[3,3] SIGMATROPIC REARRANGEMENT OF SOME FLUORINATED 1,5-HEXADIENES

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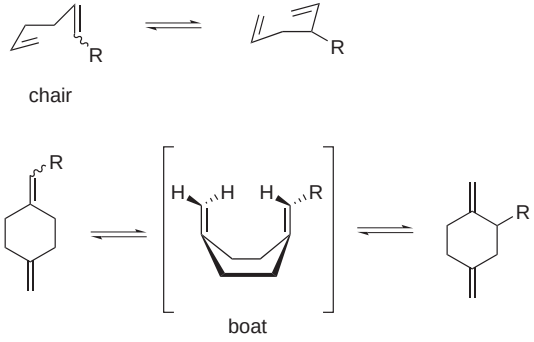
Fluorine atoms incorporated into 1,5-hexadiene molecule should influence the kinetic as well as the thermodynamic parameters of [3,3] sigmatropic rearrangement (Cope rearrangement). Within few decades is has been documented that this transformation proceeds in a concerted manner, rather than stepwise with some radical intermediates involved. Few new terminally fluorinated 1,5-hexadienes (compounds **3**, **5A**, **7**, **9** and **5B**) have been synthesized. The activation parameters of rearrangement have been determined and compared with those known for hydrocarbon analogues. While systems developing chair-like transition states (compounds **3** and **5**) showed close similarity with hydrocarbon analogues (compound **1**), those developing boat-like transition states (compounds **7**, **9** and **5B**) may proceed through radical stepwise mechanism. Computational studies of the transition states were carried out, showing that only *ab initio* methods (MP2 and especially DFT) can give approximate correlation with experimental data, whereas in the case of hydrocarbon analogues even simple semiempirical methods (AM1) were reliable enough to reproduce experimental results.

Keywords: Sigmatropic rearrangements; Cope rearrangement; Dienes; Fluorinated compounds; Transition states; *Ab initio* calculations; Conformation analysis.

It is generally understood that [3,3] sigmatropic rearrangement (Cope rearrangement) is a pericyclic, concerted reaction. This general understanding comes from the concept that the alternative mechanisms – in particular stepwise biradical mechanism – do not fulfill energetical requirements. Moreover, the concerted pathway is considered to follow the Woodward and Hoffman rules. After original reports by Hurd[1] and Cope[2] about fifty

years ago, Cope rearrangement was employed as the very useful synthetic strategy leading to new polycyclic systems.

Recently Cope rearrangement has attracted some new interest of experimental as well as theoretical chemists, trying to explore the ideas about the transition states (TS) of these reactions[3,4] (Scheme 1). The two important aspects of these studies are (i) structure and energy requirement of the transition state[3,4] and (ii) usefulness of computational methods for reaction modeling[5–9]. There are two possible structures of the transition state for Cope rearrangement: chair-like and boat-like with the latter one disfavored energetically by about 10 kcal/mol [8,9].

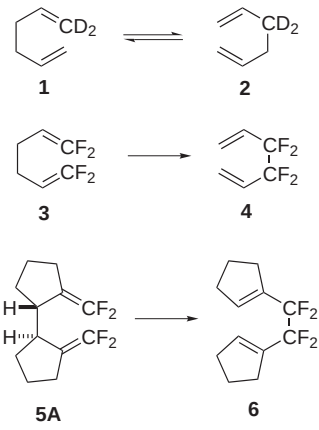


SCHEME 1

Although [3,3] sigmatropic processes are well known in literature and quite well understood, the studies of thermal rearrangement of fluorinated 1,5 dienes had received very little attention. The parent compound: 1,5-hexadiene undergoes [3,3] sigmatropic rearrangement, but due to the degeneracy in the system, the 1,1-dideutero-1,5-hexadiene was studied[10]. In this fundamental research the basic kinetic parameters were determined. Partially fluorinated (*E*)- and (*Z*)-1-fluoro-1,5-hexadienes have been reported to undergo the Cope rearrangement with almost identical activation parameters as the parent 1,5-hexadiene[15]. This finding is somehow surprising in terms of the expected fluorine influence on constrain of the transition state. In our preliminary report we presented the results showing significant fluorine steric effect being important factor in kinetic control of the rearrangement[16]. It was also shown that Cope rearrangement of highly fluorinated 1,5-hexadienes might proceed *via* radical, not concerted mechanism[17]. In this study we would like to determine the influence of fluorine atoms on [3,3] sigmatropic rearrangement: the kinetic as well as thermodynamic aspects of these reactions. The even more important issue was to get an idea about structure of the transition state and to support concerted or radical mechanism applying also computational methods.

RESULTS AND DISCUSSION

Since only few examples of terminally fluorinated dienes were studied, the synthesis of compounds **3**, **5A**, **7**, **9** and **5B** was accomplished. Fluorinated dienes **3** and **5A** should undergo Cope rearrangement with chair-like transition states (Scheme 2). The hydrocarbon analogues of these compounds are known (see Table I) and logically it was worth to compare these two systems.



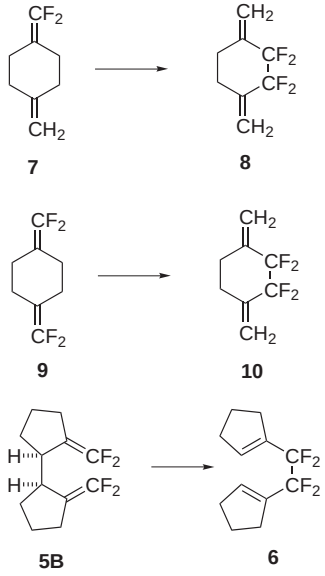
SCHEME 2

TABLE I
Kinetic parameters for [3,3] sigmatropic rearrangement of some fluorinated 1,5-hexadienes

Reaction[a]	$\Delta H^{\#}$, kcal/mol	$\Delta S^{\#}$, cal/mol deg	Reference
1→2	33.5 ± 0.5	–13.8 ± 1.0	10
3→4	29.9 ± 0.2	–18.5 ± 0.5	16
5A→6(H)	28.0 ± 1.1	–11.3 ± 2.6	12
5A→6	22.4 ± 0.2	–17.5 ± 0.4	16
7→8(H)	44.4 ± 1.8	–3.7 ± 3.2	11
7→8	40.8 ± 0.5	–6.1 ± 0.9	this work
9→10	40.7 ± 0.5	–10.1 ± 0.8	this work
5B→6(H)	41.6 ± 0.5	–0.7 ± 1.0	12
5B→6	49.5 ± 1.0	+8.1 ± 1.7	16

[a] **H** indicates hydrocarbon analogues.

