Stereochemical Aspects on the BF_3·Et_2O Catalyzed Ring Contraction of 5-Substituted 2,3-Epoxycyclohexanones

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Synopsis. In the BF_3·Et_2O catalyzed rearrangement of 5-substituted 2,3-epoxycyclohexanones, the stereochemistry of the forming quaternary carbon center was directed by the chirality at 5-position.

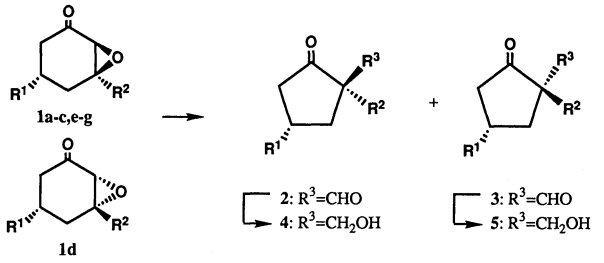
The BF_3·Et_2O catalyzed acyl migration in acyclic α,β-epoxy ketones is known to proceed through a highly concerted process which accompanies inversion of configuration at the migration terminus,[1] whereas in a cyclic version, the rearrangement of (+)-2,3-epoxy-3,5,5-trimethyl-1-cyclohexanone, the acyl migration is reported to proceed with partial or extensive racemization depending on the solvent used.[2]

In the course of our effort toward the synthesis of optically active cyclopentanone derivatives by utilizing BF_3·Et_2O catalyzed rearrangement of 2,3-epoxycyclohexanone,[3] we needed to probe the stereoselectivity in the rearrangement of diastereomeric cyclic epoxy ketones such as 5-substituted 2,3-epoxycyclohexanone (**1**). The results contained new stereochemical aspects which should be helpful to extensive utilization of the above type of rearrangement.

We started our work with the BF_3·Et_2O catalyzed rearrangement of epoxy ketone (−)-**1a** and (−)-**1b** (diastereopurity: >95%) in toluene or CH_2Cl_2 at room temperature. The ratios of the rearrangement products, **2a**, **b** and **3a**, **b**, were determined by ^1H NMR spectra of the crude mixtures based on their formyl protons and/or by isolation after chemoselective reduction of the aldehyde moiety, and their stereostructures were ultimately confirmed by the synthesis of (−)-frontalin and (−)-malyngolide.[4]

As shown in Table 1 in Entries 1—4, the results contained significant feature: The absolute stereochemistry of the quaternary carbon center of the major product is the mirror image of which should be obtained by the concerted process. These unexpected results prompted us to examine the rearrangement of **1d**, a diastereoisomer of **1a**.

The BF_3·Et_2O catalyzed rearrangement of (−)-**1d** in toluene at room temperature for 4 h and subsequent reduction with Bu_3SnH gave a 27 : 73 mixture of **4a** and **5a** (Entry 6), and in CH_2Cl_2 for 1 h gave a 21 : 79 mixture of **2a** and **3a** (Entry 7). In these reactions, we expected acceleration of the reaction rate due to the cis orientation of the TMS (trimethylsilyl) group and epoxide moiety[5] in **1d**. On the contrary, retardation of the reaction was observed. The preferential formation of **3a** from both diastereomers [(−)-**1a** and (−)-**1d**] in a similar selectivity implies that geometry of the starting epoxide is less important element for the stereoselectivity. Therefore, the 1,2-acyl migration of α,β-epoxy ketones does not always proceed predominantly via a concerted pathway, and the steric or electronic nature of the TMS group at 5-position plays the most important role in the above



a: R^1=TMS, R^2=Me; b: R^1=TMS, R^2=Nonyl; c: R^1=TMS, R^2=Et; d: R^1=TMS, R^2=Me; e: R^1=Ph, R^2=Me; f: R^1=t-Bu, R^2=Me, g: R^1=Me, R^2=Me.

Scheme 1.

