiral center is mutually enantiomeric. This means the rearrangement proceeded via a six-membered chair-like transition state despite the difference of R, in which a CF_3 group might occupy the equatorial (*E*-substrate) or axial (*Z*-substrate) position (Fig. 1). Furthermore, complete transfer of chirality in both **(*R*)-(*E*)-** and **(*Z*)-1a** was observed to give trifluoromethylated materials in enantiomerically pure forms. Accordingly, it was found that the Johnson–Claisen rearrangement could become the most important reaction for the preparation of chiral trifluoromethylated compounds.

[1] On the basis of the optical rotation value (−9.7°) of **(*S*)-3a** derived from Eshenmoser–Claisen rearrangement in Scheme 2, the Johnson–Claisen rearranged product **(*S*)-2a** was found out to be in an optical purity of 81%. From this result, the ee of **(*R*)-2a** was calculated.

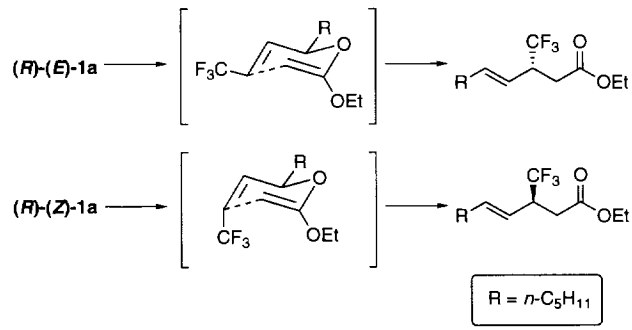
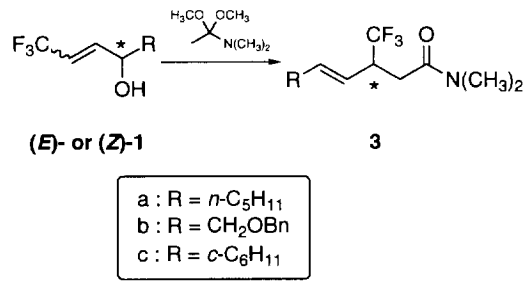


Fig. 1. A six-membered chain-like transition state.

2.2. Eshenmoser–Claisen rearrangement

At the next stage, we attempted the Eshenmoser–Claisen rearrangement which is considered to proceed more mildly than the Johnson–Claisen rearrangement (Eq. (2)).



According to the literature [3]d–f, the benzene solution of allylic alcohol **(*R*)-(*E*)-1a** (>99% ee) and *N*,*N*-dimethylacetamide dimethylacetal (10 equiv.) was stirred at reflux for several hours. Then, the reaction mixture was cooled to room temperature, extracted with ethyl acetate, and the usual work-up gave the desired rearranged product in 62% yield as a single isomer. The coupling constant of its ^{1}H-NMR spectrum at the newly formed olefinic bond was ca. 15 Hz, strongly suggesting its *E* configuration. The enantiomeric excess (ee) of the product turned out to be >99% by chiral GC analysis. Therefore it was clarified that the chirality of the substrate was completely transferred to the product. In a similar way, the other substrates were subjected to the Esh-

Table 2
Preparation of compounds 3

Entry	Substrate	Product [a]	$[\alpha]_D$ [b]	Yield (%) [c]
1	(*R*)-(*E*)-**1a** (>99% ee)	(*R*)-**3a** (>99% ee)	+9.6°	62
2	(*R*)-(*Z*)-**1a** (>99% ee)	(*S*)-**3a** (96% ee)	−9.7°	60
3	(*R*)-(*E*)-**1b** (96% ee)	(*S*)-**3b**	+11.7°	75
4	(*R*)-(*Z*)-**1b** (96% ee)	(*R*)-**3b**	−10.6°	50
5	*rac*-(*E*)-**1c**	**3c**		89
6	*rac*-(*Z*)-**1c**	**3c**		76

[a] High *E* stereoselection was observed at the newly olefinic bond.
[b] The values of the rearranged products are shown. The temperature and the concentration are described in the experimental section.
[c] Isolated yield.

enmoser–Claisen rearrangement to give rise to the desired molecules in moderate to good yield. The results are summarized in Table 2.

As depicted in Table 2, *E* selectivity was not influenced by the difference of the bulkiness of side chain R, even when a substrate possessing a bulky cyclohexyl group as a side chain was employed. All of the substrates examined exhibited high *E* stereoselection, and in addition, almost complete chirality transfer occurred. In this case, its ratio in the (*Z*)-substrate (96% transfer) was a little lower than that in the (*E*)-substrate (100% transfer). On the other hand, when (*E*)-substrates were used, higher yields were obtained.

