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Stereoselective epoxidation of 4-fluoro-4-nitrocyclohexenes

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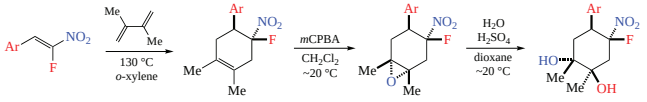
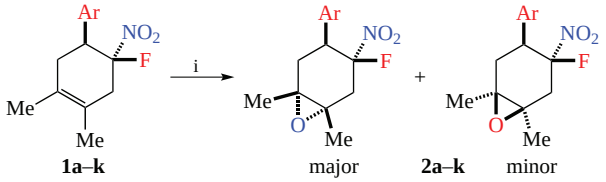
Novel fluorinated α-epoxycyclohexanes were synthesized in up to 96% yields by epoxidation of the Diels–Alder adducts of β-fluoro-β-nitrostyrenes and 2,3-dimethylbuta-1,3-diene. The epoxidation with *m*-chloroperoxybenzoic acid and subsequent hydrolysis into diols were found to proceed in a highly stereoselective manner.



Keywords: organofluorine compounds, nitrostyrenes, Diels–Alder reaction, epoxidation, ring-opening, hydrolysis, diols.

Cyclohexane-fused oxiranes (α-epoxycyclohexanes, cyclohexene oxides) are important biologically active compounds occurring in nature.[1–3] They are readily available from the corresponding cyclohexenes upon epoxidation with various reagent systems.[4–11] Epoxycyclohexanes participate in diverse ring-opening reactions,[12–15] isomerizations[16,17] and rearrangements.[18–20] These epoxides are versatile intermediates towards functionalized five-[21] and six-membered[22–26] carbocycles. On the other hand, organofluorine compounds play an exceptionally important role in various fields of science and technology.[27] The incorporation of fluorine into molecules can positively modulate their pharmacokinetic and physicochemical properties and enhance their metabolic and chemical stability.[28–32] Indeed, nearly a quarter of the currently manufactured agrochemical and pharmaceutical products contains at least one fluorine atom.[33,34]

In this context, the development of routes to fluorinated epoxycyclohexanes is of great importance and can open up straightforward way towards novel fluorine-containing cyclohexane derivatives. The use of fluorinated building blocks is a very convenient approach and in many cases an indispensable alternative to late-stage fluorinations.[35,36] Recently, we have described the Diels–Alder reaction of β-fluoro-β-nitrostyrenes[37,38] with various dienes.[39,40] This article is devoted to the study of epoxidation of the fluorinated cycloadducts **1** prepared from 2,3-dimethylbuta-1,3-diene (Scheme 1).



1a–k **2a–k**

	Ar			Ar	
a	4-BrC_6H_4	(88%, *dr* = 100:0)	**g**	4-NCC_6H_4	(89%, *dr* = 100:0)
b	2,4-$Cl_2C_6H_3$	(74%, *dr* = 100:0)	**h**	2-$O_2NC_6H_4$	(96%, *dr* = 81:19)
c	4-MeC_6H_4	(94%, *dr* = 92:8)	**i**	3-$O_2NC_6H_4$	(78%, *dr* = 100:0)
d	4-$MeOC_6H_4$	(81%, *dr* = 89:11)	**j**	4-$O_2NC_6H_4$	(87%, *dr* = 98:2)
e	4-$F_3CC_6H_4$	(94%, *dr* = 97:3)	**k**	4-ClC_6H_4	(91%, *dr* = 95:5)
f	4-$MeO_2CC_6H_4$	(87%, *dr* = 100:0)			

Scheme 1 *Reagents and conditions*: **1a–k** (0.1 mmol), *m*CPBA (0.15 mmol), CH_2Cl_2 (1 ml), room temperature, ~18 h.

We found that compounds **1a–k** could be easily oxidized with *m*-chloroperoxybenzoic acid (*m*CPBA) into novel fluorinated epoxycyclohexanes **2a–k**. To our delight, the epoxidation proceeded very efficiently in up to 96% yield and in highly stereoselective manner (see Scheme 1). In all cases, we observed the predominant or exclusive formation of one diastereomer. However, in the case of substrate **1h** with *o*-nitrophenyl substituent the stereoselectivity was somewhat lower, and the isolated product **2h** contained about 20% of the minor isomer. In the case of epoxidation of **1d**, both diastereomers **2d** were completely separated using column chromatography.