Table 1. Product Distribution of BF_3·Et_2O Catalyzed Rearangement of **1**

Entry	**1**[a]	R^1	R^2	Conditions		Yield/%	Ratio[b]	Ratio
				Solvent	Time/min	**2**+**3** or **4**+**5**	**2**:**3**	**4**:**5**
1	(−)-**1a**	TMS[c]	Me	Toluene	30	63	—	20:80[d]
2	(−)-**1a**	TMS	Me	CH_2Cl_2	0.5	88	—	20:80[d]
3	(−)-**1b**	TMS	Nonyl	CH_2Cl_2	60	95	—	25:75[e]
4	(−)-**1b**	TMS	Nonyl	CH_2Cl_2	90	98	25:75	—
5	(±)-**1c**	TMS	Et	CH_2Cl_2	90	97	21:79	—
6	(−)-**1d**	TMS	Me	Toluene	240	41	—	27:73[d]
7	(−)-**1d**	TMS	Me	CH_2Cl_2	60	81	21:79	—
8	(±)-**1e**	Ph	Me	Toluene	60	57	20:80	—
9	(±)-**1e**	Ph	Me	CH_2Cl_2	60	67	20:80	—
10	(±)-**1f**	*t*-Bu	Me	Toluene	60	46	22:78	—
11	(±)-**1f**	*t*-Bu	Me	CH_2C_2	60	64	18:82	—
12	(±)-**1g**	Me	Me	CH_2Cl_2	60	48	19:81	—

a) Diastereopurity: >95%. b) Determined by ^1H NMR. c) TMS=trimethylsilyl. d) The ratio of isolated benzoates of **4** and **5**. e) The ratio of isolated **4** and **5**.

system. The possible electronic participation by the TMS group is the carbocation stabilization effect of C–Si bond, though the participation is less effective γ-cation stabilization in this case.[5] To test the gratitude of the above electronic participation, the TMS group was replaced with the phenyl, *t*-butyl or methyl group, and the results are listed in Table 1 (in Entries 8—12). The structure of **3e** was confirmed by the NOE study on **5e**, and the structural assignment of **2c**, **f**, **g**, and **3c**, **f**, **g**, are based on the chemical shifts of their aldehyde protons.

The chemical yields are somewhat low comparing with the TMS group substituted epoxy ketones but no remarkable change of ratios was observed. Thus we concluded that the diastereoselectivity can be ascribed to the spatial influence of substituent at 5-position.

In a conformationally constrained system, the Lewis acid catalyzed 1,2-acyl migration of α,β-epoxy ketones would proceed via competitive pathways of concerted and cationic type reactions. In the case of **1** (except **1d**), usual concerted process is not preferable presumably due to the insufficient coplanarity of leaving and migrating σ-bonds. Consequently, the rearrangement mainly proceeded via a cationic type pathway, and the diastereoselectivity can be rationalized by the conformational distribution of bicyclo[3.1.0]hexane type intermediates **6a** and **6b** which would be included in a final stage of the transition state (a product-like rate determining step). Apparently, by the anchoring effect of substituent at 5-position, **6a** is the more preferable one which gives **3** (Shcheme 2). In the case of **1d**, it is obscure whether the rearrangement mainly proceeds via the above process or concerted one.

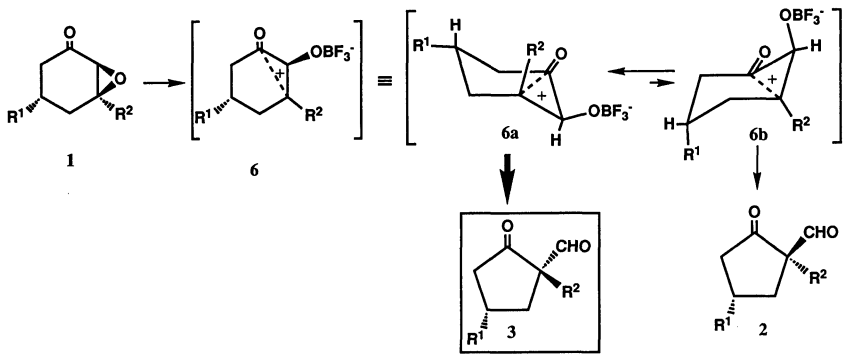
The rearrangement of the *t*-butyldimethylsilyl (TBDMS) ether of 2,3-epoxycyclohexanols **7a** and **7b** was also examined (Scheme 4). As expected from the two transition states **8a** and **8b**, **9** was obtained as an exclusive product from both diastereomers, and after reduction with $NaBH_4$, alcohol **10**, whose structure was established by the conversion to **12**,[4] was isolated in 48 and 35% overall yields respectively.[6]

In conclusion, our results provided the evidence that unlike acyclic 2,3-epoxy ketones, the $BF_3{\cdot}Et_2O$ catalyzed rearrangement of 5-substituted 2,3-epoxycyclohexanones and cyclohexanol derivatives proceeds not only a concerted pathway but also cationic one. Therefore, in the Lewis acid catalyzed rearrangement of conformationally constrained epoxides, conformational analysis of intermediary cationic transition states is indispensable for the stereochemical prediction.