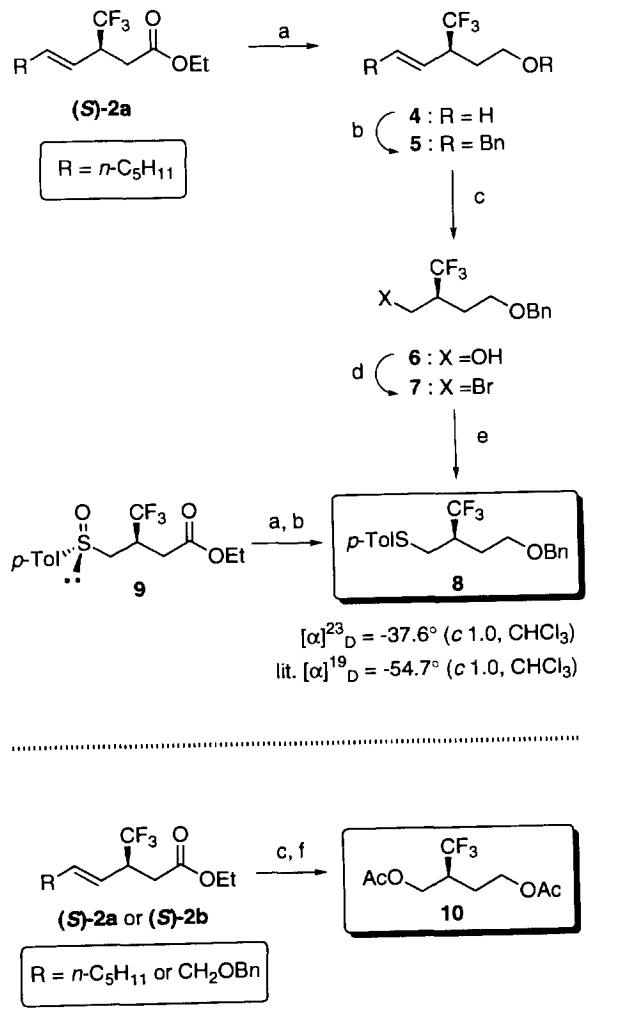
Considering the same stereoselective sense as Johnson–Claisen rearrangement, this rearrangement is also considered to proceed via a six-membered chair-like transition state.

2.3. Clarification of the stereochemistry

The stereochemistry of the Johnson–Claisen rearranged products was determined as outlined in Scheme 1.

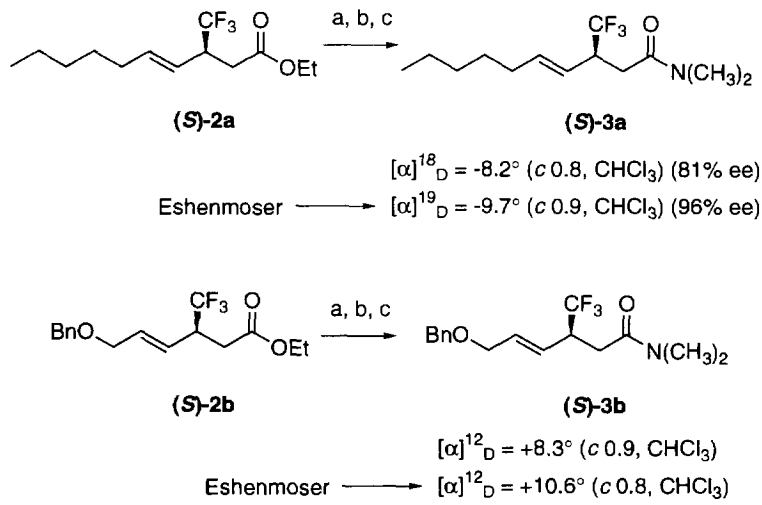
Treatment of the rearranged product (*S*)-**2a** (81% ee) with $LiAlH_4$ gave the corresponding alcohol **4**, which was transformed into benzyl ether **5** by the usual method. Sequential ozonolysis of the benzyl ether and the reduction of the resultant aldehyde afforded **6**, which was subjected to bromination by the Ph_3P/CBr_4 reagent to give rise to the desired compound **7** in a good yield. S_N2 reaction of **7** by the thiolate anion gave the sulfide **8** in a high yield without any β-elimination. On the other hand, **8** was produced from the sulfoxide **9** in two steps according to the literature [6]. By comparison of both optical rotation values, the stereochemistry of the rearranged product (*S*)-**2a** was determined as *S*.

