Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 2, pp. 223–230, 1997

Printed in Great Britain
PII: S0957-4166(96)00492-2
0957-4166/97 $17.00 + 0.00

Synthesis of trifluoromethylated compounds with four consecutive asymmetric centers via sequential [3,3]-Ireland–Claisen rearrangement and iodolactonization

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Abstract: Iodolactonization and osmylation of enantiomerically pure α-methoxy-β-trifluoromethyl-γ,δ-unsaturated carboxylic acid derivatives, which were prepared via [3,3]-Ireland–Claisen rearrangement of α-methoxyacetic acid (γ-trifluoromethyl)allylesters, were investigated. The former proceeded in a highly stereoselective manner, and the construction of four successive asymmetric centers was achieved in a high yield. On the other hand, the latter gave the desired γ-lactone in moderate yield. The mechanism is also discussed by using MOPAC AM1 calculation. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

The synthesis of highly functionalized materials possessing a CF_3 group remains a significant challenge to synthetic organic chemist. This might be because the preparation sometimes encounters specific difficulties derived from the trifluoromethyl moieties strong electronwithdrawing effect, the electronical bulkiness, and so on.[1] For example, the compound **1**[2] (Figure 1), which contains three consecutive stereogenic centers bearing a CF_3 and two hydroxyl groups, one on each carbon, is very difficult to be prepared because aldol reaction using α-CF_3 aldehyde[3] or α-CF_3 enolate,[4] which has been one of the most powerful tools for the preparation of the nonfluorinated counterpart, could not be performed due to epimerization and defluorination of the substrate.

Recently, we have found that [2,3]-Wittig rearrangement of (γ-trifluoromethyl)allyloxy acetic acid methyl esters **2** and [3,3]-Ireland–Claisen rearrangement of α-methoxyacetic acid (γ-trifluoromethyl)allylesters **3** and **4** proceeded in a highly stereoselective manner to produce α-hydroxyl-β-trifluoromethyl-γ,δ-unsaturated carboxylic acid derivatives **5**, **6**, and **7** in high yields[5] (Scheme 1). Thus, two consecutive stereocenters with a CF_3 and a hydroxyl groups have been constructed efficiently in the rearrangements. Therefore, as an extension of our study, we have attempted iodolactonization and osmylation of the rearranged products as methods for the preparation of **1**. In this paper, we describe our results of these reactions and the calculation of the transition state using MOPAC AM1 in detail.

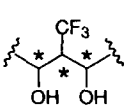

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Figure 1.

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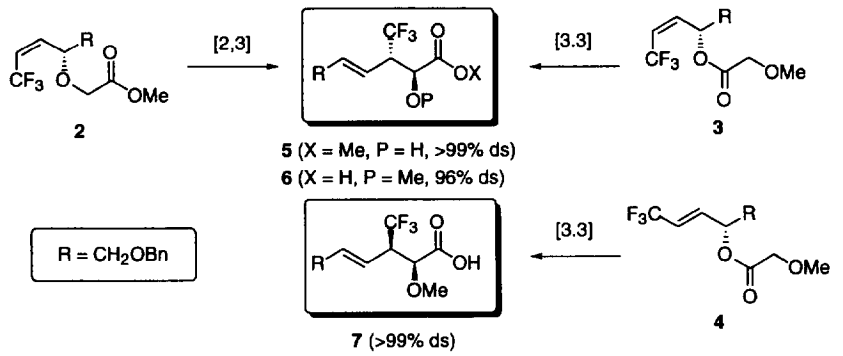
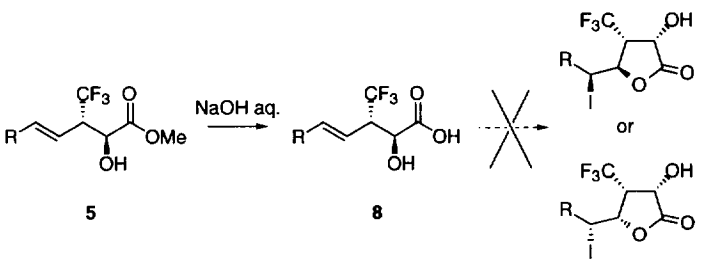


Scheme 1.



Scheme 2.