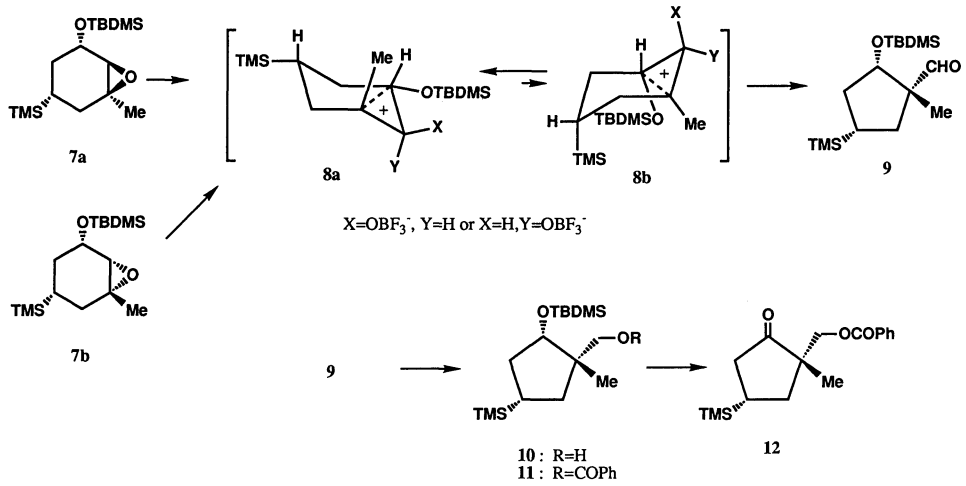
Experimental

IR was recorded on a Hitachi 260-50. ^1H and ^{13}C NMR are recorded on a Hitachi R-24B, JEOL JNM-FX-90Q, or JEOL JNM-EX 270 in $CDCl_3$.

Preparation of 2,3-Epoxycyclohexanones. 5-Substituted 2,3-epoxycyclohexanones except (−)-**1d** were synthesized by



Scheme 2.



Scheme 3.

the epoxidation of the corresponding 2-cyclohexenones with 35% H_2O_2 under basic conditions.[4]

(2*S,3*S**,5*S**)-2,3-Epoxy-3-ethyl-5-(trimethylsilyl)cyclohexanone [(±)-1c]:** ^{1}H NMR δ=0.0 (9H, s), 0.8—3.4 (7H, m) 0.94 (3H, t, *J*=7.0 Hz), and 3.56 (1H, br s); ^{13}C NMR δ=−3.74, 8.68, 14.00, 27.69, 28.39, 37.13, 60.45, 65.08, and 207.02; IR (neat) 1700 cm^{-1} (C=O). Found: C, 62.12; H, 9.86%. Calcd for $C_{11}H_{20}O_2Si$: C, 62.21; H, 9.49%.

(2*S,3*S**,5*S**)-2,3-Epoxy-3-methyl-5-phenylcyclohexanone [(±)-1e]:** ^{1}H NMR δ=1.47 (3H, s), 1.7—2.95 (4H, m), 3.14 (1H, s), 3.1—3.75 (1H, m), and 7.20 (5H, s); ^{13}C NMR δ=21.6, 33.7, 36.4, 43.5, 61.0, 126.7, 128.6, 143.1, and 204.9; IR (neat) 1710 cm^{-1} (C=O). Found: C, 77.43; H, 6.92%. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98%.

(2*S,3*S**,5*S**)-2,3-Epoxy-3-methyl-5-*t*-butylcyclohexanone [(±)-1f]:** ^{1}H NMR δ=0.87 (9H, s), 1.46 (3H, s), 1.3—2.7 (5H, m), and 3.03 (1H, s); ^{13}C NMR δ=22.1, 27.0, 30.0, 31.7, 37.1, 38.2, 61.4, and 207.3; IR (neat) 1710 cm^{-1} (C=O).

(2*S,3*S**,5*S**)-2,3-Epoxy-3,5-dimethylcyclohexanone [(±)-1g]:** ^{1}H NMR δ=0.95 (3H, d, *J*=6 Hz), 1.45 (3H, s), 1.3—2.7 (5H, m), and 3.03 (1H, s); ^{13}C NMR δ=21.0, 21.9, 23.4, 37.2, 44.2, 61.1, 61.4, and 205.8; IR (neat) 1713 cm^{-1} (C=O). Found: C, 68.18; H, 9.11%. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63%.

