Tetrahedron Letters, Vol. 33, No. 24, pp. 3483-3486, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Synthesis and Optical Resolution of *dl-cis*-2-Fluorocyclopropylamine, the Key Component of the New Generation of Quinolonecarboxylic Acid, DU-6859

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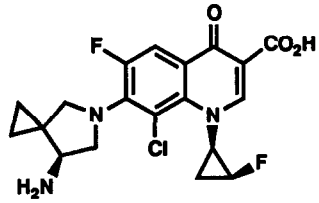
Key words: quinolonecarboxylic acids; dl-cis-2-fluorocyclopropylamine; N-vinylcarbamate; cis-selective cyclopropanation; optical resolution

***Abstract:** The title synthesis was accomplished by featuring highly cis-selective cyclopropanation of an N-vinylcarbamate with zinc-monofluorocarbenoid followed by deprotection of the formed N-(cis-2-fluorocyclopropyl)carbamate. Optical resolution of dl-cis-2-fluorocyclopropylamine was also achieved by employing l-menthyl chloroformate as a resolving agent.*

Antibacterial quinolonecarboxylic acids (new quinolones) are medicinally important and widely used for therapy of various infections.[2] Quite recently, DU-6859 (**1**) was found as the new generation of quinolonecarboxylic acid exhibiting excellent antibacterial activity and little side effects.[3] One of the structural characteristics of **1** is its possession of the *cis*-oriented (1*R*,2*S*)-2-fluorocyclopropylamine (**2**) moiety which has been disclosed to be indispensable for its promising characteristics.



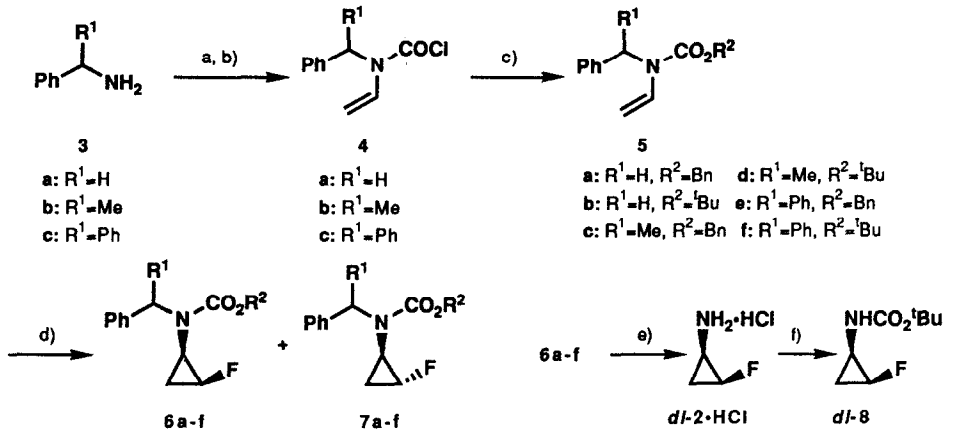
DU-6859 (1)

2

In order to produce **2** more effectively than initially reported,[3,4] a novel preparation method was sought which can afford **2** in short synthetic steps. We have now found that the *N*-vinylcarbamates (**5**) can react with zinc-monofluorocarbenoid[5] in a highly *cis*-selective manner to afford the *N*-(*cis*-2-fluorocyclopropyl)carbamates (**6**) as major products and that *dl*-**2** can be readily elaborated from **6**. It was also found that optical resolution of *dl*-**2** can be accomplished by employing *l*-menthyl chloroformate as a resolving agent.

As shown in **Scheme 1**, condensation of the benzylamine derivatives (**3a-c**) with acetaldehyde followed by treatment with trichloromethyl chloroformate in the presence of triethylamine (Et_3N) gave the *N*-vinyl-

Scheme 1



a) CH_3CHO, $MgSO_4$, Et_2O, 0°C, 100% b) $ClCO_2CCl_3$, Et_3N, toluene, rt→80 °C; **4a**, 58%; **4b**, 78%; **4c**, 53% c) R^2OH, NaH, THF, 0 °C→rt, see **Table 1** d) $CHFI_2$, Et_2Zn, CH_2Cl_2, -40°C, see **Table 1** e) 1) H_2, (3-4 kg/ cm^2), 10% Pd-C, AcOH, rt 2) HCl-MeOH for **6a,c,e** or 1) CF_3CO_2H, CH_2Cl_2, 0 °C 2) H_2 (3-4 kg/ cm^2), 10% Pd-C, AcOH 3) HCl-MeOH for **6b,d,f**, see **Table 1** f) $(Boc)_2O$, Et_3N, CH_2Cl_2, 73%

Table 1. Chemical yields of *N*-vinylcarbamate formation (**4**→**5**), cyclopropanation (**5**→**6** and **7**)[a], and deprotection of **6** (**6**→*dl*-**2**•HCl).