Similarly, there are known hydrocarbon systems of Cope rearrangement in which boat-like transition states have to be developed to proceed the rearrangement, and their fluorinated analogues were compared with them as well (compounds **7**, **9** and **5B**, see Table I and Scheme 3).



SCHEME 3

Thermal Cope rearrangement of these species (compounds **3**, **5A**, **7**, **9** and **5B**) was studied in a gas phase (compounds **3**, **7** and **9**) or by NMR kinetic studies (low volatility of dienes **5A** and **5B** did not allow to do direct gas phase studies). Kinetic parameters ($\Delta H^{\neq}$ and $\Delta S^{\neq}$) of these processes have been determined and are presented in Table I.

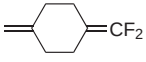
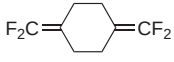
One can conclude from the above data that fluorinated and non-fluorinated systems show similar activation parameters with a significant negative $\Delta S^{\neq}$ characteristic of a well organized transition state (chair-like transition state). Different activation parameters describe and illustrate the process undergoing through the boat-like transition state. In this case $\Delta H^{\neq}$ is about 10 kcal/mol higher in comparison with the chair-like transition state. Small, but still negative $\Delta S^{\neq}$ may support the idea about concerted pathway with the exception of compound **11**, where both relatively high $\Delta H^{\neq}$ and high positive $\Delta S^{\neq}$ strongly suggest a radical mechanism.

In all studied fluorinated systems the rearrangement led irreversibly to products (compounds **4**, **6**, **8** and **10**) and equilibria were not observed. It is well known that alkenes bearing fluorine atoms on sp^2 hybridized carbon

atoms are usually less stable than the products with fluorine atoms located on sp^3 carbons.

Computational methods were employed to get an insight into the structure of the transition states of the above processes: to determine their geometry and to estimate energy barrier between the substrate and transition states. Originally simple semiempirical (AM1) calculations were carried out. This method - successfully used by Dewar *et al.*[8,13] – in the case of fluorinated species gave very poor agreement with experimental kinetic data. Also the thermodynamic equilibria between the substrates and products were unreliable in terms of experimental results. The problem of a calculated structure and an energy of transition states of pericyclic processes (including [3,3] sigmatropic rearrangement) has been discussed in detail by Houk *et al.*[14]. It seems that only advanced *ab initio* calculation could – to some extent – reproduce experimental results. As an illustration of the problem, activation energies of transition states of a few simple fluorinated alkenes were determined, comparing reliability of computational methods (Table II).

TABLE II
Ab initio calculations of $\Delta H^{\neq}$ (in kcal/mol) for [3,3] sigmatropic rearrangements of some fluorinated 1,5-hexadienes

Substrate	RHF/4-31G	RHF/6-31G*	MP2(fc)6-31G*//RHF/6-31G*	Experimental
	chair: 48.2 boat: 58.6	chair: 54.7 boat: 65.2	chair: 30.7 boat: 41.68	34.0
	boat: 59.3	boat: 64.9	boat: 30.0	40.8
	boat: 63.6	boat: 68.2	boat: 31.2	40.7

Nevertheless, the most accurate numerical results have been obtained using DFT method. It seems that the computation results dealing with the chair TS are in good agreement with experimental ones. Contrary to these, calculated results for rearrangement undergoing through the boat TS are again dramatically off expectations, which may suggest a radical, not concerted mechanism of transformations (Table III).

The influence of terminal geminal difluorination in [3,3] sigmatropic rearrangement involving chair *vs* boat transition states is fundamentally different. The chair-like transition states accommodate terminal fluorines to any degree without detrimental kinetic effects. The changes in the activation parameters in this case can be attributed to changes in the relative thermodynamics of the 1,5-diene systems as the degree of terminal geminal difluorination is increased. This is consistent with a mechanism involving a high degree of C1–C6 bond formation with little C3–C4 bond cleavage. The boat-like transition state undergoes the same relative changes in thermodynamics upon increased fluorination but the twisting of terminal fluorine atoms in this conformation leads to highly repulsive interactions. This gives rise to activation parameters consistent with a transition state more resembling a pair of allyl radicals involving a high degree of C3–C4 bond cleavage without a similar degree of C1–C6 bond formation.

TABLE III

DFT calculations of enthalpy of activation, $\Delta H^{\neq}$ and entropy of activation $\Delta S^{\neq}$ for boat and chair transition states of some fluorinated 1,5-hexadienes at 298.15 K and 1 atm (B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d)). Thermal energy were corrected by factor 0.9804. $\Delta\Delta H_f$ represents thermodynamic stability difference between product and substrate in the reaction

Compound	$\Delta H^{\neq}_{boat}$ kcal/mol	$\Delta S^{\neq}_{boat}$ cal/mol	$\Delta H^{\neq}_{chair}$ kcal/mol	$\Delta S^{\neq}_{chair}$ cal/mol	$\Delta\Delta H_f$ kcal/mol
1	41.1	–6.6	34.8	–8.6	
(*Z*)-1-Fluoro-1,5-hexadiene	41.6	–7.7	35.2	–10.1	–0.92
1,1-Difluoro-1,5-hexadiene	41.2	–8.2	33.0	–10.9	–5.6
3	44.3	–9.7	34.2	–12.8	–5.2
7(H)[a]	47.9	–2.2			
7	44.7	–5.9			–7.3
9	46.5	–3.6			–6.2

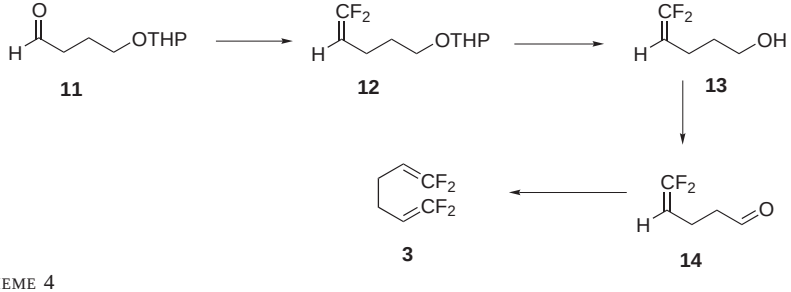
[a] **H** indicates hydrogen analogues.