On the other hand, (*S*)-**2a** and (*S*)-**2b** were transformed into the same material **10**. Thus, sequential ozonolysis of the above compounds and the reduction of the resultant aldehydes gave the corresponding diols, which were acetylated by the usual method without purification to afford diacetate derivatives. It was shown that both compounds were identical by comparison of the optical rotation values. Thus, the stereochemistry of (*S*)-**2b** was assigned as *S*. Accordingly, the stereochemistry of (*R*)-**2a** or (*R*)-**2b** was determined as *R* on the basis of the optical rotation value of the corresponding enantiomers.



a) $LiAlH_4$ b) NaH, BnBr c) i) O_3, MeOH then Me_2S ii) $LiAlH_4$
d) CBr_4, Ph_3P e) *p*-TolSH, NaH f) AcCl, Py.

Scheme 1.



a) NaOH/THF b) $(COCl)_2$, cat. DMF c) $(CH_3)_2NH$

Scheme 2.

The stereochemistry of the Eshenmoser–Claisen rearranged products was determined as depicted in Scheme 2.

Thus, the Johnson–Claisen rearranged products (*S*)-**2a**, (*S*)-**2b** were subjected to hydrolysis by NaOH/THF to afford the corresponding carboxylic acids. Without purification, the obtained molecules were treated with an excess of oxalyl chloride and a catalytic amount of dimethylformamide. After several hours, to the reaction mixture was added an aqueous solution of dimethyl amine (excess). The usual work-up gave the corresponding amides, which were the same as the Eshenmoser–Claisen rearranged products. By comparison of their optical rotation values with ones derived from Eshenmoser–Claisen rearranged products, the absolute configurations of (*S*)-**3a** or (*S*)-**3b** were determined as *S*, respectively.

3. Conclusion

In summary, we have investigated the scope and limitations of Johnson–Claisen or Eshenmoser–Claisen rearrangements of chiral γ-trifluoromethylated allylic alcohols. Both reactions proceeded smoothly to give the highly functionalized trifluoromethylated materials with high optical purity. Accordingly, these rearrangements could constitute valuable synthetic methods for such compounds.

4. Experimental details

^{1}H- and ^{19}F-NMR) spectra were recorded at 500 MHz (Varian VXR-500), ^{13}C-NMR spectra were taken at 50 MHz (Varian XL Gemini-200 spectrometer). All spectra were recorded in $CDCl_3$, and the chemical shifts are reported in parts per million (δ ppm) relative to tetramethylsilane (Me_4Si, δ 0.00 ppm for ^{1}H- and ^{13}C-NMR) and hexafluorobenzene (C_6F_6, δ 0.00 ppm for ^{19}F-NMR). Coupling constants are reported in hertz (Hz). Infrared spectra (IR) were recorded on a JASCO A-102 DIP-140 spectrometer. Chrompack (CP-Chiralsil-Dex CB) was employed in the Chiral GC analysis.

4.1. General procedure for the Johnson–Claisen rearrangement

A solution of the allylic alcohol (0.51 mmol), triethylorthoester (1 ml), and a catalytic amount of propionic acid was stirred for 12 h at 130°C in a sealed tube. The reaction mixture was cooled and evaporated in vacuo. The resultant materials were purified by silica gel column chromatography to afford the desired compound.

*4.1.1. (3R)-Ethyl 3-trifluoromethyl-4-decenoate ((**R**)-**2a**)*

Yield: 96%. ^{1}H-NMR δ 0.87 (3 H, t, J = 7.08 Hz) 1.25 (3 H, t, J = 7.33 Hz) 1.20–1.40 (6 H, m) 2.03 (2 H, q, J = 6.83 Hz) 2.45 (1 H, dd, J = 9.77, 15.38 Hz) 2.69 (1 H, dd, J = 4.64, 15.62 Hz) 3.28 (1 H, dsex., J = 4.64, 9.28 Hz) 4.14 (2 H, dq, J = 1.47, 7.08 Hz) 5.28 (1 H, ddt, J = 1.46, 7.08, 15.38 Hz) 5.74 (1 H, dt, J = 6.84, 14.65 Hz). ^{13}C-NMR δ 13.96, 14.13, 22.41, 28.47, 31.12, 32.38, 33.95 (q, J = 2.4 Hz) 43.89 (q, J = 27.7 Hz) 60.88, 121.44 (q, J = 2.4 Hz) 126.46 (q, J = 279.3 Hz) 138.28, 170.26. ^{19}F-NMR δ 90.00 (d, J = 9.16 Hz). IR (neat) ν 2950, 2932, 2870, 2860, 1743. $[\alpha]^{21}_D$ = −14.7° (c0.9, $CHCl_3$) (90% ee).

*4.1.2. (3S)-Ethyl 3-trifluoromethyl-4-decenoate ((**S**)-**2a**)*

Yield: 88%. $[\alpha]^{23}_D$ = +13.2° (c0.8, $CHCl_3$) (81% ee).