			Yield (%)[b]		
	R^1	R^2	**5**	**6** and **7** (**6**:**7**)	*dl*-**2**•HCl
a	H	Bn	79	78 (70:30)[c]	94
b	H	^{t}Bu	63	69 (62:38)[c,d]	75
c	Me	Bn	100	96 (89:11)[e,f]	77
d	Me	^{t}Bu	92	67 (91:9)[c,f]	81
e	Ph	Bn	82	90 (93:7)[c]	73
f	Ph	^{t}Bu	28[g]	88 (93:7)[c]	66

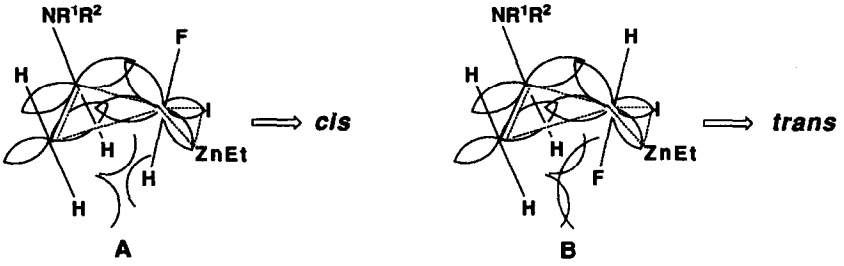
a) Otherwise noted, all the reactions were carried out in dichloromethane at -40 °C by employing two equivalents of fluorodiiodomethane and diethylzinc. Two sorts of the addition products (**6** and **7**) were readily separated by column chromatography (SiO_2, hexane-AcOEt). b) Isolated yield. c) Determined by the weights of separated **6** and **7**. d) The reaction was carried out in hexane at -20 °C. e) Determined by the integration of ^{19}F-NMR spectrum. f) Each of the products (**6** and **7**) was a mixture of diastereomers. **6c** (1:1), **7c** (3:2), **6d** (1;1), **7d** (3:2). g) Not optimized.

carbamoyl chlorides (**4a-c**). The chlorides (**4a-c**) were treated with sodium benzyloxide (NaOBn) or sodium *tert*-butoxide (NaO^{t}Bu), respectively, to afford the *N*-vinylcarbamates (**5a-f**).

Treatments of **5a-f** with zinc-monofluorocarbenoid generated from fluorodiiodomethane and diethylzinc[5] underwent smooth cyclopropanation, giving rise to the *N*-(2-fluorocyclopropyl)carbamates (**6a-f** and **7a-f**) with moderate to high *cis*-selectivity. The results summarized in **Table 1** deserve some comments concerning novel aspects of this cyclopropanation. Thus, the bulkiness of alkoxy group in **5** obviously gives no influence on the stereoselectivity (**5a,c,e** *vs* **5b,d,f**). Increase of the steric hindrance on the nitrogen of **5** raises the *cis*-selectivity

(**5a,b** *vs* **5c-f**). The chirality of 1-phenylethyl group in **5c,d** showed almost no diastereoface selectivity [foot note f) in **Table 1**]. The best chemical yield (96%) and *cis*-selectivity (93:7) were realized for the reactions employing **5c** and **5e,f**, respectively. Considering the chemical yield and *cis*-selectivity, the reaction of **5c** seems to be most rewarding. Stereochemistries of **6a-f** and **7a-f** were tentatively assigned by their ^{1}H-NMR spectra and confirmed by successful synthesis of *dl*-**2** from **6a-f** (*vide infra*).

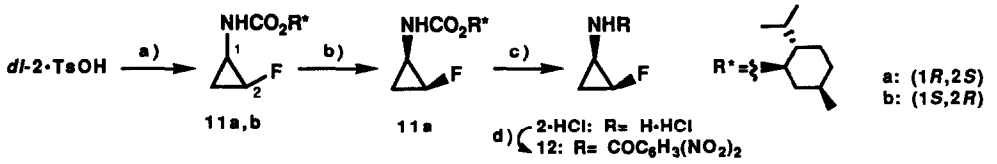
While details of the mechanism for the reactions of **5** with zinc-monofluorocarbenoid remain unknown, steric factor seems to play more important role than electronic effect.[6] Among four possible transition states, **A** and **B** may be considered for the reaction of **5** by taking into account both steric hindrance of substituents (R^1 and R^2) and the "bent" transition state proposed by Schlosser.[5b] It appears evident that the steric interaction is more released in **A** than in **B** because a fluorine atom is obviously larger than a hydrogen atom. The "bent" transition state would be favored in **5c-f** carrying sterically more bulky benzylic alkyl groups. Accordingly, **5c-f** are anticipated to undergo highly *cis*-selective cyclopropanations by way of **A**.