EXPERIMENTAL

All nuclear magnetic resonance chemical shifts are reported in ppm (δ-scale) using internal reference TMS for ^{1}H and ^{13}C NMR spectra and $CFCl_3$ for ^{19}F NMR spectra. Coupling constants (*J*) are given in Hz. All NMR spectra were obtained on Varian VXR 300 or Varian XL-200 instruments. Gas chromatographic separations were performed by gas-liquid phase chromatography on packed columns. Quantitative GLPC analyses were run on Hewlett Packard 5890 Series II gas chromatograph with a flame ionization detector. Preparative GLPC was accomplished on Varian Aerograph A-90 chromatograph with thermal conductivity detector. Conditions and columns used are described in each case in relevant experiments. Low and high resolution mass spectra were determined on Kraytos/AEI-30 spectrometer at 70 eV.

Synthesis of 1,1,6,6-Tetrafluoro-1,5-hexadiene (**3**)

Compound **3** was accomplished according to Scheme 4.



SCHEME 4

4-[(Tetrahydro-2H-pyran-2-yl)oxy]-1-butanol was prepared according to the method of Hoffmann and Rabe[18]. 1,4-Butanediol (60.0 ml, 0.68 mol) was placed in a round-bottom flask equipped with a strong magnetic stirrer. Diethyl ether (50 ml) and 5 drops of concentrated HCl were then added. 3,4-Dihydro-2*H*-pyran (DHP; 41.1 ml, 37.9 g, 0.45 mol) was dissolved in 50 ml of diethyl ether and added dropwise at room temperature with rapid stirring to the heterogeneous diol/ether mixture. The reaction mixture became homogeneous after addition of approximately 10 ml of DHP/ether solution. Upon completion of addition of the DHP solution, the reaction mixture was stirred at room temperature for 3 h, then extracted with 2 × 50 ml of 10% aqueous KOH. The aqueous solution was extracted with 50 ml of diethyl ether, then ether extracts were combined and dried over $MgSO_4$. The ether was then removed on a rotary evaporator and the remaining clear colorless liquid was fractionally distilled through an 12-cm Vigreaux column. 4-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-1-butanol (52.8 g, 67%) was obtained as an early fraction boiling at 100–109 °C at 0.1 mm Hg as a colorless viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 1.45–1.85 (m, 10 H); 3.22 (s, 1 H); 3.37 (m, 6 H); 4.60 (t, 1 H, $^{3}J_{HH}$ = 3). ^{13}C NMR (50 MHz, $CDCl_3$, $CHCl_3$): 19.3, 25.2, 26.1, 29.6, 30.4, 62.0, 62.1, 67.2, 98.6.

4-[(Tetrahydro-2H-pyran-2-yl)oxy]butanal (**11**) was prepared by adapted procedure as described by Corey and Schmidt[19]. A 1-liter round-bottom flask was flame-dried under argon purge and equipped with a strong magnetic stirrer and septum. 4-[(Tetrahydro-2*H*-pyran-

2-yl)oxy]-1-butanol (17.9 g, 1.03 mmol) was syringed into the flask followed by 400 ml of dry CH_2Cl_2. Pyridinium dichromate (PDC; 58.3 g, 0.155 mol) was quickly added and rapid stirring was started. The solution turned dark brown-black within minutes of addition of PDC. Stirring was continued at room temperature for 15 h and then the reaction mixture was diluted with 400 ml of diethyl ether. The black solid residue was gravity-filtered and the resultant brown-black solution filtered through a bed of 150 mesh, basic activated (Brockmann I) aluminum oxide. The resultant solution was concentrated on a rotary evaporator to yield a colorless slightly viscous liquid. This material was fractionally distilled through a 6-cm Vigreaux column and 12.7 g (72%) of colorless, pleasantly smelling aldehyde **11** was obtained as an early fraction boiling at 85–90 °C at 0.05 mm Hg. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 1.45–1.85 (m, 6 H); 1.94 (quintet, 2 H, $^3J_{HH}$ = 6.7); 2.54 (dt, 2 H, $^3J_{HH}$ = 7.0, 1.7); 3.35–3.55 (m, 2 H); 3.73–3.88 (m, 2 H); 4.56 (t, 1 H, $^3J_{HH} \approx 3$); 9.78 (t, 1 H, $^3J_{HH}$ = 1.7). ^{13}C NMR (50 MHz, $CDCl_3$, $CHCl_3$): 19.5, 22.7, 25.5, 30.6, 41.1, 62.2, 66.4, 98.8, 202.2.

1,1-Difluoro-5-[(tetrahydro-2H-pyran-2-yl)oxy]-pent-1-ene (**12**) was prepared by adapted procedure as described by Naae and Burton[20]. A three-neck 1-liter flask was assembled under argon purge with a mechanical stirrer, septum and two addition funnels. The system was flame-dried under argon purge. Dibromodifluoromethane (29.1 g, 0,139 mol) was transferred to a Rotaflow tube, dissolved in 60 ml of dry THF and then syringed into the reaction vessel followed by an additional 160 ml of dry THF. This solution was cooled to –5 °C by an ice/salt bath. Dry THF (140 ml) was placed in an addition funnel followed by 50.0 ml (44.9 g, 0.275 mol) of $P(N(CH_3)_2)_3$. Rapid stirring was started and the $P(N(CH_3)_2)_3$ was added dropwise to the CF_2Br_2 solution over 1 h with cooling. A fine white precipitate formed as addition continued. Upon completing addition of the $P(N(CH_3)_2)_3$, the mixture was stirred at –5 °C for 1 h and then brought to room temperature. Aldehyde **11** (16.0 g, 92.9 mmol) was dissolved in 50 ml of dry THF and placed in the second addition funnel. The solution of **11** was then added to the ylide solution at room temperature over 15 min and then stirred at room temperature for 16 h. At this time the reaction mixture was a yellow-brown solution with a fine yellow precipitate settling on the bottom of the reaction vessel. The solids were gravity-filtered and rinsed with 100 ml of diethyl ether. This solution was concentrated on a rotary evaporator to about 25 ml volume which was taken up in 200 ml of diethyl ether and exhaustively extracted with water. The ether solution was then dried over $MgSO_4$ and the ether was removed by distillation. Alkene **12** (11.1g, 58% by ^{19}F NMR; about 80% pure, the reminder being diethyl ether or traces of THF) was obtained as a clear, light brown liquid. It seems, that the compound **12** forms azeotropic mixtures with diethyl ether and/or THF and as an 80% pure material was used for further synthesis. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 1.45–1.85 (m, 8 H); 2.03–2.17 (m, 2 H); 3.33–3.57 (m, 2 H); 3.75–3.92 (m, 2 H); 4.17 (dtd, 1 H, $^3J_{transHF}$ = 25.2, $^3J_{HH}$ = 7.94, $^3J_{cisHF}$ = 2.54); 4.55 (t, 1 H, $^3J_{HH} \approx 3$). ^{13}C NMR (50 MHz, $CDCl_3$, $CHCl_3$): 18.9 (d, 1 C, $^3J_{CF}$ = 4.3); 19.4, 25.3, 29.3 (t, 1 C, $^4J_{CF} \approx 2$); 30.6, 62.1, 66.3, 77.6 (t, 1 C, $^2J_{CF}$ = 21.2); 98.7, 156.2 (t, 1 C, $^1J_{CF}$ = 283.9). ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$): –89.8 (d, 1 F, $^2J_{FF}$ = 48.4); –92.3 (dd, 1 F, $^2J_{FF}$ = 48.4, $^3J_{HF}$ = 25.2).