*4.1.3. (3S)-Ethyl 3-trifluoromethyl-6-benzyloxy-4-hexenoate ((**S**)-**2b**)*

Yield: 79%. ^{1}H-NMR δ 1.24 (3 H, t, J = 7.08 Hz) 2.50 (1 H, dd, J = 9,77, 15.87 HZ) 2.73 (1 H, dd, J = 4.64, 15.87 HZ) 3.39 (1 H, dsex., J = 5.19, 9.19 Hz) 4.02 (2 H, dd, J = 1.71,

5.61 Hz) 4.15 (2 H, dq, J=2.44, 7.33 Hz) 4.49 (2 H, s) 5.62 (1 H, ddt, J=1.70, 8.55, 15.39 Hz) 5.89 (1 H, dt, J=5.37, 15.62 Hz) 7.20–7.40 (5 H, m). ^{13}C-NMR δ 14.10, 33.58 (q, J=2.3 Hz) 43.45 (q, J=27.9 Hz) 61.03, 69.50, 72.05, 124.18 (q, J=2.6 Hz) 126.23 (q, J=279.5 Hz) 127.69, 127.73, 128.40, 133.76, 137.93, 170.05. ^{19}F-NMR δ 90.30 (d, J=9.15 Hz). IR (neat) ν 2984, 2859,1740. $[\alpha]^{22}_{D}$= +18.2°(c0.7, $CHCl_3$).

4.1.4. (3R)-Ethyl 3-trifluoromethyl-6-benzyloxy-4-hexenoate ((R)-2b)

Yield: 77%. $[\alpha]^{22}_{D}$= −16.2°(c0.9, $CHCl_3$).

4.1.5. Ethyl 5-cyclohexyl-3-trifluoromethyl-4-pentenoate (2c)

Yield: 62%. (The yield was obtained from Johnson–Claisen rearrangement of (*E*)-**1c**.) 66%. (The yield was obtained from Johnson–Claisen rearrangement of (*Z*)-**1c**.) ^{1}H-NMR δ 0.8–1.4 (4 H, m) 1.25 (3 H, t, J=7.08 Hz) 1.5–1.7 (6 H, m) 1.9–2.0 (1 H, m) 2.43 (1 H, dd, J=10.01, 15.28 Hz) 2.69 (1 H, dd, J=4.4, 15.39 Hz) 3.26 (1 H, dsex., J=4.64, 9.04 Hz) 4.13 (2 H, dq, J=1.71, 7.32 Hz) 5.24 (1 H, ddd, J=1.22, 8.78, 15.62 Hz) 5.68 (1 H, dd, J=6.84, 15.63 Hz). ^{13}C-NMR δ 14.15, 25.78, 26.00, 32.46, 34.08 (q, J=2.3 Hz) 40.55, 43.98 (q, J=27.6 Hz) 60.86, 119.00 (q, J=2.6 Hz) 126.46 (q, J=279.4 Hz) 170.23. ^{19}F-NMR δ 89.94 (d, J=9.15 Hz). IR (neat) ν 3000, 2927, 2854, 1743.

4.2. General procedure for Eshenmoser–Claisen rearrangement

A mixture of allylic alcohol (1.10 mmol), *N,N*-dimethylacetamide dimethylacetal (1.61 ml, 11 mmol), and benzene (15 ml) was stirred at 100°C for 2 h. The reaction was cooled to room temperature, and the mixture was poured into 1 N HCl solution (10 ml) and the whole mixture was extracted with ethyl acetate three times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford the corresponding amide.

4.2.1. (3R)-N,N-dimethyl-3-trifluoromethyl-4-decenamide ((R)-3a)

Yield: 62%. ^{1}H-NMR δ 0.87 (3 H, t, J=7.08 Hz) 1.18–1.40 (6 H, m) 2.02 (2 H, dq, J=1.46,7.08 Hz) 2.52 (1 H, dd, J=9.04, 15.63 Hz) 2.62 (1 H, dd, J=3.91, 15.91 Hz) 2.95 (3 H, s) 3.02 (3 H, s) 3.50 (1 H, dsex., J=3.91, 9.28 Hz) 5.26 (1 H, dd, J=8.55, 15.83 Hz) 5.75 (1 H, dt, J=6.84, 15.38 Hz). ^{13}C-NMR δ 13.93, 22.35, 28.39, 313.07, 32.03 (q, J=2.1 Hz) 32.39, 35.58, 37.17, 43.48 (q, J=27.0 Hz) 122.03 (q, J=2.6 Hz) 127.00 (q, J=279.3 Hz) 133.77, 169.15. ^{19}F-NMR δ90.41 (d, J=9.16 Hz). IR (neat) ν 2930, 2859, 1654. $[\alpha]^{27}_{D}$= +9.6° (c0.7, $CHCl_3$) (>99% ee).