Elaboration of **6a-f** to *dl*-**2** was readily achieved in short synthetic steps. In the cases of **6a,c,e** protected with a benzyloxycarbonyl (Cbz) group, simultaneous reductive removals of the Cbz and *N*-benzylic alkyl groups were accomplished by hydrogenolysis in the presence of 10% palladium on charcoal, affording *dl*-**2**•HCl, mp 119-120 °C (decomp.), after treatment with methanolic hydrogen chloride. In the cases of **6b,d,f** bearing a *tert*-butoxycarbonyl (Boc) group, acidic removal of the Boc groups with trifluoroacetic acid followed by hydrogenolysis of the *N*-benzylic alkyl groups and treatments with methanolic hydrogen chloride furnished *dl*-**2**•HCl. Treatment of *dl*-**2**•HCl with di-*tert*-butyl dicarbonate in the presence of triethylamine gave *tert*-butyl *dl*-*N*-(*cis*-2-fluorocyclopropyl)carbamate (**8**), mp 65.5-66 °C, whose ^{1}H-NMR and IR spectra were identical with those of an authentic sample.[3,7]

With *dl*-**2** in hand, its optical resolution was finally attempted. As shown in **Scheme 2**, we found that *dl*-**2** can be effectively resolved by employing *l*-menthyl chloroformate as a resolving agent. Thus, *dl*-**2**•TsOH[8] was

Scheme 2



a) *l*-menthyl chloroformate, CH_2Cl_2, $NaHCO_3$aq, 95% b) Four recrystallizations from hexane-AcOEt, 26% (based on **11a,b**) (52% based on **11a**) c) conc. HCl, MeOH, reflux, 88% d) 3,5-$(NO_2)_2C_6H_3COCl$, Et_3N, THF

acylated with *l*-menthyl chloroformate to give a 1:1 mixture of the diastereomeric carbamates (**11a,b**) as a crystalline solid in 95% yield. Four repeated recrystallizations of **11a,b** from hexane-ethyl acetate afforded **11a**, mp 119.5-120.5 °C, $[\alpha]_D^{20}$ -45.9° (*c* 1.05, MeOH), in 26% yield based on **11a,b** (52% yield based on **11a**). Acidic hydrolysis of **11a** under usual conditions furnished **2** in 88% yield as its hydrochloride (**2**•HCl), mp 153-157 °C (decomp.), $[\alpha]_D^{20}$ -19.0° (*c* 0.738, MeOH) (96% ee). The absolute stereochemistry and optical purity were determined by chiral HPLC analysis of the 3,5-dinitrobenzamide (**12**) derived from **2**•HCl.[9]

As mentioned above, we have succeeded in developing a short and stereoselective synthetic route to *dl*-**2**, and an efficient optical resolution method of *dl*-**2** providing highly optically pure **2**.

References and Notes

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5. Only one example is known for the reaction of zinc-monofluorocarbenoid. a) Nishimura, J.; Furukawa, J. *Chem. Commun.* **1971**, 1375. For lithium-monofluorocarbenoid, see, b) Schlosser, M.; Heinz, G. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 820.
6. It was reported that in the reaction of cyclohexene with zinc-carbenoids, the reaction of more bulky phenyl-substituted carbenoid gave much better *cis*-selectivity than that with methyl-substituted one. This observation also suggests importance of steric factor in the cyclopropanation of zinc-carbenoids. See, Furukawa, J.;Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1968**, 3495.
7. Hydrogenation of **7a** followed by treatment with methanolic hydrogen chloride similarly gave *trans-dl*-2-fluorocyclopropylamine hydrochloride (*dl*-**9**•HCl) in 83% yield. This was protected with a *tert*-butoxycarbonyl group to afford *tert*-butyl *dl-N*-(*trans*-2-fluorocyclopropyl)carbamate (*dl*-**10**). In the ^{1}H-NMR spectra of *dl*-**2**•HCl, *dl*-**8**, *dl*-**9**•HCl, and *dl*-**10**, the coupling constants between the C_1- and C_2-protons are as follows: *dl*-**2**•HCl, 5.5 Hz; *dl*-**8**, 6.0 Hz; *dl*-**9**•HCl, 1.3 Hz; *dl*-**10**, 0.8 Hz. These spectral characteristics unambiguously suggest that *dl*-**2**•HCl, *dl*-**8** and *dl*-**9**, *dl*-**10** bear *cis*- and *trans*-stereochemistries, respectively.
8. This was prepared in 52 % from **6c** or 83 % from **6e** by the same procedure as described for **2**•HCl using TsOH in place of hydrogen chloride.
9. The analysis conditions were as follows: column, Sumipax OA-4600; mobile phase, hexane:1,2-dichloroethane:ethanol=60:40:5; flow rate, 1.0 ml/min; detector, UV (254 nm). Retention time: (1*R*,2*S*)-isomer (**12**), 10.9 min; (1*S*,2*R*)-isomer (the enantiomer of **12**), 14.9 min (base line separation).

(Received in Japan 5 March 1992)