5,5-Difluoro-4-penten-1-ol (**13**). Compound **12** was deprotected to alkohol **13** by adaptation of the procedure described by Beier and Mundy[21]. Alkene **12** (11.1 g, 43 mmol, 80% pure, impurities being diethyl ether or traces of THF) was dissolved in 70 ml of 1,4-butanediol. Acid activated Dowex 50X80–200 ion exchange resin (5.0 g) was added and the mixture stirred rapidly for 2.5 h. The reaction was flash-distilled down to pressure of 0.5 mm Hg. Approximately 2 ml of THF and ether was collected upon pump down of the system. At this

stage it was possible to remove traces of diethyl ether and THF introduced as impurities with alkene **12**. The fraction boiling between 55 and 110 °C (bath temperature) was collected to yield about 5 ml of clear, colorless liquid. Being slightly acidic, this material was distilled off from 2 g of dry $NaHCO_3$ to yield 4.37 g (83%) of alcohol **13**, b.p. 74–78 °C at 115 mm Hg. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 1.63 (tt, 2 H, $^3J_{HH}$ = 7.42, 6.36); 2.07 (m, 2 H); 2.78 (bs, 1 H); 3.62 (t, 2 H, $^3J_{HH}$ = 6.34); 4.16 (dtd, 1 H, $^3J_{transHF}$ = 25.38, $^3J_{HH}$ = 7.78, $^3J_{cisHF}$ = 2.54). ^{13}C NMR (50 MHz, $CDCl_3$, $CHCl_3$): 18.5 (d, 1 C, $^3J_{CF}$ = 4.2); 32.1 (t, 1 C, $^4J_{CF}$ = 2.1); 61.6, 77.3 (t, 1 C, $^2J_{CF}$ = 21.3); 156.3 (dd, 1C, $^1J_{CF}$ = 284.9, 285.1). ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$): –89.6 (d, 1 F, $^2J_{FF}$ = 48.6); –92.2 (dd, 1 F, $^2J_{FF}$ = 48.6, $^3J_{transHF}$ = 25.5). MS EI, *m/z* (% rel. int.): 104 (100), 84 (16), 77 (69).

5,5-Difluoro-4-pentenal (**14**) was prepared according to the procedure described by Corey and Schmidt[19]. A round-bottom flask was flame dried under argon purge and 150 ml of dry CH_2Cl_2 was added. Alcohol **13** (4.37 g, 35.8 mmol) was then added followed by 20.17 g (53.6 mmol) of pyridinium dichromate. The reaction mixture was stirred at room temperature for 18 h then diluted with 250 ml of diethyl ether. The mixture was gravity-filtered to remove the black solids which were rinsed with diethyl ether and the resultant brown-black solution was filtered through the bed of 150 mesh base-activated (Brockmann I) aluminum oxide. Contamination with pyridine was detected by GLPC, so the solution was extracted with 2 × 50 ml of half-saturated $CuSO_4$ solution, then with 2 × 50 ml of water. By GLPC pyridine had been removed and the solution was dried over $MgSO_4$. Ether and CH_2Cl_2 were carefully distilled off through a 6-cm Vigreaux column and the residue was transferred to a microdistillation apparatus. As the heating bath temperature raised to about 40 °C with the applied pressure of 100 mm Hg, the rest of material bumped over. Due to small amount of material, distillation was not attempted again. A clear light yellow liquid was 87% pure aldehyde **14** (3.37 g, 70%) contaminated with diethyl ether and CH_2Cl_2. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 2.22–2.35 (m, 2 H); 2.53 (tm, 2 H, $^3J_{HH}$ = 6.92); 4.22 (dtd, 1 H, $^3J_{transHF}$ = 25.10, $^3J_{HH}$ = 7.78, $^3J_{cisHF}$ = 2.38); 9.76 (t, 1 H, $^3J_{HH}$ = 1.2). ^{13}C NMR (50 MHz, $CDCl_3$, $CHCl_3$): 14.9 (d, 1 C, $^3J_{CF}$ = 4.9); 43.0 (t, 1 C, $^4J_{CF}$ = 2.6); 77.0 (t, 1 C, $^2J_{CF}$ = 31.9); 156.2 (dd, 1 C, $^1J_{CF}$ = 285.6, 286.2); 200.6. ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$): –88.9 (d, 1 F, $^2J_{FF}$ = 46.4); –91.0 (dd, 1 F, $^2J_{FF}$ = 46.4, $^3J_{transHF}$ = 25.0). MS EI, *m/z* (% rel. int.): 120 (10), 100 (11), 91 (7), 7 7(66), 69 (100), 64 (19). HRMS, calculated for $C_5H_6F_2O$: 120.0386; found: 120.0356.