4.2.2. (3S)-N,N-dimethyl-3-trifluoromethyl-4-decenamide ((S)-3a)

Yield: 60%. $[\alpha]^{19}_{D}$= −9.7°(c0.9, $CHCl_3$) (96% ee).

4.2.3. (3S)-N,N-dimethyl-6-benzyloxymethyl-3-trifluoromethyl-4-hexenamide ((S)-3b)

Yield: 75%. ^{1}H-NMR δ 2.55 (1 H, dd, J=9.28, 16.12 Hz) 2.67 (1 H, dd, J=3.91, 16.11 Hz) 2.95 (3 H, s) 3.01 (3 H, s) 3.62 (1 H, dsex., J=3.42, 9.04 Hz) 4.02 (2 H, dd, J=1.46, 5.37 Hz) 4.49 (2 H, s) 5.62 (1 H, ddt, J=1.71, 8.30, 15.63 Hz) 5.90 (1 H, dt, J=5.38, 15.39 Hz). ^{13}C-NMR δ 31.54 (q, J=2.2 Hz) 35.24, 36.69, 42.68 (q, J=27.2 Hz) 69.35, 71.67, 124.66 (q, J=2.7 Hz) 126.62 (q, J=279.3 Hz) 127.31, 127.44, 128.04, 132.90, 137.77, 168.46. ^{19}F-NMR δ 90.76 (d, J=9.16 Hz). IR (neat) ν 2924, 2852, 1652. $[\alpha]^{28}_{D}$= +11.7° (c 0.8, $CHCl_3$).

4.2.4. (3R)-N,N-dimethyl-6-benzyloxymethyl-3-trifluoromethyl-4-hexenamide ((R)-3b)

Yield: 50%. $[\alpha]^{30}_{D}$= −10.6°(c0.8, $CHCl_3$).

4.2.5. N,N-dimethyl-5-cyclohexyl-3-trifluoromethyl-4-pentenamide (3c)

Yield: 89% (The yield was derived from (*E*)-**1c**.). 76% (The yield was derived from (*Z*)-**1c.**). ^{1}H-NMR δ 1.04–1.34 (5 H, m) 1.60–1.75 (5 H, m) 1.90–1.99 (1 H, m) 2,51 (1 H, dd, J=9.04, 15.38 Hz) 2.62 (1 H, dd, J=4.15, 15.38 Hz) 2.95 (3 H, s) 3.02 (3 H, s) 3.47 (1 H, dsex., J=4.21, 10.62 Hz) 5.23 (1 H, ddd, J=1.28, 8.61, 15.57 Hz) 5.69 (1 H, dd, J=6.72, 15.51 Hz). ^{13}C-NMR δ 25.77, 25.80, 26.00, 32.11 (q, J=2.0 Hz) 32.36, 32.48, 35.60, 37.29, 40.46, 43.66 (q, J=27.1 Hz) 119.54 (q, J=2.6 Hz) 127.00 (q, J=279.4 Hz) 143.25, 169.24. ^{19}F-NMR δ 90.39 (d, J=9.16 Hz). IR (neat) ν 3070, 3050, 3032 2932, 2850, 1654.

4.3. Determination of the stereochemistry

4.3.1. (3S)-3-Trifluoromethyl-4-decen-1-ol (4)

To a stirred slurry of lithium aluminium hydride (ca. 0.047 g, 1.24 mmol) in THF (2 ml) was added a solution of the Johnson–Claisen rearranged product, (3*S*)-ethyl 3-trifluoromethyl-4-decenoate ((*S*)-**2a**) (0.549 g, 2.06 mmol) in THF (3 ml) at 0°C and the whole was stirred for several hours at room temperature. The reaction was quenched with 4 N KOH aq., and the usual work-up gave the crude materials, which were purified by silica gel column chromatography to afford the alcohol (0.422 g, 1.88 mmol).