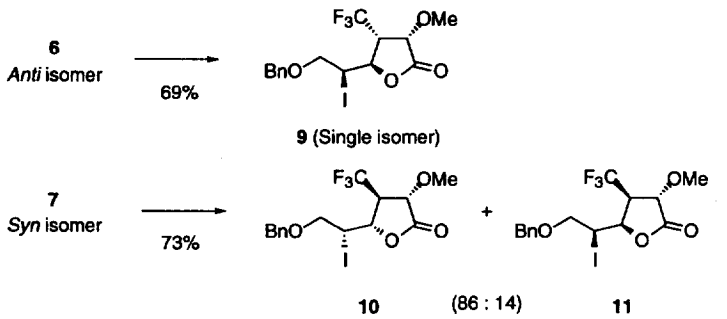
Results and discussion

Lactonization of [2,3]-Wittig- or [3,3]-Ireland–Claisen rearranged products

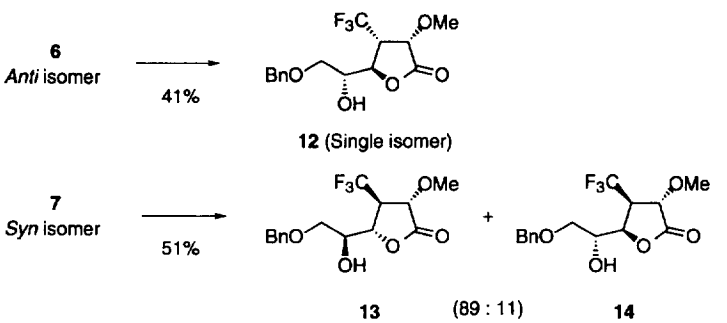
First of all, [2,3]-Wittig rearranged product **5** was hydrolyzed under conventional methods (NaOH aq./THF) to afford α-hydroxyl-β-trifluoromethyl-γ,δ-unsaturated carboxylic acid **8**, which was subjected to iodolactonization.[6] Thus, to a solution of iodine, potassium iodide and potassium carbonate in water was added the carboxylic acid at 0°C and the reaction mixture was allowed to warm to room temperature, and stirred for several days. However, the desired γ-lactone was not obtained, and the starting material was recovered quantitatively. Also the iodolactonization under the other reaction condition (I_2/CH_3CN) was a disappointment. Considering the success of nonfluorinated counterparts,[6] this phenomenon might be surprising, but unfortunately remains unclear at present (Scheme 2).

At the next stage, [3,3]-Ireland–Claisen rearranged product **6**, whose hydroxyl moiety was protected as a methyl ether, was subjected to iodolactonization according to Bartlett's procedure.[6a] Thus, **6** was treated with sodium hydrogen carbonate and iodine (excess) in chloroform at room temperature for two days (Kinetic condition). Surprisingly, the desired γ-lactone **9** was obtained in 69% yield. In addition the diastereomeric ratio of the product was found out to be 100:0 from ^{19}F NMR analysis. This satisfactory result encouraged us to examine the iodolactonization of *syn* isomer **7**. As a result, iodolactonization of **7** gave rise to **10** and **11** in 73% yield in a diastereomeric ratio of 86:14. The diastereomer mixture was proved to be inseparable by silica gel column chromatography (Scheme 3). On the other hand, iodolactonization of **6** or **7** was also performed under thermodynamic conditions (I_2/CH_3CN, at room temperature), and the desired γ-lactones with the same absolute configuration as **9** or **10**, **11** were obtained in the same stereoselective manner but in low yields.

Our next investigation was directed toward the osmylation of the rearranged products.[7] According to the literature procedure, **6** and **7** were treated with a catalytic amount of OsO_4 and *N*-methylmorpholine



Scheme 3.



Scheme 4.

N-oxide as a co-oxidant in acetone at room temperature. The reaction proceeded relatively slowly, like iodolactonization, and after stirring for two days, the desired γ-lactones **12** or **13**, **14** were obtained from the *anti* or *syn* isomer, respectively, in a moderate yield (Scheme 4). Interestingly, the same phenomenon as iodolactonization was observed. Thus, the *anti*-substrate afforded γ-lactone as a single isomer, while the *syn*-substrate gave the desired materials with the stereoselectivity similar to that in the iodolactonization. On the other hand, prolonged reaction time led to the formation of complex mixture.

