Synthesis of *cis*-2-Fluorocyclopropylamine by Stereoselective Cyclopropanation Under Phase-transfer Conditions

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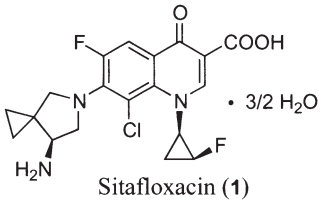
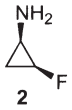
cis-2-Fluorocyclopropylamine is stereoselectively synthesized by cyclopropanation of 3-aryl-2-vinyl-3-(methoxy)isoindol-1-one by treating dibromofluoromethane with saturated aqueous KOH solution in the presence of 18-crown-6 in dichloromethane, followed by removal of a bromine atom of the formed bromofluorocyclopropane derivative with Raney Ni, and successive three steps-deprotection procedures for generating an amino group on the cyclopropane ring.

Quinolonecarboxylic acids are widely used for therapy of various infections,[1] and sitafloxacin (**1**) was recently found as a new generation of quinolone antibacterial agent having excellent antibacterial activity.[2] In order to synthesize **1** efficiently, stereoselective synthesis of (1*R*,2*S*)-2-fluorocyclopropylamine (**2**) is an important key step. Therefore, several synthetic trials have been reported:[3,4] e.g., Terashima et al. reported that cyclopropanation of an *N*-vinylcarbamate with zinc-monofluorocarbenoid generated from fluorodiiodomethane and diethylzinc gave *N*-(2-fluorocyclopropyl)carbamates stereoselectively (*cis*/*trans* = 93:7).[3a,c,e] However, pyrophoric nature of diethylzinc is a major drawback of the above method, especially in large-scale synthesis. Then, stereoselective cyclopropanation under phase-transfer conditions was planned to establish a useful and safe method. Only one non-stereoselective cyclopropanation of enamide under phase-transfer conditions affording an equal amount of *cis*- and *trans*-fluorocyclopropylamines was reported to date.[4] We would like to describe here *cis*-selective cyclopropanation of cyclic enamides with bromofluorocarbene under phase-transfer conditions and transformation of thus-obtained bromofluorocyclopropane derivative to *cis*-2-fluorocyclopropylamine salt.



Sitafloxacin (**1**)



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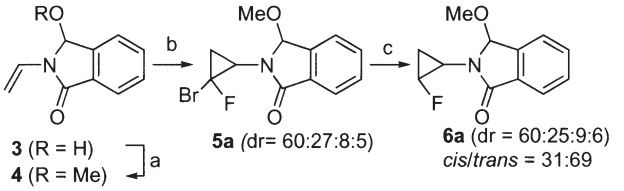
Cyclopropanation of commercially available *N*-vinylphthalimide was tried first under phase-transfer conditions by using Br_2CHF, saturated aq KOH, and a catalytic amount of $BnBu_3N^+Cl^-$: however, only a trace amount of the desired bromofluorocyclopropane derivative was obtained[4] probably because electron density of the vinyl group of *N*-vinylphthalimide was insufficient for the reaction with the electrophilic bromofluorocarbene. Then, one of the two carbonyl groups of *N*-vinylphthalimide was reduced in order to increase the electron density of the vinyl group. 2-Vinyl-3-(methoxy)isoindol-1-one (**4**) was afforded in 95% yield by the following procedure; *N*-vinylphthalimide was reduced by using $NaBH_4$ in EtOH to afford 2-vinyl-3-hydroxyisoindol-1-one (**3**),[5] followed by methylation with NaH and MeI (Scheme 1).

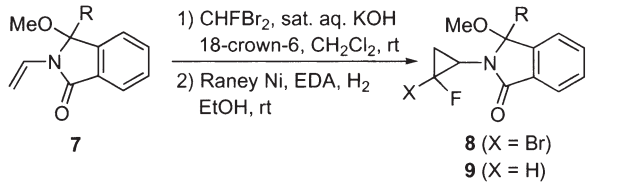


Scheme 1. a) NaH, MeI, DMF (95%); b) $CHFBr_2$, sat. KOH, BnN^nBu_3Cl, $CHCl_2$ (92%); c) Raney Ni, H_2, EtOH (90%).