Yield: 91%. ^{1}H-NMR δ 0.884 (3 H, t, J=7.08 Hz) 1.2–1.4 (6 H, m) 1.6–1.7 (1 H, m) 1.98 (1 H, dddd, J=3.66, 6.10, 9.03, 13.91 Hz) 2.06 (2 H, dq, J=1.46, 7.81 Hz) 2.90 (1 H, dsex, J=3.66, 9.04 Hz) 3.60–3.66 (1 H, m) 3.72–3.78 (1 H, m) 5.23 (1 H, ddt, J=1.47, 9.28, 15.38 Hz) 5.72 (1 H, dt, J=6.59, 15.38 Hz). ^{13}C-NMR δ 13.92, 22.39, 28.70, 30.68 (q, J=2.1 Hz) 31.22, 32.41, 44.07 (q, J=26.9 Hz) 59.13, 122.46, 127.08 (q, J=279.2 Hz) 138.22. ^{19}F-NMR δ 90.42 (d, J=9.15 Hz). IR (neat) ν 3421, 2927. $[\alpha]^{23}_{D}$=27.7° (c0.8, $CHCl_3$ (81% ee).Anal. Calcd. for $C_{11}H_{19}O_1F_3$: C, 58.91; H, 8.54. Found: C, 58.87; H, 8.85.

*4.3.2. (3S)-1-benzyloxy-3-trifluoromethyl-4-decene (**5**)*

To a stirred slurry of 60% NaH (0.113 g, 2.82 mmol) in THF (10 ml), the above alcohol 4 (0.422 g, 1.88 ml) was added at 0°C and the whole was stirred for 30 min. After this solution was treated with benzyl bromide (0.335 ml, 2.82 mmol), the reaction mixture was stirred overnight. The reaction was quenched with water and 1 N HCl aq., and the mixture was extracted with ethyl acetate three times. The combined extracts were washed successively with water and brine. CH_2Cl_2 was removed in vacuo, giving the crude benzyl ether which was purified by silica gel column chromatography to afford pure benzyl ether (0.525 g, 1.71 mmol).

Yield: 91%. ^{1}H-NMR δ 0.89 (3 H, t, J=6.84 Hz) 1.20–1.40 (6 H, m) 1.50–1.70 (1 H, m) 2.00–2.20 (3 H, m) 2.93 (1 H, dsex., J=3.66, 9.03 Hz) 3.43 (1 H, dt, J=4.89, 9.28 Hz) 3.50–3.56 (1 H, m) 4.44 (1 H, d, J=11.97 Hz) 4.51 (1 H, d, J=11.96 Hz) 5.18 (1 H, ddt, J=1.47, 9.03, 15.14 Hz) 5.62 (1 H, dt, J=6.83, 15.13 Hz) 7.20–7.40 (5 H, m). ^{13}C-NMR δ 22.43, 28.08 (q, J=2.3 Hz) 28.65, 31.25, 32.43, 44.19 (q, J=26.8 Hz) 66.26, 72.93, 122.37 (q, J=2.6 Hz) 127.21 (q, J=279.2 Hz) 127.64, 127.68, 128.37, 138.11, 138.27. ^{19}F-NMR δ 90.44 (q, J=9.16 Hz). IR (neat) ν 3150, 3100, 2950, 2929, 2859. $[\alpha]^{23}_D$=36.7° (c0.8, $CHCl_3$) (81% ee).

*4.3.3. (2R)-4-benzyloxy-1-bromo-2-trifluoromethylbutane (**7**)*

A solution of (3S)-1-benzyloxy-3-trifluoromethyl-4-decene 5 (0.127 g, 0.404 mmol) in methanol was treated with ozone for 30 min at −78°C. At this point, substrate almost disappeared, then dimethyl sulfide was added to the reaction mixture, which was allowed to warm to room temperature. The mixture was stirred at that temperature for 30 min and concentrated in vacuo. The residue was added to a suspension of lithium aluminium hydride (excess) in THF (5 ml) at 0°C, and the reaction mixture was stirred at room temperature for 1 h. Quenched with 4 N KOH solution, the usual work-up gave the crude materials, which were purified by silica gel column chromatography to yield the mixture of the desired compound 6 and 1-pentanol. To a solution of CBr_4 (0.999 g, 3.01 mmol) and the above crude material in CH_2Cl_2 (10 ml) was added triphenylphosphine (0.787 g, 3.00 mmol) at 0°C, and the mixture was stirred at room temperature for several hours. A large amount of hexane was added to the reaction mixture, which was filtered and evaporated. The residue was purified by silica gel column chromatography to give the desired bromide **7** as a pure form (0.083 g, 0.267 mmol).

Yield: 66%. ^{1}H-NMR δ 1.90–2.10 (2 H, m) 2.40–2.70 (1 H, m) 3.52 (2 H, d, J=4.86 Hz) 3.56–3.64 (2 H, m) 4.51 (1 H, d, J=11.96 Hz) 4.54 (1 H, d, J=11.96 Hz) 7.25–7.40 (5 H, m). ^{13}C-NMR δ 26.89 (q, J=1.0 Hz) 27.87 (q, J=1.5 Hz) 41.37 (q, J=26.2 Hz) 66.23, 73.00, 126.72 (q, J=280.8 Hz) 127.60, 127.75, 128.43, 137.96. ^{19}F-NMR δ 92.15 (d, J=9.16 Hz). IR (neat) ν 3070, 3040, 3032, 3000, 2980, 2864. $[\alpha]^{24}_D$= + 14.0 (c 0.9, $CHCl_3$).