(2*R*,3*R*,5*S*)-2,3-Epoxy-3-methyl-5-(trimethylsilyl)cyclohexanone [(−)-1d]: (−)-**1d** was synthesized applying the method of Chamberlain et al.[7] Reduction of (+)-(5*S*)-3-methyl-5-trimethylsilyl-2-cyclohexenone with $NaBH_4$ gave an allylic *syn*-alcohol which was subjected to epoxidation with *m*-CPBA, and subsequent oxidation with PDC gave (−)-**1d** in 45% overall yield. $[\alpha]_D^{16}$ −96.04° (*c* 0.68, $CHCl_3$). ^{1}H NMR δ=0.0 (9H, s), 1.46 (3H, s), 1.13—1.6 (1H, m), 1.73—2.8 (4H, m), and 3.0 (1H, s); ^{13}C NMR δ=−3.79, 23.85, 25.96, 29.10, 35.28, 61.62, 69.26, and 208.66; IR (neat) 1714 cm^{-1} (C=O). Found: C, 60.22; H, 9.37%. Calcd for $C_{10}H_{18}O_2Si$: C, 60.56; H, 9.15%.

A Typical Procedure of the BF_3·Et_3O Catalyzed Rearrangement. To a solution of epoxy ketone **1** (10 mmol) in dry solvent (50 ml) was added BF_3·Et_2O (628 µl, 5 mmol), and the resulted solution was stirred under Ar at room temperature for 1 h. After diluted with the solvent, the solution was washed with water, dried over $MgSO_4$, and concentrated to give a crude mixture of **2** and **3**.

The Chemoselective Reduction of Keto Aldehydes. The above crude mixture was dissolved in absolute methanol (50 ml). To the solution was added Bu_3SnH (5.36 ml, 20 mmol), and the reaction mixture was stirred under Ar at room temperature for 4 h. After usual work-up, chromatographical purification gave a mixture of **4a** and **5a**, and the ratio was determined by ^{13}C NMR and/or subsequent separation as their benzoates. In the case of **4c** and **5c**, the keto alcohols were easy separated by column chromatography.

The Ratio Determination of Keto Aldehydes by ^{1}H NMR. The rearrangement was carried out with 1 mmol of **1**, and to the crude mixture of **2** and **3** was added freshly distilled 1 mmol of *o*-chlorobenzaldehyde, and the yield and the product ratio were determined immediately by 90 or 270 MHz ^{1}H NMR based on their aldehyde protons. The Chemical shifts of their aldehyde protons (ppm) are listed below.

Compound	a	b	c	e	f	g
2	9.38	9.33	9.39	9.59	9.30	9.37
3	9.54	9.52	9.57	9.70	9.47	9.53

Spectral Data of a Mixture of 4e and 5e: IR (KBr) 3440 (OH) and 1730 (C=O) cm^{-1}. Found: C, 76.06; H, 7.79%. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90%.

4e: ^{1}H NMR (500 MHz) δ=1.15 (3H, s), 1.90 (1H, dd, *J*=12.1 and 13.1 Hz), 2.17 (1H, m), 2.52 (1H, m), 2.53 (1H, ddd, *J*=2.1, 7.5, and 18.5 Hz), 3.60 (1H, dd, *J*=4.0 and 10.6 Hz), 3.68 (1H, dd, *J*=7.2 and 10.5 Hz), 7.23—7.36 (5H, m); ^{13}C NMR δ=20.8, 38.6, 42.9, 45.8, 51.4, 68.9, 126.8, 128.7, 142.9, 143.3, and 222.2.

5e: ^{1}H NMR (500 MHz) δ=1.15 (3H, s), 2.09 (1H, ddd, *J*=2.3, 6.6, and 12.5 Hz), 2.27 (1H, t, δ=12.5 Hz), 2.29 (1H, dd, *J*=4.6 and 6.7 Hz), 2.40 (1H, dd, *J*=112.5 and 18.5 Hz), 2.79 (1H, ddd, *J*=2.3, 7.6, and 18.5 Hz), 3.47 (1H, ddt, *J*=6.6, 7.6, and 12.5 Hz), 3.53 (1H, dd, *J*=4.6 and 11.0 Hz), 3.75 (1H, dd, *J*=6.7 and 11.0 Hz), 7.23—7.36 (5H, m); ^{13}C NMR δ=19.4, 38.0, 40.7, 46.4, 52.1, 67.1, 126.8, 128.7, 142.9, 143.3, and 222.4.