Cyclopropanation of thus-obtained **4** under the above-mentioned phase-transfer conditions proceeded smoothly to give the desired compound **5** in 92% yield as a mixture of four diastereomers (60:27:8:5). Since it was difficult to determine *cis*/*trans* selectivity of **5** directly, it was determined after a bromine atom of **5** was reductively removed by using Raney Ni in EtOH under a hydrogen atmosphere: a fluorocyclopropane derivative **6** was then obtained as a mixture of diastereomers (60:25:9:6), and its *cis*/*trans* selectivity was found to be *cis*/*trans* = 31:69 by ^{1}H NMR analysis (Scheme 1). In order to improve the *cis*/*trans* selectivity, the reaction conditions concerning phase-transfer catalysts (Aliquatoo® 336, 18-crown-6), solvents (1,2-dichloroethane, benzene, toluene, benzotrifluoride, petroleum ether, ether, CCl_4), and bases (NaOH, CsOH) were further investigated. However, not only the *cis*/*trans* selectivity but the diastereomer ratio did not change drastically. On the other hand, protecting groups of the hydroxy group of **3** gave slight influence on the diastereomer ratio: that is, only two diastereomers were formed when the 3-hydroxy group was protected with trityl group (dr = 70:30:0:0, *cis*/*trans* = 30:70).[6] It was then suggested that when the 3-hydroxy group was protected with the bulky group, bromofluorocarbene would approach to the *N*-vinyl group from the π-face opposite to the triyl group, while the direction of a fluorine group was still not controlled on that π-face. Then, a bulky substituent was introduced at the 3-carbon of **5** in order to control the orientation of the fluorine group *cis* to the 2-nitrogen group.

3-Aryl(alkyl)-2-vinyl-3-methoxyisoindol-1-ones **7** were prepared by 1,2-addition of Grignard reagent to vinylphthalimide, followed by protection of a hydroxy group by using NaH and MeI in DMF. Cyclopropanation of thus-prepared enamides **7** with bromofluorocarbene under phase-transfer conditions was shown in Table 1. By introducing phenyl group at

Table 1. Cyclopropanation of **7**



7

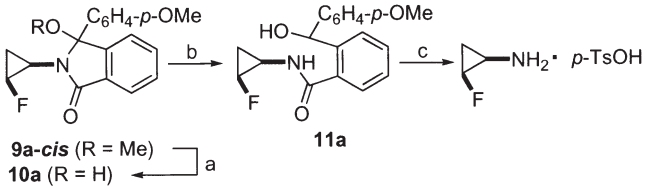
8 (X = Br)
9 (X = H)

		8	**9**		
Entry	R	Yield/%	Yield/%	D.r.[a]	*Cis*/*trans*[a]
1	Ph	60	90	46:26:14:14	72/28
2	*o*-MeC_6H_4	42	90	44:33:13:10	77/23
3	*m*-MeC_6H_4	78	80	50:28:12:10	78/22
4	*p*-MeC_6H_4	44	87	49:29:13:9	78/22
5	*o*-$MeOC_6H_4$	52	86	47:26:15:12	73/27
6[b]	*o*-$MeOC_6H_4$	88	86	47:26:15:12	73/27
7	*p*-$MeOC_6H_4$	64	71	46:32:12:10	78/22
8	1-Naph	44	73	50:34:9:7	84/16
9	^{i}Pr	86	79	40:16:30:14	56/44
10	^{t}Bu	67	82	33:33:18:16	66/34

[a]Ratios were determined by ^{1}H NMR. [b]Cyclopropanation was performed at 0 °C.

the 3-carbon, the *cis*/*trans* ratio was inversed compared to the case using **5**, and a *cis*-fluorocyclopropylamine derivative was preferentially formed (*cis*/*trans* = 72/28, Entry 1). After screening aryl or alkyl groups to be introduced at the 3-carbon, 1-naphthyl group gave the best result (*cis*/*trans* = 84/16). By introducing alkyl groups such as *tert*-butyl or isopropyl group at the 3-carbon, the corresponding cyclopropane derivative was formed in a less selective manner. It was further found that the use of other protecting groups such as ethyl, benzyl, and isopentyl groups instead of the methyl group of **7** did not improve the *cis*/*trans* selectivity.

The obtained *cis*-product **9a** was converted to a *cis*-fluorocyclopropylamine salt as a model (Scheme 2). Namely, methyl



Scheme 2. a) 1 N HCl, THF, reflux (79%); b) $NaBH_4$, *i*-PrOH-H_2O (60%); c) *p*-TsOH, Et_2O (71%).

group was deprotected in refluxing aqueous 1 N HCl-THF to give a hemiaminal **10a** which was in turn reduced to amido alcohol **11a** with $NaBH_4$ in *i*-PrOH-H_2O. Finally, *cis*-fluorocyclopropylamine *p*-toluenesulfonic acid salt was obtained by treating **11a** with *p*-TsOH in Et_2O.

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References and Notes

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5 Cyclopropanation of **3** and Br_2CHF under phase-transfer conditions did not proceed.

6 Diastereomer and *cis*/*trans* ratios are as follows concerning other protecting groups: Bn (dr = 65:26:5:4, *cis*/*trans* = 30/70), 1-NaphCH_2 (dr = 63:26:6:5, *cis*/*trans* = 31/69), 2-NaphCH_2 (dr = 65:25:6:4, *cis*/*trans* = 29/71).

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