X-ray diffraction analysis of a single crystal **2a** showed that the major diastereomer has *rel*-(1*S*,3*S*,4*S*,6*R*) configuration (Figure 1). The predominant formation of this isomer can be explained by steric hindrance resulted from the bulky aryl substituent and possible H-bonding of *m*CPBA with the nitro group of the starting alkene. Compound **2a** crystallized as racemate in centrosymmetric space group $P2_1/c$. The six-membered ring has conformation of distorted sofa with the deviation of carbon atom bearing the aryl group. The aryl and nitro groups are in equatorial positions, while the fluorine is in axial one.†

† *Crystal data for* **2a**. $C_{14}H_{15}BrFNO_3$, M = 344.18, monoclinic, space group $P2_1/c$, T = 120 K, a = 14.493(4), b = 9.043(2) and c = 10.888(3) Å, β = 94.491(10)°, V = 1422.7(7) Å^3, Z = 4. A total of 12456 ($2\theta_{max}$ = 58°, R_{int} = 0.0938) reflections were collected and 3783 independent reflections were used for the structure solution and refinement, which converged to R_1 = 0.0534 (for 2666 observed reflections), wR_2 = 0.1450, GOF = 1.015. The refinement of the disordered part of the molecule was performed with EADP and DFIX instructions.

Crystal data for **3c**. $C_{15}H_{20}FNO_4$, M = 297.32, monoclinic, space group $P2_1/c$, T = 100 K, a = 6.0892(6), b = 20.7008(18) and c = 11.6921(8) Å, β = 98.682(3)°, V = 1456.9(2) Å^3, Z = 4 (Z' = 1). A total of 13546 ($2\theta_{max}$ = 58°, R_{int} = 0.0503) reflections were collected and 3868 independent reflections were used for the structure solution and refinement. Refinement converged to R_1 = 0.0532 (for 3263 observed reflections), wR_2 = 0.1270, GOF = 1.132.

CCDC 2232770 and 2232771 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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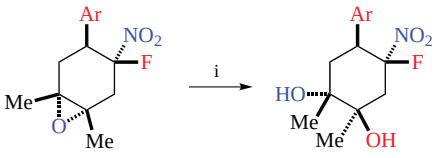


2a–i **3a–i**

Ar		Ar	
a 4-BrC_6H_4	(69%)	**f** 4-$MeO_2CC_6H_4$	(80%)
b 2,4-$Cl_2C_6H_3$	(89%)	**g** 4-NCC_6H_4	(76%)
c 4-MeC_6H_4	(62%)	**h** 2-$O_2NC_6H_4$	(81%)
d 4-$MeOC_6H_4$	(78%)	**i** 3-$O_2NC_6H_4$	(74%)
e 4-$F_3CC_6H_4$	(70%)		

Scheme 2 *Reagents and conditions*: **2a–i** (0.1 mmol), 0.4 M H_2SO_4 in dioxane/water 2 : 1 (2.12 ml), room temperature, ~18 h.

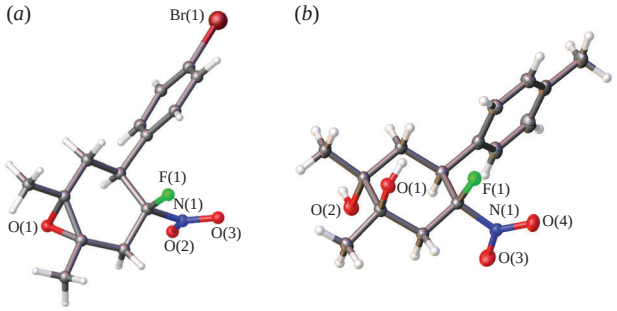
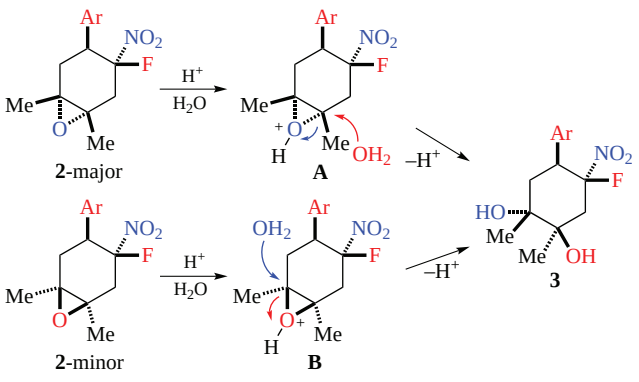


Figure 1 The general view of (*a*) molecule **2a** and (*b*) molecule **3c** in representation of atoms by atomic displacement parameters with 50% probability.