Clarification of the stereochemistry

The stereochemistry of the obtained γ-lactones **9**, **10** was deduced by comparison of the calculated and the observed ^{1}H NMR coupling constants. 4-Trifluoromethyl-4,5-dihydro-5-iodomethyl-3-methoxy-2(3*H*)-furanone was selected as a model compound for the convenience of the calculation.[8]

According to the calculated results of the model compound, the *trans* configuration is considered to possess the smaller vicinal (less than 5 Hz) coupling constants between ring protons H_a and H_b or H_b and H_c than the corresponding *cis* configuration (more than 7 Hz). On the basis of these consideration, close analysis of the ^{1}H NMR spectra of **9** and **10** demonstrated these vicinal coupling constants as 9.04, 2.68 Hz, and 4.39, 4.89 Hz, strongly suggesting the 3,4-*cis*-4,5-*trans* and 3,4-*trans*-4,5-*trans* configurations, respectively (Figure 2). Although there is a little difference between experimental (2.68 Hz) and calculated data (5.13 Hz) in *anti* isomer, the configuration of **9** was confirmed as 3,4-*cis*-4,5-*trans* from an NOE experiment as depicted in Figure 3.

The stereochemistry of **12** was also determined in the similar way. Thus, as depicted in Figure 4, it was revealed from careful analysis of ^{1}H NMR of **12** that coupling constant of H_a–H_b or H_b–H_c was 8.30 or 3.17 Hz, respectively, strongly suggesting the 3,4-*cis*-4,5-*trans* configuration. Unfortunately,

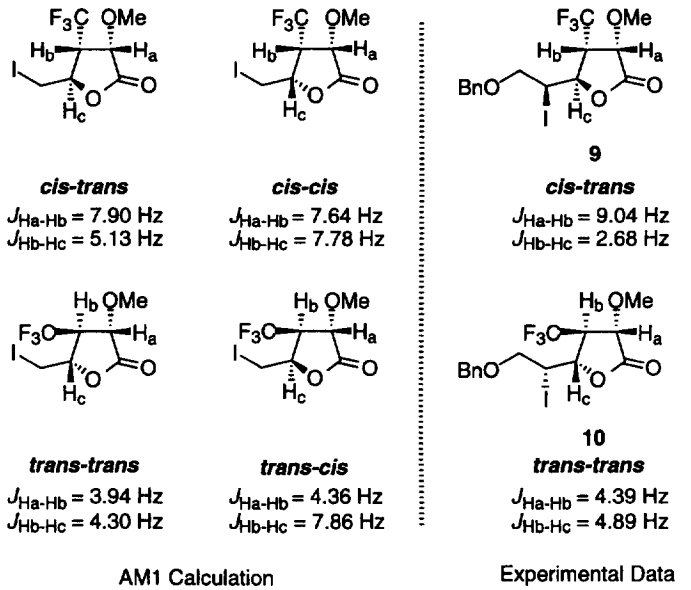


Figure 2.

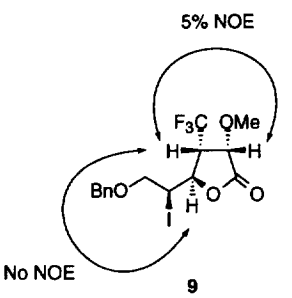
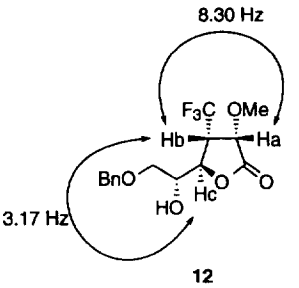


Figure 3.

the stereochemistry of **13** was very difficult to be confirmed from ^{1}H NMR analysis, however, it is highly possible that **13** might possess the configuration shown in Scheme 4. This is based on the assumption that as the case of *anti* isomer, *syn* isomer might give the γ-lactone **13** preferentially which could be formed when OsO_4 might attack the olefinic bond, avoiding a CF_3 group.

