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A NOVEL STEREOSELECTIVE SYNTHESIS OF *CIS*-2-FLUORO-CYCLOPROPANE-1-CARBOXYLIC ACID

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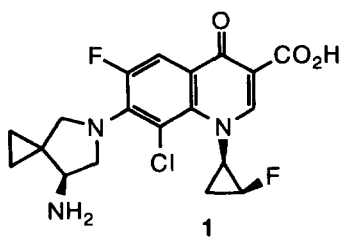
Abstract: A novel method consisting four-step from *tert*-butyl acrylate (**4**) and chloromethyl phenyl sulfoxide (**5**) for preparing *cis*-2-fluorocyclopropane-1-carboxylic acid (*cis*-**3**) was elaborated. The method involves initial formation of the *cis*-2-phenylsulfinylcyclopropanecarboxylate (*cis*-**6**), fluorination by molecular fluorine to *trans*-**7**, reductive desulfonylation to the ester (*cis*-**9**) and acid-catalyzed hydrolysis to the final product (*cis*-**3**). Copyright © 1996 Elsevier Science Ltd

Since the Daiichi group discovered 7-[(7*S*)-7-amino-5-azaspiro[2.4]heptan-5-yl]-8-chloro-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**1**) as the most prospective quinolinecarboxylic acid,[1] a number of synthetic methods for the key (1*R*,2*S*)-2-fluorocyclopropylamine [(1*R*,2*S*)-**2**] have been reported. Though the direct routes to this amine are available by using cyclopropanation of enamines with fluorocarbene,[2] the original synthesis of this amine involves *cis*-2-fluorocyclopropane-carboxylic acid (*cis*-**3**) derived from the cyclopropanation of butadiene with bromofluorocarbene as the intermediate.[3] Though its optical resolution to (1*S*,2*S*)-**3** and subsequent Curtius reaction to (1*R*,2*S*)-**2** were found to proceed efficiently, the demerits of this method were, in addition to the use of costy bromofluorocarbene, undesired *trans*-selectivity in the cyclopropanation step. We report herein the four-step synthesis of *cis*-2-fluorocyclopropane-1-carboxylic acid (*cis*-**3**) in complete diastereoselection without using any fluorinated carbene.

As shown in Scheme 1, our method consists of reaction of *tert*-butyl acrylate (**4**) and chloromethyl phenyl sulfoxide (**5**) to give *tert*-butyl *cis*-2-phenylsulfinylcyclopropane-1-carboxylate (*cis*-**6**), its fluorination to *trans*-**7** and reductive desulfonylation. Only problem in this plan is to obtain stereospecifically *cis*-**9** which has thermodynamically unstable *cis*-orientation. Formation of *cis*-**7** offers no problem, because the *cis* isomer if formed may be equilibrated by strong base to the more stable *trans* isomer.[4]