*4.3.4. (2R)-4-benzyloxy-2-trifluoromethyl-1-(4′-methylphenyl)sulfenylbutane (**8**)*

To a THF solution of NaH (ca. 0.04 g, 1.00 mmol) was added a solution of p-toluene thiol (0.124 g, 1.00 mmol) in THF at 0°C, and the whole was stirred for 20 min at that temperature. To this solution was added (2R)-4-benzyloxy-1-bromo-2-trifluoromethylbutane (0.083 g, 0.267 mmol) in THF (3 ml) and then the whole was stirred for 2 h at 0°C. The reaction was quenched with water and the mixture was extracted with ether three times. The combined organic layer was washed successively with sat. $NaHCO_3$ and brine, and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford the desired compound (0.088 g, 0.249 mmol).

Yield: 93%. Physical properties of this compound were the same as those described in the literature [6a]. $[\alpha]^{23}_D$ = −37.6° (c 1.0, $CHCl_3$).

*4.4. General procedure for the preparation of (2S)-1,4-diacetoxy-2-trifluoromethylbutane (**10**)*

A solution of Johnson–Claisen rearrangement product (1 mmol) in methanol was treated with ozone for 30 min. To this solution was added dimethyl sulfide (excess) and the mixture was allowed to warm to room temperature and stirred at that temperature for 30 min, then evaporated. To a suspension of lithium aluminium hydride (excess) in THF was added the residue in THF at 0°C and the mixture was stirred for 15 min. The reaction was quenched with 4 N KOH solution and the usual work-up gave the crude materials, which were passed through silica gel to afford the desired compound containing unidentified impurities. This mixture was dissolved in a solution of CH_2Cl_2 and acetyl chloride (0.284 ml, 4 mmol), and to this was added pyridine (0.324 ml, 4 mmol) at 0°C. The whole was stirred for 2 h at room temperature then quenched with 1 N HCl. The mixture was extracted with CH_2Cl_2, washed sat. $NaHCO_3$ and brine, then evaporated. The residue was purified by silica gel column chromatography to yield diacetyl compound **10**.

^{1}H-NMR δ 1.86 (1 H, ddt, J=5.98, 8.30, 14.16 Hz) 2.01–2.10 (1 H, m) 2.06 (3 H, s) 2.08 (3 H, s) 2.53–2.64 (1 H, m) 4.16–4.20 (2 H, m) 4.23 (1 H, dd, J=5.12, 11.96 Hz) 4.28 (1 H, dd, J=5.37, 11.72 Hz). ^{13}C-NMR δ 20.56, 20.70, 24.56 (q, J=2.3 Hz) 39.73 (q, J=26.4 Hz) 60.38, 60.41 (q, J=3.1 Hz) 126.66 (q, J=280.1 Hz) 170.41, 170.67. ^{19}F-NMR δ 91.96 (d, J=9.15 Hz). IR (neat) ν 3000, 2970, 2960, 2950, 1753, 1740. $[\alpha]^{23}_D$= + 7.8° (c 0.8, $CHCl_3$).

4.5. Determination of absolute configuration of the Eshenmoser–Claisen rearranged products

A mixture of (3S)-ethyl 3-trifluoromethyl-4-decenoate (**(S)-2a**) (0.49 g, 1.84 mmol), 2 N NaOH solution (1.5 ml), THF (5 ml), and methanol (5 ml) was stirred at room tem-

perature for 1.5 h. The solvent was removed under reduced pressure, and then the resultant solution was diluted with ether (10 ml). The aqueous solution was separated and the organic layer was extracted with 1 N NaOH solution three times. The combined aqueous layer was acidified with 1 N HCl solution and the whole was extracted with ether three times, then the organic layer was dried over anhydrous $MgSO_4$, and evaporated. To a solution of the resulting crude materials and oxalyl chloride in CH_2Cl_2, was added a catalytic amount of dimethylformamide (three drops), and the whole was stirred at room temperature overnight. The solvent and an excess amount of oxalyl chloride (0.429 ml, 5 mmol) were removed under reduced pressure and to THF solution of the resulting oil was added dimethylamine solution (50% in water, 0.21 ml) at 0°C. The reaction mixture was stirred for 1 h, then poured into 1 N HCl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography to yield the Eshenmoser–Claisen rearrangement product (0.077 g, 0.29 mmol).