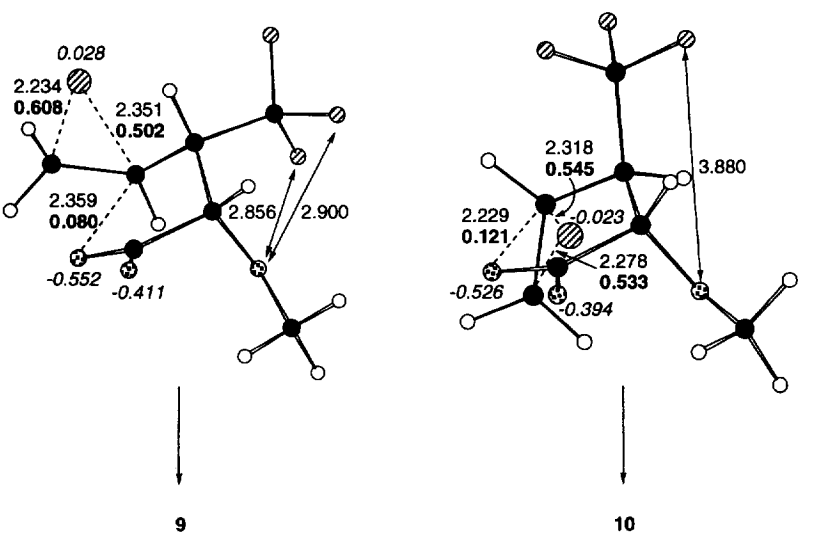
Transition state

As described above, it was verified that iodolactonization might be very useful as well as convenient for the preparation of **1**, although osmylation gave the desired γ-lactone in low yield. Then, for obtaining deeper information on the mechanistic stereochemistry of the iodolactonization, semiempirical MO calculation of transition states (TSs) were performed using the above model compound.[8] In Figure 5 are shown the most stable transition states derived from *anti*- or *syn*-substrate. From this result, it was revealed that in *anti* isomer, a carboxyl group might attack the *Si* face of the double bond preferentially, while *Re* face might be attacked in *syn* isomer favorably. In any case, a carboxyl moiety might attack the sp^2 carbon at the double bond, avoiding a CF_3 group. Thus, iodonium ion might attack the olefin from the same direction as the CF_3 group.[9] Therefore, *anti*- or *syn*-substrate



12

Figure 4.



9 10

Figure 5. (Bond length: plain, Bond order: bold, Charge: italic)

gives γ-lactone with 3,4-*cis*-4,5-*trans*, or 3,4-*trans*-4,5-*trans* configuration, respectively. Importantly, in the transition state derived from *anti* isomer, there is a severe steric as well as electronic repulsion between a CF_3 and a methoxy groups. Therefore, as shown in Figure 5, the length of the forming C–O bond is 2.359 Å in TS derived from *anti* isomer while the length is 2.229 Å in the TS derived from *syn* isomer. Thus, the former is *ca.* 6% longer than the latter. Accordingly, the increase of this repulsion might cause a destabilization of the transition state and no cyclization in a certain case.[10] Therefore, the high stereoselection in this reaction is considered to be attributed to the effect of both a remarkably bulky CF_3 and a relatively small methoxy groups.

Conclusion

In summary, we have attempted to construct highly functionalized trifluoromethylated compounds with three successive asymmetric centers such as **1** by using iodolactonization or osmylation as a key step. As a result, in the former, *syn* or *anti* isomer gave the desired γ-lactones with four consecutive stereogenic centers in a high yield as well as at the useful level of diastereoselectivity.

Experimental

^1H and ^{19}F nuclear magnetic resonance (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 were reported in parts per million (δ ppm) relative to tetramethylsilane (Me_4Si, δ 0.00 ppm for ^1H and ^{13}C NMR) and hexafluorobenzene (C_6F_6, δ 0.00 ppm for ^{19}F NMR). Coupling constants were reported in hertz (Hz). For minor isomers were shown only the chemical shifts for the representative peaks. Infrared spectra (IR) were recorded on a JASCO A-102 DIP-140 spectrometer.