Next, we studied acid-catalyzed ring-opening hydrolysis[41] of epoxides **2a–i** into diols **3a–i** which were isolated in up to 89% yields (Scheme 2). The structure of diol **3c** determined by X-ray (see Figure 1) had *rel*-(1*R*,2*R*,4*S*,5*S*) configuration, and it crystallized as racemate. The opening of the oxirane leads to product having the chair conformation of six-membered ring with the hydroxyl group and fluorine atom in axial positions, while tolyl and nitro groups are located in equatorial ones.

To our surprise, all diols **3a–i** were formed as individual diastereomers. For example, acidic hydrolysis of epoxide **2h** obtained as the 81 : 19 mixture resulted in diol **3h** with 100% diastereomeric purity.

Since favorable isomers **3a–i** having both methyl groups arranged equatorially were formed, we proposed that both diastereomers of epoxide **2** were transformed into the same product *via* S_N2 opening of the epoxy group (Scheme 3). Each diastereomer is protonated to form intermediate **A** or **B**. The subsequent S_N2 nucleophilic attack of water can proceed on either one of the epoxide carbons. Most probably, the reaction is thermodynamically controlled to give the same product *via* attack of water on different carbon atoms for intermediates **A**



Scheme 3

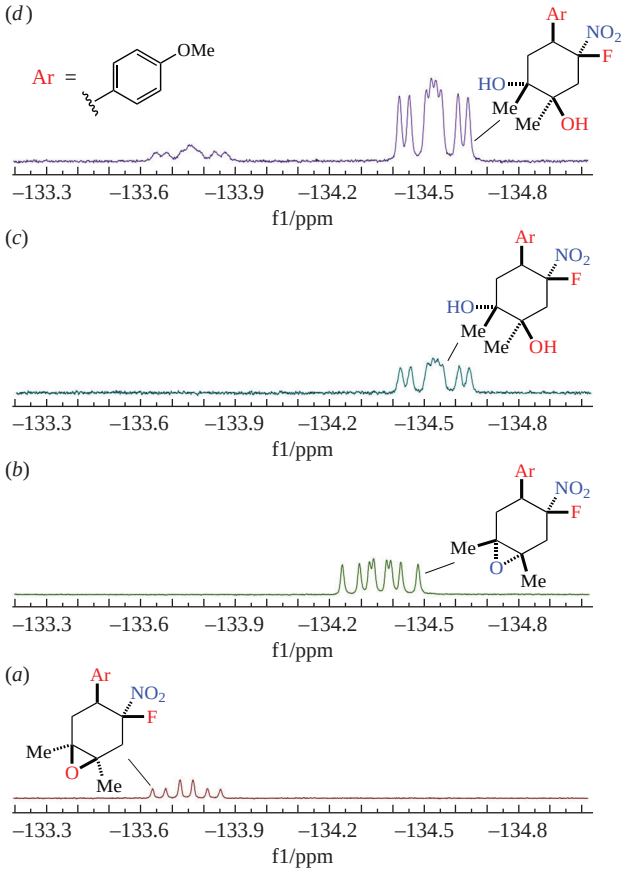


Figure 2 ^{19}F NMR spectra of dioxane/water (2 : 1) solutions of (*a*) initial *rel*-(1*R*,3*S*,4*S*,6*S*)-**2d** (minor); (*b*) *rel*-(1*S*,3*S*,4*S*,6*R*)-**2d** (major); (*c*) and (*d*) hydrolyzed minor and major **2d**, respectively.

and **B**. To confirm this supposition, we performed hydrolysis of each individual isomer of epoxide **2d** in NMR tubes. ^{19}F NMR experiment demonstrated that in both cases the same product **3d** was formed (Figure 2). These data are in full agreement with the Fürst–Plattner rule, which postulates a preference for the reaction pathway proceeding through the more stable chair-like transition state compared to the one proceeding through the unfavorable twist boat-like transition state.[42,43]

In summary, stereoselective protocols for the synthesis of novel fluorinated cyclohexane epoxides and diols have been reported. Stereochemistry of these processes were determined by X-ray diffraction analysis.

This work was carried out within the framework of the project ‘Synthesis and study of physical, chemical and biological properties of organic and organometallic compounds’ (AAAA-A21-121012290046-4).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.06.007.

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