1,1,6,6-Tetrafluoro-1,5-hexadiene (**3**) was prepared by the method described by Naae and Burton[20]. A three-necked round-bottom flask was assembled with two septa, a pressure-equalizing addition funnel, magnetic stirrer and flame dried under argon purge. Dibromodifluoromethane (1.55 g, 7.39 mmol) was transferred to a Rotaflow tube, then dissolved in 15 ml of dry triglyme and added to the reaction vessel with a syringe. This solution was cooled to –5 °C with an ice/salt bath. $P(N(CH_3)_2)_3$ (2.6 ml, 2.3 g, 14 mmol) was dissolved in 10 ml of dry triglyme in the addition funnel and then added to the CF_2Br_2 solution over 15 min with good stirring and cooling at –5 °C. The resultant cloudy solution, thick with white precipitate, was stirred at –5 °C for 1 h and then brought to room temperature. Aldehyde **14** (0.90 g, 7.5 mmol) was dissolved in 5 ml of dry triglyme and added to the ylide solution at room temperature over 5 min. This mixture was allowed to stir at room temperature for 18 h. The reaction mixture was then flash-distilled into a two-necked Rotaflow trap up to a bath temperature of 40 °C at 0.5 mm Hg. 1,1,6,6-Tetrafluoro-1,5-hexadiene (0.44 g, 38%) was obtained as a clear, colorless liquid containing traces of diethyl ether, methylene chloride and $OP(N(CH_3)_2)_3$. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 2.05–2.08 (m, 4 H); 4.06–4.20 (dm, 2 H, $^3J_{transHF}$ = 25.5). ^{13}C NMR (75 MHz, $CDCl_3$, $CHCl_3$):

22.3 (m, 2 C); 76.8 (t, 2 C, $^2J_{CF}$ = 21.5); 156.6 (dd, 2 C, $^1J_{CF}$ = 285.6, 285.7). ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): –89.0 (d, 2 F, $^2J_{FF}$ = 46.4); –91.2 (dd, 2 F, $^2J_{FF}$ = 46.4, $^3J_{transHF}$ = 25.5). MS EI, *m/z* (% rel. int.): 154 (1), 134 (1), 115 (2), 95 (2), 85 (23), 77 (100), 64 (2). HRMS, calculated for $C_6H_6F_4$: 154.0405; found: 154.0410.

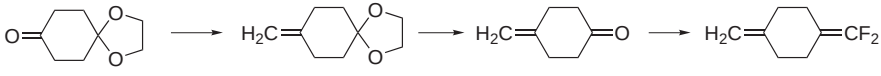
Gas Phase Thermolysis of 1,1,6,6-Tetrafluoro-1,5-hexadiene (**3**)

An about 100 mg sample of diene **3** was obtained 98% pure by preparative GLPC separation from NMR solution in C_6D_6 (column 8 mm × 4 m, 20% SE-30 on Chromosorb P 80/100). Vapor of diene **3** was expanded into the gas kinetic vessel to the pressure of about 1 kPa, and conversion to 3,3,4,4-tetrafluoro-1,5-hexadiene (**4**) was followed by GLPC (column 4 mm × 4 m, 30% of $AgNO_3/C_6H_5CH_2CN$ on Chromosorb Z 80/100, internal standard *n*-octane). The yield of this transformation was >99%. Reversibility of **4** to **3** was not observed.

3,3,4,4-Tetrafluoro-1,5-hexadiene (**4**). Solution (30%) of diene **3** in C_6D_6 was sealed in a Carius tube and thermolyzed at 185 °C for 42 h. ^{19}F NMR spectrum showed only presence of diene **4** which was isolated by preparative scale GLPC from this solution (column 8 mm × 6.5 m, 20% Triton X-305 on Chromosorb W 80/100). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 5.66–5.72 (m, 2 H); 5.81–6.08 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$, $CHCl_3$): 114.9 (tt, 2 C, $^1J_{CF}$ = 247.1, $^2J_{CF}$ = 35.7); 124.0 (m, 2 C); 126.5 (t, 2 C, $^2J_{CF}$ = 24.6). ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): –115.6 (dm, 4 F, $^3J_{HF}$ = 12.1). MS EI, *m/z* (% rel. int.): 154 (1), 135 (5), 134 (2), 115 (8), 85 (13), 78 (3), 77 (100), 57 (3), 51 (16). HRMS, calculated for $C_6H_6F_4$: 154.0405; found: 154.0400.

1-(Difluoromethylene)-4-methylenecyclohexane (**7**)

Preparation of diene **7** was accomplished according to the Scheme 5.



15 **16** **17** **7**

SCHEME 5

4-Methylene-1-cyclohexanone ethylene ketal (**16**) was prepared by adaptation of a general procedure[22]. A 250-ml three-necked, round-bottom flask was assembled with a magnetic stirrer and two pressure equalizing addition funnels with septa. The system was then flame dried under argon purge. Methyltriphenylphosphonium bromide (22.6 g, 63.3 mmol) was added and a slurry was created by the addition of 80 ml of dry THF. This slurry was cooled to 0 °C by ice-water bath. Butyl lithium (BuLi) in pentane (31.7 ml of 2.0 M solution, 63.4 mmol) was added to an addition funnel with a Teflon stopcock. While vigorously stirring the slurry, BuLi was added over 40 min. The solution turned canary yellow. In the course of 30 min of the addition, the mixture became a clear, deep yellow-red homogeneous solution. Upon completion of the addition, the solution was warmed to room temperature and stirred for 1 h. Next the ylide was cooled to 5 °C and 9.0 g (57.6 mmol) of 1,4-cyclohexanedione monoethylene ketal **15** in 20 ml of dry THF was added dropwise from the second addition funnel over 20 min. The reaction mixture was then stirred at room temperature for 15 h to yield a clear, light yellow solution containing much fine white precipitate.

Water (3 ml) was then added to decompose any possible remaining ylide. The solids were gravity-filtered and rinsed with 40 ml of THF and 50 ml of hexanes. The solution was then concentrated on a rotary evaporator to yield an oil with some white solid. This material was dissolved in 100 ml of methanol and extracted with 3 × 100 ml of hexanes. The combined hexanes extracts were then washed with 3 × 100 ml of saturated aqueous NaCl. The hexane solution was dried over $MgSO_4$ and concentrated on a rotary evaporator to yield about 5 ml of clear oil containing some white crystals. This material was dissolved in 25 ml of hexanes and set aside in a freezer at –5 °C for 18 h. The solution was vacuum filtered (while cold) to remove the white crystalline $OP(C_6H_5)_3$. The resultant clear, colorless solution was concentrated on a rotary evaporator to yield 6.2 g (69%) of ketal **16**. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 1.69 (t, 4 H, $^3J_{HH}$ = 6.2); 2.27 (t, 4 H, $^3J_{HH}$ = 6.2); 3.96 (s, 4 H); 4.66 (s, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$, $CHCl_3$): 31.9, 35.8, 64.2, 108.1, 108.5, 147.2.