4.5.1. (3S)-N,N-dimethyl-3-trifluoromethyl-4-decenamide ((S)-3a)

Yield: 16%. $[\alpha]^{18}_{D} = -8.2°$ (*c* 0.8, $CHCl_3$).

4.5.2. (3S)-N,N-dimethyl-6-benzyloxymethyl-3-trifluoromethyl-4-hexenamide ((S)-3b)

(3*S*)-Ethyl 6-benzyloxy-3-trifluoromethyl-4-hexenoate (**(*S*)-2b**) was converted into the title compound using the same method described above.

Yield: 54%. $[\alpha]^{12}_{D} = +8.3°$ (*c* 0.9, $CHCl_3$).

References

[1] (a) J.F. Liebman, A. Greenberg, W.R. Dolbier, Jr., S. Eswarakrishnan, Fluorine-Containing Molecules; Structure, Reactivity, Synthesis, VCH Publisher, New York, 1988. (b) J.T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, Wiley, New York, 1990. (c) R. Filler, Y. Kobayashi, Biomedicinal Aspects of Fluorine Chemistry, Kodansha and Elsevier Biomedical, Tokyo, 1982.

[2] (a) P.V. Ramachandran, A.V. Teodorovic, H.C. Brown, Tetrahedron 49 (1993) 1725. (b) T. Kitazume, T. Yamazaki, in Welch, J.T. (Ed.), Selective Fluorination in Organic and Bioorganic Chemistry, ACS Symposium Series No. 456, ACS, Washington, DC, 1991. (c) D. Seebach, M.A. Sutter, R.H. Weher, M.F. Züger, Organic Synthesis, Collect. Vol. VII, Wiley, New York, 1990, p. 215. (d) T. Kitazume, T. Sato, T. Kobayashi, J.-T. Lin, J. Org. Chem. 51 (1986) 1003. (e) J.-T. Lin, T. Yamazaki, T. Kitazume, J. Org. Chem. 52 (1987) 3211. (f) T. Yamazaki, K. Mizutani, T. Kitazume, J. Org. Chem. 58 (1993) 4346. (g) K. Mikami, T. Yajima, T. Takasaki, S. Matsukawa, M. Terada, T. Uchimaru, M. Maruta, Tetrahedron 52 (1996) 85. (h) N. Shinohara, J. Haga, T. Yamazaki, T. Kitazume, S. Nakamura, J. Org. Chem. 60 (1995) 4363. (i) T. Yamazaki, N. Shinohara, T. Kitazume, S. Sato, J. Org. Chem. 60 (1995) 8140. (j) T. Yamazaki, J. Haga, T. Kitazume, Chem. Lett. (1991) 2171. (k) T. Yamazaki, J. Haga, T. Kitazume, Chem. Lett. (1991) 2175. (l) K. Iseki, T. Nagai, Y. Kobayashi, Tetrahedron Lett. 35 (1994) 3137.

[3] (a) W.S. Johnson, L. Werthemann, W.R. Bartlett, T.J. Brockson, T.T. Li, D.J. Faulkner, M.R. Petersen, J. Am. Chem. Soc. 92 (1970) 741. (b) D.J. Faulkner, Synthesis (1971) 175. (c) G. Stork, S. Raucher, J. Am. Chem. Soc. 98 (1976) 1583. (d) A.E. Wick, K. Felix, K. Steen, A. Eshenmoser, Helv. Chim. Acta 47 (1964) 2425. (e) A.E. Wick, K. Felix, K. Steen, A. Eshenmoser, Helv. Chim. Acta 52 (1969) 1030. (f) E.J. Corey, M. Shibasaki, J. Knolle, Tetrahedron Lett. (1977) 1625.

[4] There are some reports concerning [3,3]-Claisen rearrangement of nonchiral γ-trifluoromethylated allylic alcohols. (a) Y. Hanzawa, K. Kawagoe, A. Yamada, Y. Kobayashi, Tetrahedron Lett. 26 (1985) 219. (b) T. Yamazaki, T. Kitazume, in Oae, S. (Ed.), Reviews On Heteroatom Chemistry, Volume 7, Myu, Tokyo, 1992, p. 132. (c) T. Yamazaki, N. Ishikawa, Bull. Soc. Chim. Fr. (1986) 937.

[5] T. Konno, H. Umetani, T. Kitazume, J. Org. Chem. 62 (1997) 137.

[6] (a) T. Konno, T. Yamazaki, T. Kitazume, Tetrahedron 52 (1996) 199. (b) T. Yamazaki, N. Ishikawa, Chem. Lett. (1985) 889. (c) T. Yamazaki, N. Ishikawa, H. Iwatsubo, T. Kitazume, J. Chem. Soc., Chem. Commun. (1987) 1340.