A Mixture of 4f and 5f: ^{1}H NMR δ=0.90 and 0.91 (**4f** and **5f**, 9H, s), 1.11 and 1.06 (**4f** and **5f**, 3H, s), 1.48—2.48 (5H, m), 3.37—3.66 (2H, m); IR (neat) 3450 (OH) and 1740 (C=O) cm^{-1}.

4f: ^{13}C NMR δ=20.8, 27.3, 31.6, 34.5, 42.0, 44.1, 51.2, 67.7, and 223.9.

5f: ^{13}C NMR δ=19.7, 27.2, 31.6, 34.1, 40.8, 43.4, 52.0, 67.2, and 224.0.

A Mixture of 2g and 3g: IR (neat) 1720 and 1750 cm^{-1} (C=O).

3g: ^{1}H NMR δ=1.3 (3H, s), 1.19 (3H, d, *J*=6.3 Hz), 1.90 (1H, ddd, *J*=2.0, 6.3, and 13.2 Hz), 1.95 (1H, dd, *J*=10.9 and 17.8 Hz), 2.14 (1H, dd, *J*=10.6 and 13.2 Hz), 2.35 (1H, dddt, *J*=6.9, 10.6, 10.9, and 6.3 Hz), 2.55 (1H, ddd, *J*=2.0, 6.9, and 17.8 Hz), 9.53 (1H, s); ^{13}C NMR δ=18.8, 20.2, 27.8, 39.1, 46.9, 63.3, 199.6, and 215.5.

2g: ^{1}H NMR δ=1.17 (3H, d, *J*=6.3 Hz), 1.33 (3H, s), 1.8—2.6 (4H, m), 2.71 (1H, ddd, *J*=2.3, 6.3, and 13.2 Hz), 9.37 (1H, s); ^{13}C NMR δ=18.8, 20.4, 28.3, 39.9, 46.3, 65.0, 198.2, and 215.0.

Preparation of 7a and 7b. These compounds were synthesized from 5-trimethylsilyl-3-methyl-2-cyclohexenol by *m*-CPBA oxidation after alcohol protection (**7a**) or by epoxidation followed by alcohol protection (**7b**).

7a: ^{1}H NMR δ=−0.04 (9H, s), 0.10 (3H, s), 0.11 (3H, s), 0.58 (1H, m), 0.91 (1H, m), 0.92 (9H, s), 1.33 (3H, s), 1.46 (1H, dd, *J*=14.8 and 13.2 Hz), 1.72 (1H, m), 1.85 (1H, dd, *J*=14.8 and 3.6 Hz), 2.87 (1H, s), and 3.79 (1H, dd, *J*=6.6 and 10.2 Hz); ^{13}C NMR δ=−4.9, −4.6, −3.7, 14.0, 18.2, 22.9, 25.9, 31.1, 32.3, 58.7, 64.8, and 68.6; IR (neat) 1240 cm^{-1} (C–O–C).

7b: ^{1}H NMR δ=−0.05 (9H, s), 0.10 (3H, s), 0.11 (3H, s), 0.57 (1H, m), 0.92 (9H, s), 1.32 (3H, s), 1.22—1.62 (3H, m), 2.96 (1H, s), and 3.94 (1H, ddd, *J*=10.6, 5.6, and 1.5 Hz); ^{13}C NMR δ=−4.5, −4.4, −3.7, 18.3, 20.6, 24.4, 25.9, 27.9, 28.8, 62.0, 63.6, and 71.6; IR (neat) 1250 cm^{-1} (C–O–C).

10: ^{1}H NMR δ=−0.03 (9H, s), 0.08 (3H, s), 0.10 (3H, s), 0.91 (9H, s), 0.99 (3H, s), 0.8—1.2 (1H, m), 1.32 (1H, dd, *J*=8.3 and 12.5 Hz), 1.38 (1H, m), 1.59 (1H, dd, *J*=12.9 and 12.8 Hz), 1.96 (1H, m), 3.16 (1H, br s), 3.41 (1H, d, *J*=10.8 Hz), 3.51 (1H, d, *J*=10.8 Hz), and 3.84 (1H, dd, *J*=6.6 and 8.3 Hz); ^{13}C NMR δ=−4.4, −3.6, −3.1, 17.9, 20.3, 23.8, 25.8, 35.5, 37.7, 45.2, 69.0, and 85.0; IR (neat) 3480 cm^{-1} (OH).

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