General procedure for iodolactonization

A mixture of carboxylic acid (0.314 mmol), $NaHCO_3$ (0.050 g, 0.61 mmol), and water (2 mL) was stirred until a homogeneous solution was obtained. Chloroform (2 mL) was added, the mixture was cooled in an ice bath, and 0.16 g (0.62 mmol) of iodine was added. The mixture was stirred at room temperature for 2 days, the layers were separated, and the organic phase was washed with 10% aqueous $Na_2S_2O_3$ until colorless, and with water and brine. The organic layer was dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure, and the crude iodolactone was obtained as a yellow oil, which was purified by silica gel column chromatography to afford pure material.

(1′S,3S,4R,5R)-4-Trifluoromethyl-4,5-dihydro-5-(1′-iodo-2′-benzyloxyethyl)-3-methoxy-2(3H)-furanone ***9***

Yield: 69%. $[\alpha]^{17}_D=-16.4$ (*c* 0.6, $CHCl_3$). IR (neat) ν 3050, 2937, 2862, 1795. Anal. Calcd for $C_{15}H_{16}O_4F_3I$: C, 40.56; H, 3.63. Found: C, 40.53; H, 3.61. ^1H NMR δ 3.54 (1 H, dquint, *J*=3.18, 9.04 Hz) 3.63 (3 H, s) 3.84 (1 H, dd, *J*=4.64, 10.75 Hz) 3.77 (1 H, dd, *J*=7.81, 10.50 Hz) 4.41 (1 H, dt, *J*=4.40, 7.81 Hz) 4.39 (1 H, d, *J*=4.39, 8.79 Hz) 4.56 (1 H, d, *J*=11.71 Hz) 4.53 (1 H, d, *J*=1.72 Hz) 4.86 (1 H, t, *J*=3.66 Hz) 7.30–7.40 (5 H, m). ^{13}C NMR δ 29.36, 45.94 (q, *J*=27.5 Hz) 60.35, 71.07, 73.42, 74.16, 76.37, 77.48 (q, *J*=3.0 Hz) 124.41 (q, *J*=279.8 Hz) 127.86, 128.12, 128.52, 136.76, 171.11. ^{19}F NMR δ 95.70 (d, *J*=9.16 Hz).

(1′R,3S,4S,5S)-4-Trifluoromethyl-4,5-dihydro-5-(1′-iodo-2′-benzyloxyethyl)-3-methoxy-2(3H)-furanone ***10***

Yield: 74% (Combined yield). Diastereoselectivity=86:14. $[\alpha]^{16}_D=-28.4$ (*c* 0.6, $CHCl_3$). IR (neat) ν 3050, 3000, 2864, 2850, 1802. Anal. Calcd for $C_{15}H_{16}O_4F_3I$: C, 40.56; H, 3.63. Found: C, 40.61; H, 3.64. ^1H NMR δ 3.74 (1 H, dquint, *J*=4.39, 8.79 Hz) 3.62 (3 H, s) 3.78 (1 H, dd, *J*=6.84, 10.50 Hz) 3.85 (1 H, dd, *J*=4.89, 10.75 Hz) 4.09 (1 H, d, *J*=4.64 Hz) 4.41 (1 H, dt, *J*=4.63, 6.59 Hz) 4.55 (1 H, d, *J*=11.72 Hz) 4.58 (1 H, d, *J*=11.72 Hz) 4.80 (1 H, dd, *J*=4.64, 6.35 Hz) 7.30–7.40 (5 H, m). ^{13}C NMR δ 29.85, 50.83 (q, *J*=28.3 Hz) 59.22, 70.63, 73.30, 75.44 (q, *J*=2.6 Hz) 76.93 (q, *J*=2.5 Hz) 124.94 (q, *J*=278.2 Hz) 127.83, 127.99, 128.47, 137.03, 170.64. ^{19}F NMR δ 91.84 (d, *J*=7.63 Hz).

(1′S,3S,4S,5R)-4-Trifluoromethyl-4,5-dihydro-5-(1′-iodo-2′-benzyloxyethyl)-3-methoxy-2(3H)-furanone ***11***

^1H NMR δ 3.35 (1 H, ddq, *J*=3.35, 1.70, 5.61, 9.03 Hz) 4.30 (1 H, dt, *J*=4.64, 10.74 Hz) 4.65 (1 H, d, *J*=10.01 Hz). ^{13}C NMR δ 24.07, 49.85 (q, *J*=20.1 Hz) 58.65, 71.49, 79.28, 128.45, 137.32. ^{19}F NMR δ 97.97 (d, *J*=9.16 Hz).