4-Methylenecyclohexanone (**17**) was prepared by adaptation of a procedure described by Huet *et al.*[23]. Silica gel (73 g) was suspended in 180 ml of CH_2Cl_2 by rapid stirring in a round-bottom flask. Sulfuric acid (15%, 7.3 g) was dropwise added to the silica gel slurry. After 5 min the aqueous acid had been adsorbed into the silica gel. Ketal **16** (6.2 g, 40 mmol) was then added and rapid stirring continued. After 3 h, GLPC analysis showed a 4 : 1 ratio of deprotected to protected ketone. The solution was filtered and then subjected to a second treatment as above (38 g of silica gel, 4.8 g of 15% H_2SO_4). After 3 h of stirring, GLPC showed 10.2 : 1 ratio of compounds **17** and **16**. The solution was then filtered and the silica gel was rinsed with 2 × 100 ml of CH_2Cl_2. Combined solutions were concentrated on a rotary evaporator to yield 4.6 g of light yellow oil. This material was distilled yielding 3.9 g (90%) of clear, colorless ketone **17** boiling at 99–102 °C at 115 mm Hg. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 2.35–2.60 (m, 8 H); 4.89 (s, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$, $CHCl_3$): 32.9, 41.4, 110.5, 144.2, 210.3.

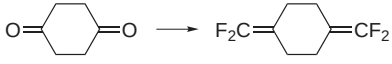
1-(Difluoromethylene)-4-methylenecyclohexane (**7**) was prepared by adaptation of the procedure as described by Naae and Burton[20]. A 250-ml three-neck flask was assembled under argon purge with a mechanical stirrer, septum and pressure equalizing funnel. The system was flame dried under argon purge. Dibromodifluoromethane (5.8 g, 28 mmol) was dissolved in 75 ml of dry THF, then transferred to the reaction vessel by syringe. This solution was cooled to –5 °C by an ice/salt bath. $P(N(CH_3)_2)_3$ (10.2 ml, 9.1 g, 56 mmol) was transferred to the addition funnel, dissolved in 40 ml of dry THF and then dropwise added to the CF_2Br_2 solution over 30 min with cooling. The resultant slurry of white precipitate was stirred for 1 h and then brought to room temperature. 4-Methylidenecyclohexanone (**17**; 1.92 g, 17 mmol) was dissolved in 5 ml of dry THF and added dropwise to the ylide solution. The mixture was stirred at room temperature for 14 h. The yellow solid was gravity filtered. The liquid was then dissolved in 200 ml of diethyl ether and exhaustively extracted with water. The ether solution was then dried over $MgSO_4$, filtered and distilled through a 6-cm Vigreaux column. The reminder of the material was transferred to a microdistillation apparatus and distilled under vacuum to yield 1.5 g (60%) of diene **7** boiling at 55–59 °C at 115 mm Hg. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 2.18 (m, 8 H); 4.70 (s, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$, $CHCl_3$): 25.5, 34.4 (t, 2 C, $^3J_{CF}$ = 2); 87.1 (t, 1 C, $^2J_{CF}$ = 18.9); 108.6, 147.3, 150.9 (t, 1 C, $^1J_{CF}$ = 279.5). ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): –98.4 (m, 2 F). MS EI, *m/z* (% rel. int.): 144 (100), 129 (65), 127 (12), 115 (20), 109 (40), 97 (9), 79 (15), 77 (18). HRMS, calculated for $C_6H_{10}F_2$: 144.0750; found: 144.0753.

Gas Phase Thermolysis of 1-(Difluoromethylene)-4-methylenecyclohexane (**7**)

An about 100 mg sample of diene **7** was obtained >99% pure by preparative GLPC (column 8 mm × 3.5 m, 20% SE-30 on Chromosorb P 80/100). Vapor of diene **7** was expanded into the gas kinetics vessel to the pressure of about 1 kPa (8 mm Hg). The conversion of diene **7** to 1,1-difluoro-2,5-dimethylenecyclohexane **8** was followed by GLPC (column 4 mm × 3.5 m, 20% DNP on Chromosorb 60/80, internal standard *n*-octane). The yield of the transformation was more than 98%. Reversibility of compound **8** to **7** was not observed. 1,1-Difluoro-2,5-dimethylenecyclohexane (**8**) was isolated by repeated preparative gas phase thermolysis (at vapor pressure of about 1.5 kPa each run). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 2.25–2.30 (m, 2 H); 2.36–2.41 (m, 2 H); 2.67 (tt, 2 H, $^3J_{HF}$ = 13.7, $^4J_{HH}$ = 1.2); 4.87 (m, 1 H); 4.92 (m, 1 H); 5.09 (m, 1 H); 5.39 (m, 1 H). ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): –100.9 (t, 2 F, $^3J_{HF}$ = 13.7). MS EI, *m/z* (% rel. int.): 144 (100), 129 (88), 115 (27), 109 (86), 97 (29). HRMS, calculated for $C_8H_{10}F_2$: 144.0750; found: 144.0748.

1,4-Bis(difluoromethylene)cyclohexane (**9**)

It was prepared according to Scheme 6.