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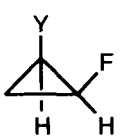
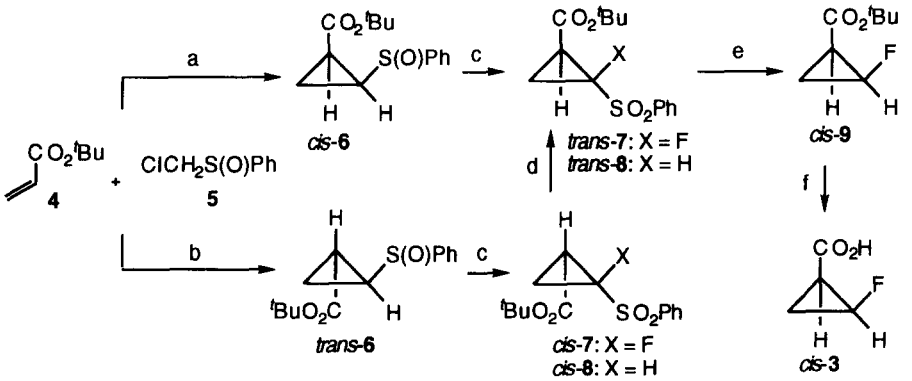
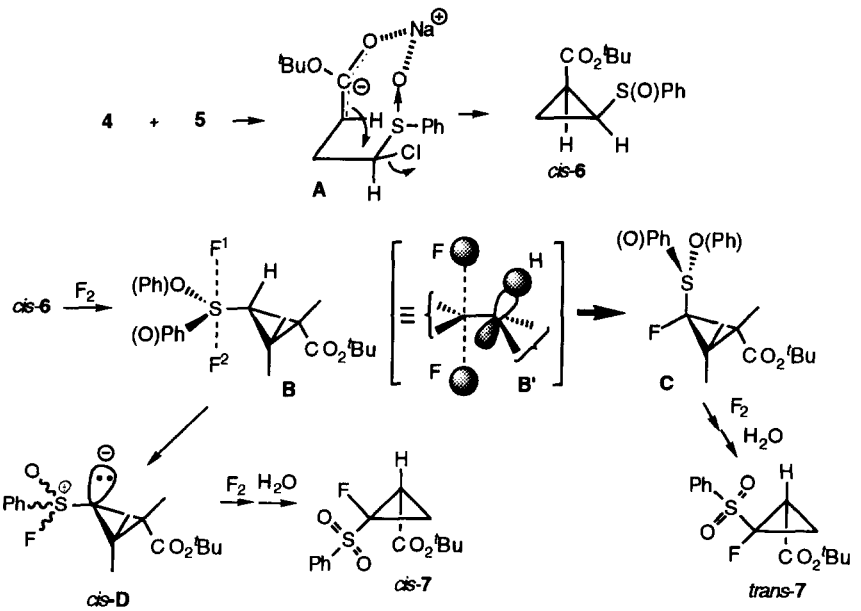


(1*R*,2*S*)-**2**: Y = NH_2
(1*S*,2*S*)-**3**: Y = CO_2H



Scheme 1. a, NaHMDS, THF, -78 °C→0 °C; b, NaH, DMF; c, 5%F_2/N_2, MeCN, -20 °C; d, NaO^{t}Bu, THF; e, Mg, cat. $HgCl_2$, EtOH; f, 10% *aq.* HCl, THF.

For the synthesis of **6**, we applied McCoy's method[5] originally used for the synthesis of 1,2-cyclopropanedicarboxylates by the reaction of α-halo esters with α,β-unsaturated esters in the presence of a base.[5] Reaction of chloromethyl phenyl sulfoxide (**5**) with *tert*-butyl acrylate (**4**) in THF at -78 °C→0 °C in the presence of 1 equiv. of NaHMDS gave *cis*-**6** as one diastereoisomeric sulfoxide[6a] in 51% yield, together with the recovered starting material (**5**) (40%). This indicates that the reaction proceeds *via* the enolate which serves as a bidentate ligand for the sodium cation (cf. **A**). In accordance with this explanation, the same reaction



Scheme 2

Table 1. Fluorination of *cis*-**6** and *trans*-**6**[a]

Run	Substrate	Yield (%) *trans*-**7**	*cis*-**7**	*trans*-**8**	*cis*-**8**
1	*cis*-**6**	35	14	28	13
2	*trans*-**6**	16	26	34	none

[a] All reactions were run in MeCN at -20 °C using 3 equiv. of F_2 in the presence of 2 equiv. of NEt_3.

carried out in DMF in the presence of NaH resulted in the formation of *trans*-**6**[6b] (1 : 1 mixture of the diastereoisomeric sulfoxides) in 58% yield, together with *cis*-**6** (5%, 1 : 1 mixture of the diastereomers).

Next, fluorination of *cis*- and *trans*-**6** by 5% F_2/N_2 was carried out according to the procedure reported in our previous work.[7] As expected, the fluorinated and unfluorinated sulfones (**7** and **8**) were obtained as shown in Table 1.