General procedure of osmylation

To a solution of *N*-methylmorpholine *N*-oxide (50% in water, 0.1 mL) and the carboxylic acid (0.096 g, 0.302 mmol) in acetone (3 mL) was added a 2.5 wt% solution of OsO_4 in *t*-BuOH (0.176 mL) under N_2 at 0°C. The reaction mixture was allowed to warm to room temperature, and then stirred for 2 days. After the addition of Na_2SO_3 aq. (1 mL) and the precipitates were removed through

a pad of Celite, the filtrate was extracted with ether, washed with NH_4Cl aq., brine, and evaporated. Purification by silica gel column chromatography gave the desired γ-lactone.

(1′R,3S,4R,5R)-4-Trifluoromethyl-4,5-dihydro-5-(1′-hydroxy-2′-benzyloxyethyl)-3-methoxy-2(3H)-furanone ***12***

Yield: 51%. $[\alpha]^{24}_D$=−36.5 (*c* 0.6, $CHCl_3$). IR (neat) ν 3502, 3000, 2934, 2950, 1792. ^{1}H NMR δ 3.45 (1 H, dquint, *J*=3.17, 8.95 Hz) 3.59 (1 H, dd, *J*=8.55, 9.52 Hz) 3.63 (1 H, dd, *J*=4.39, 9.52 Hz) 3.64 (3 H, s) 3.93–3.98 (1 H, m) 4.49 (1 H, d, *J*=8.30 Hz) 4.55 (1 H, d, *J*=11.72 Hz) 4.59 (1 H, d, *J*=11.72 Hz) 7.30–7.40 (5 H, m). ^{13}C NMR δ 44.47 (q, *J*=27.5 Hz) 60.11, 70.09, 70.72, 73.58, 74.30 (q, *J*=1.3 Hz) 76.09 (q, *J*=3.1 Hz) 124.79 (q, *J*=279.4 Hz) 127.85, 128.05, 128.50, 137.12, 172.53. ^{19}F NMR δ 95.18 (d, *J*=9.15 Hz).

(1′S,3S,4S,5S)-4-Trifluoromethyl-4,5-dihydro-5-(1′-hydroxy-2′-benzyloxyethyl)-3-methoxy-2(3H)-furanone ***13***

Yield: 41% (Combined yield). Diastereoselectivity=89:11. $[\alpha]^{23}_D$=−7.0 (*c* 0.7, $CHCl_3$). IR (neat) ν 3447, 3000, 2926, 2900, 1792. ^{1}H NMR δ 2.40 (1 H, d, *J*=5.62 Hz) 3.50–3.58 (1 H, m) 3.61 (1 H, dd, *J*=5.62, 9.52 Hz) 3.65 (1 H, dd, *J*=7.32, 9.52 Hz) 3.66 (3 H, s) 3.91–3.95 (1 H, m) 4.22 (1 H, d, *J*=8.06 Hz) 4.52–4.55 (1 H, m) 4.56 (1 H, d, *J*=11.48 Hz) 4.58 (1 H, *J*=11.72 Hz) 7.30–7.40 (5 H, m). ^{13}C NMR δ 46.09 (q, *J*=28.5 Hz) 59.14, 69.39, 70.18, 73.64, 74.65 (q, *J*=2.4 Hz) 75.36 (q, *J*=2.4 Hz) 125.33 (q, *J*=280.0 Hz) 127.85, 128.06, 128.56, 137.23, 171.57. ^{19}F NMR δ 92.38 (d, *J*=9.15 Hz).

(1′R,3S,4S,5R)-4-Trifluoromethyl-4,5-dihydro-5-(1′-hydroxy-2′-benzyloxyethyl)-3-methoxy-2(3H)-furanone ***14***

^{1}H NMR δ 2.40–2.50 (1 H, m) 3.30–3.40 (1 H, m). ^{19}F NMR δ 95.75 (d, *J*=9.16 Hz).

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by their force calculation giving only one imaginary frequencies, but also by the intrinsic reaction coordinate calculation affording the corresponding substrates and products.

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(Received in Japan 16 October 1996; accepted 18 November 1996)