9

SCHEME 6

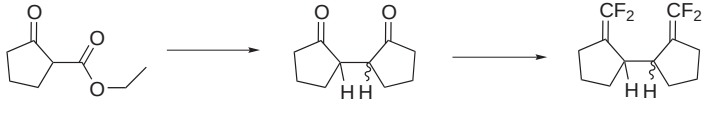
Diene **9** was prepared by adaptation of the procedure described by Naae and Burton[20]. A 500-ml three-necked round-bottom flask was equipped with a mechanical stirrer, septum and pressure-equalizing addition funnel and flame dried under argon purge. Dibromodifluoromethane (16.93 g, 80.7 mmol) was transfered to a Rotaflow tube and then dissolved in 70 ml of dry THF. This solution was transferred to the reaction vessel by syringe followed by an additional 70 ml of dry THF. This solution was cooled to –5 °C by an ice/salt bath. $P(N(CH_3)_2)_3$ (29.5 ml, 26.5 g, 0.162 mol) was dissolved in 70 ml of dry THF in the addition funnel. The CF_2Br_2 solution was cooled to about –5 °C with an ice/salt bath and added dropwise over 1 h with cooling. This mixture was stirred at –5 °C for 2 h and then brought to room temperature. 1,4-Cyclohexanedione (4.5 g, 40 mmol) was dissolved in 40 ml of dry THF and added to the ylide solution over 35 min. The reaction mixture was then stirred at room temperature for 18 h. The pale yellow solids were filtered off from yellow-brown solution. The solution was then concentrated on a rotary evaporator to a volume of about 15 ml and was taken up in 200 ml of diethyl ether. The ether solution was exhaustively extracted with water and then dried over $MgSO_4$. The ether solution was distilled through a 6-cm Vigreaux column to leave about 3 ml of clear brown liquid. This material was transferred to a microdistillation apparatus and distilled under reduced pressure. After initial removal of ether, the fraction of diene **9** (2.5 g, 36%) boiling at 60–62 °C at 1.3–1.6 kPa was collected. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 2.15 (m, 8 H, $^4J_{HF}$ = 1.3). ^{13}C NMR (75 MHz, $CDCl_3$, $CHCl_3$): 23.9 (m, 4 C); 86.5 (t, 2 C, $^2J_{CF}$ = 19.2); 151.2 (t, 2 C, $^1J_{CF}$ = 280.2). ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): –97.7 (septet, 4 F, $^4J_{HF}$ = 1.3). MS EI, *m/z* (% rel. int.): 180 (100), 165 (12), 145 (19), 127 (15), 111 (61), 109 (26), 103 (19), 77 (24). HRMS, calculated for $C_8H_8F_4$: 180.0562; found: 180.0571.

Gas Phase Thermolysis of 1,4-Bis(difluoromethylene)cyclohexane (**9**)

An about 100 mg sample of **9** was obtained >99% pure by preparative GLPC (column 8 mm × 3.5 m, 20% SE-30 on Chromosorb P 80/100). Vapor of diene **9** was expanded into the gas kinetics vessel to the pressure of about 1 kPa (8 mm Hg) and conversion of **9** to 1,1,2,2-tetrafluoro-3,6-dimethylenecyclohexane **10** was followed by GLPC (column 4 mm × 3.5 m, 20% QF-1 on Chromosorb 100/120, internal standard *n*-octane). The yield of the transformation was more than 99%. Reversible transformation of **10** to **9** was not observed. 1,1,2,2-Tetrafluoro-3,6-dimethylenecyclohexane (**10**) was isolated by double thermolysis of diene **9** (at vapor pressure of about 1.5 kPa) at 360 °C for 200 min. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 2.42 (bs, 4 H); 5.35 (s, 1 H); 5.63 (s, 1 H). ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): –123.1 (s, 4 F). MS EI, *m/z* (% rel. int.): 180 (60), 165 (17), 145 (19), 111 (100), 77 (23). HRMS, calculated for $C_8H_{10}F_2$: 180.0562; found: 180.0564.

Preparation of 1,1′-Bi(cyclopentane)-2,2′-dione (**19**)

It was accomplished according to Scheme 7.



18 **19A** and **19B** **5A** and **5B**

SCHEME 7

Diketone **19** (mixture of diastereoisomers **19A** and **19B**) was prepared by the procedure of Paul[24]. A three-necked round-bottom flask was equipped with a condenser, magnetic stirrer and pressure-equalizing addition funnel and then flame dried under argon purge. Freshly cut sodium metal (0.75 g, 33 mmol) was placed in the flask followed by 20 ml of dry toluene. The system was heated to reflux and stirred rapidly breaking sodium into small spheres. Ethyl 2-oxocyclopentanecarboxylate (**18**; 5.0 g, 32 mmol) was dissolved in 5 ml of dry toluene and added dropwise to the sodium in refluxing toluene while stirring. Upon completion of addition the mixture was heated to reflux for 1 h after which all sodium metal had been consumed. 2-Chlorocyclopentanone (3.97 g, 33 mmol) was dissolved in dry toluene and added dropwise to the refluxing enolate solution. Upon completion of addition the mixture was held at a gentle reflux for 9 h. The resultant solids were filtered off, the reaction solution was washed with 3 × 50 ml of water and then dried with $MgSO_4$. Toluene was removed on a rotary evaporator to yield 3.4 g (66%) of crude product which was purified by kugelrohr distillation to give 2.4 g (47%) of white solid ethyl 2,2′-dioxo-1,1′-bi(cyclopentane)-1-carboxylate. This material was added to a round-bottom flask containing 15 ml of 20% HCl, assembled with a condenser. The mixture was brought to a gentle reflux and ethanol was added (about 5 ml) until the mixture became homogeneous. The solution was heated to a gentle reflux for 24 h at which time GLPC analysis showed the decarboxylation to be about 90% complete. The reaction mixture was extracted with 4 × 50 ml of diethyl ether, washed with water and dried with $MgSO_4$. Diethyl ether was removed on a rotary evaporator and the resultant material was purified by kugelrohr distillation to yield 0.91 g (55%) of white solid being a mixture of diastereoisomers **19A** and **19B**. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 1.52–1.88 (m, 8 $H_{meso\ and\ rac}$); 1.98–2.39 (m, 16 $H_{meso\ and\ rac}$); 2.53 (t, 2 $H_{meso\ or\ rac}$,

$^3J_{HH}$ = 8.9); 2.63 (t, 2 $H_{meso\ or\ rac}$, $^3J_{HH}$ = 9.1). ^{13}C NMR (75 MHz, $CDCl_3$, $CDCl_3$): 20.2, 20.4, 24,9, 26.3, 37.4, 37.6, 48.0, 48.7, 218.3, 219.2.