Comparison of two fluorination reactions has revealed that fluorine is introduced to **6** preferentially from the side of phenylsulfinyl group. This means that the fluorine substitution occurs preferentially with inversion of configuration. Assuming that sulfurane-like intermediate (**B**) is formed initially from *cis*-6, one can explain this stereoselectivity by intramolecular dehydrofluorination (cf. HF^1) and fluorine (F^2) migration to give the fluorinated sulfoxide (**C**).[8] This intramolecular reaction is supported by HOMO-LUMO interaction in which HOMO around S atom mostly resides to F-S-F whose two fluorines occupy in axial position in a trigonal bipyramid, hence, the HOMO belongs to the well known three-center four-electron bond (cf. **B'** in which only 2*s* atomic orbital of F is shown).[9] Then, oxidative fluorination of **C** followed by hydrolysis afforded *trans*-**7**.

Dehydrofluorination without fluorine migration from the same intermediate (**B**) accounts for the formation of minor fluorinated product (*cis*-**7**) and unfluorinated sulfones (**8**), because the resulted ylide species (*cis*-**D**) would give *cis*-**7** by addition of fluorine and **8** by addition of HF (or H_2O).[10]

When *cis*-**7** was stirred in THF in the presence of NaO^tBu at room temperature, *trans*-**7** was formed in nearly quantitative yield. This fact shows that both *cis*-**6** and *trans*-**6** are useful precursors for *cis*-**3**.

Finally, *trans*-**7** was treated with 3 equiv. of Mg in ethanol in the presence of catalytic amount of $HgCl_2$[11] at room temperature to give *cis*-**9** in 85% yield. Treatment of *cis*-**9** with 10% *aq.* HCl afforded *cis*-2-fluorocyclopropane-1-carboxylic acid (*cis*-**3**) quantitatively.

In summary, we have elaborated a practical four-step synthesis of *cis*-**3** from readily available compounds (**4** and **5**) *via cis*-**9**. The method not only avoids the cyclopropanation by using fluorinated carbenes, but also affords *cis*-**9** (the precursor of *cis*-**3**) in complete diastereoselection.

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6. a) The diastereoisomeric pure sulfoxide (*cis*-**6**) was also obtained in 51% yield by the same reaction using NaH in THF at room temperature. b) After examinations, more improved chemical yield (84%) of *trans*-**6** (14 : 3 mixture of the diastereoisomeric sulfoxides) was found to be obtained by the reaction using 2 equiv. of NaO^{t}Bu in THF at 0 °C→ room temperature. Under these conditions, initially formed *cis*-**6** was observed to isomerize to *trans*-**6** by tlc analysis.
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8. In Pummerer reaction of arylsulfinylcyclopropanes with acetic anhydride giving 1-phenylthio-1-acetoxycyclopropanes, the acetate anion attacked the α-carbon predominantly from the back side of the proton removed. A similar mechanism involving initial formation of sulfurane-like intermediate (cf. **B**) followed by subsequent intramolecular acetoxy migration was proposed. Masuda, T.; Numata, T.; Furukawa, N.; Oae, S. *J. C. S. Perkin II* **1978**, 1302-1308. See also a review for the Pummerer reaction of sulfinyl compounds, Lucch, O. D. *Organic Reactions* **1991**, *40*, Chap. 3, 157-405.
9. Amplitude of HOMO of AH_5 is mostly resides on the axial ligands (H-A-H), and hence fits well to the depicted mechanism. The reverse interaction [i.e. LUMO of SL_5 (L: ligand) and HOMO of C-H] is not important, because MO amplitudes of axial ligands in the former are very small. Hoffmann, R.; Howell, J. M.; Muetterties, E. L. *J. Am. Chem. Soc.* **1972**, *94*, 3047-3058.
10. Obviously, *cis*-**D** should be less stable than *trans*-**D**. Hence, while *trans*-**6** affords stereoselectively *trans*-**8** *via trans*-**D**, *cis*-**6** gives *trans*-**8** as the major product through inversion of initially formed *cis*-**D** to *trans*-**D** (cf. Table 1).
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