Preparation of (1*R**,1′*R**)- and (1*R**,1′*S**)-2,2′-bis(difluoromethylene)-1,1′-bi(cyclopentane) (**5A** and **5B**)

A mixture of diastereoisomers **5A** and **5B** was prepared by adaptation of the procedure described by Naae and Burton[20]. A 500-ml three necked round-bottom flask was equipped with a mechanical stirrer, septum and pressure-equalizing addition funnel and flame dried under argon purge. Dibromodifluoromethane (21.25 g, 0.101 mol) was transferred to a Rotaflow tube and then dissolved in 80 ml of dry THF. This solution was then transferred to the reaction vessel with a syringe followed by an additional 150 ml of dry THF. This solution was cooled to –5 °C with an ice/salt bath. $P(N(CH_3)_2)_3$ (36.0 ml, 32.3 g, 0.198 mol) was dissolved in 100 ml of dry THF, transferred to the addition funnel and added dropwise over 1.5 h to the cooled CF_2Br_2 solution. The resultant slurry of white solid was stirred at –5 °C for 1.5 h after which it was heated to 40 °C. Dione **19** (4.27 g, 25.7 mmol) was dissolved in 20 ml of dry THF and added dropwise to ylide mixture at 40 °C over 1 h with vigorous stirring. The mixture was then stirred at 40 °C for 17 h. At this time the yield of mixture of diastereoisomers **5A** and **5B** is 31% as checked by ^{19}F NMR *vs* internal standard $C_6H_5CF_3$. The resultant reaction mixture was filtered to remove tan solids and the solution was concentrated on a rotary evaporator to yield about 3 ml of a dark brown viscous liquid. Diethyl ether (250 ml) was added and this solution was exhaustively extracted with water. The ether phase was then dried over $MgSO_4$ and concentrated on a rotary evaporator to yield 1.9 g (28%) of light brown oil being a mixture of diastereoisomers **5A** and **5B** (approximately ratio 5.4 : 1 based on integration of ^{19}F NMR spectrum)[16], contaminated with THF, diethyl ether and $OP(N(CH_3)_2)_2$). Mixture of **5A** and **5B**: ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 1.43 (m, 8 H_{5A} and H_{5B}); 2.78 (bs, 2 H_{5B}); 2.96 (bs, 2 H_{5A}). ^{13}C NMR (50 MHz, $CDCl_3$, $CHCl_3$): diastereoisomers **5A** and **5B**: 23.9, 24.6, 26.0, 26.6, 29.3, 30.9, 41.0 (m, 2 C), 93.0 (t, 2 C, $^2J_{CF}$ = 19.2); 151.2 (t, 2 C, $^1J_{CF}$ = 280.9). ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) of **5A**: –91.1 (d, 1 F, $^2J_{FF}$ = 63.0); –92.8 (d, 1 F, $^2J_{FF}$ = 63.0). ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) of **5B**: –91.2 (d, 1 F, $^2J_{FF}$ = 61.6); –91.5 (d, 1 F, $^2J_{FF}$ = 61.6). MS EI, *m/z* (% rel. int.) of **5A**: 234 (30), 214 (4), 118 (7), 117 (100), 116 (12), 115 (5), 97 (22), 77 (4). MS EI, *m/z* (% rel. int.) of **5B**: 234 (21), 214 (6), 118 (7), 117 (100), 116 (12), 115 (5), 97 (22), 77 (4). HRMS, calculated for $C_{12}H_{14}F_4$: 234.104; found: 234.103.

Solution Phase Thermolysis of (1*R**,1′*R**)- and (1*R**,1′*S**)-2,2′-Bis(difluoromethylene)-1,1′-bi(cyclopentane) (**5A** and **5B**)

A 0.160 g sample of a mixture of diastereoisomers **5A** and **5B** was obtained 97% pure by preparative GLPC (contaminated only with 3% of 1,2-di(cyclopent-1-en-1-yl)-1,1,2,2-tetrafluoroethane (**6**) (column 8 mm × 1.8 m, 20% OF-1 on Chromosorb WHP 80/100). This material was dissolved in 1.47 ml of dry, degassed dodecane and 0.033 g of C_6H_5F was added as ^{19}F NMR internal standard. 0.25-ml aliquots were drawn with syringe and placed in thick wallet NMR tubes (washed successively with base, deionized water, acetone and flame dried) and next flame sealed under N_2. Lower temperature rearrangement of diastereoisomer **5A** to diene **6** (94–124 °C) was carried out by thermolysing the sample for a specified time in a Statin thermostated oil bath, then rapidly cooled and stored in an ice bath until ^{19}F NMR analysis was accomplished. Higher temperature rearrangement of

diastereoisomer **5B** to diene **6** (274–293 °C) was carried out analogously by thermolysing the sample for a specified time in the thermostat with molten salt bath. The relative concentrations of all reaction components were monitored by integration of the ^{19}F NMR signals *vs* internal standard C_6H_5F. Each sealed sample yielded one rate constant for each diastereoisomeric component: one from following the rearrangement of diastereoisomer **5A** at the lower temperature (94–124 °C), and one from following the reaction at elevated temperature (274–293 °C). After collecting sufficient data from the sample for thermolysis of diastereoisomer **5A** at a given temperature the sample was further thermolyzed at a lower temperature until no **5A** remained before beginning thermolysis and data collection for diastereoisomer **5B** at an elevated temperature. Rearrangement of diastereoisomer **5A** to diene **6** was found to follow the first-order kinetics and also was quantitative and irreversible toward formation of diene **6** over the temperature range 94.0–124.1 °C. In thermolysis of diastereoisomer **5B** traces (less than few percent by integration after prolonged time of rearrangement) of other materials were detected by ^{19}F NMR. The product **6** was obtained for characterization by thermolysing a crude sample (about 90% pure) of mixture of diastereoisomers **5A** and **5B** at 140 °C for 2 h and then isolating it from unreacted compound **5B** by preparative GLPC (column 8 mm × 1.8 m, 20% QF-1 on Chromosorb WHP 80/100). ^1H NMR (300 MHz, $CDCl_3$, TMS): 1.96 (quintet, 4 H, $^3J_{HH}$ = 7.54); 2.40–2.57 (m, 8 H); 6.19 (bs, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$, $CHCl_3$): 23.3, 31.4 (m, 2 C, $^3J_{CF}$ = 1.9); 32.7, 135.9 (m, 2 C, $^3J_{CF}$ = 4.1). ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): –91.1 (d, 1 F_{5A}, $^2J_{FF}$ = 63.0); –91.2 (d, 1 F_{5B}, $^2J_{FF}$ = 61.6); –110.5 (s, 4 F). MS EI, *m/z* (% rel. int.): 234 (38), 118 (7), 117 (100), 116 (11), 115 (5), 97 (18), 77 (6), 67 (5). HRMS, calculated for $C_{12}H_{14}F_4$: 234.104; found: 234.102.

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