Tetrahedron Letters, Vol. 33, No. 24, pp. 3487-3490, 1992
Printed in Great Britain

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

Asymmetric Synthesis of (1*R*,2*S*)-2-Fluorocyclopropylamine, the Key Intermediate of the New Generation of Quinolonecarboxylic Acid, DU-6859

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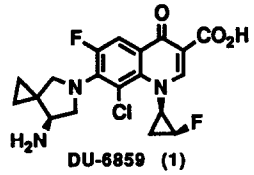
Key Words: asymmetric synthesis; quinolonecarboxylic acid; (1R,2S)-2-fluorocyclopropylamine; (4R,5S)-4,5-diphenyl-3-vinyl-2-oxazolidinone.

Abstract: *The title synthesis was achieved by featuring diastereoface selective cyclopropanation of (4R,5S)-4,5-diphenyl-3-vinyl-2-oxazolidinone, the chiral and conformationally rigid N-vinylcarbamate, with zinc-monofluorocarbenoid followed by hydrogenolysis of formed (4R,5S)-3-[(1R,2S)-2-fluorocyclopropyl]-4,5-diphenyl-2-oxazolidinone.*

DU-6859 (**1**) was found as the new generation of quinolonecarboxylic acid exhibiting marked antibacterial activity and little side effects.[2] The pronounce characteristics of **1** has been also disclosed to be closely related with its (1*R*,2*S*)-2-fluorocyclopropylamine (**2**) moiety.



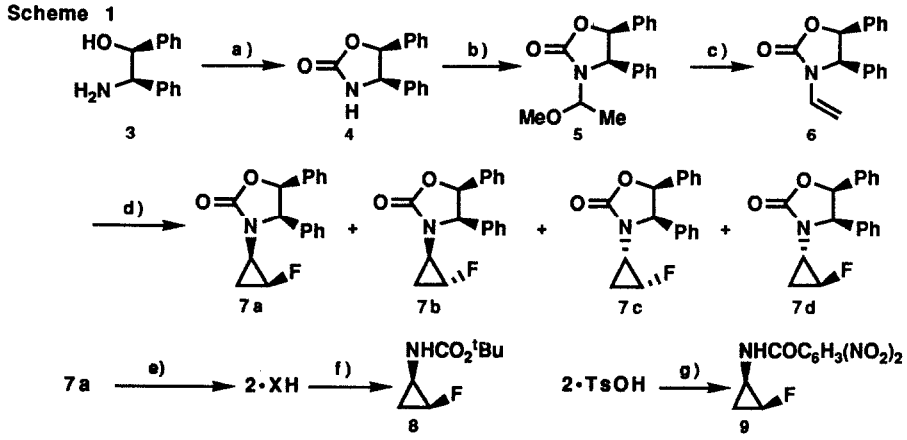
DU-6859 (1)

2

In the preceding papers,[3] it was reported that *dl*-**2** can be readily prepared from benzylamine derivatives by employing *cis*-selective cyclopropanation of an *N*-vinylcarbamate with zinc-monofluorocarbenoid. However, no diastereoface selectivity was observed when chiral *N*-(1-phenylethyl)-*N*-vinylcarbamates derived from 1-phenylethylamine were employed as reaction substrates probably due to conformational flexibility of the chiral 1-phenylethyl moiety. Accordingly, the preparation of **2** was achieved by optical resolution of *dl*-**2** with *l*-menthyl chloroformate. We have now found that (4*R*,5*S*)-4,5-diphenyl-3-vinyl-2-oxazolidinone (**6**), the chiral and conformationally rigid *N*-vinylcarbamate, derived from (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**3**), reacts with zinc-monofluorocarbenoid in a highly diastereoface selective manner and the 3-(2-fluorocyclopropyl)-2-oxazolidinone derivative (**7a**) produced as a major product can be readily elaborated to **2**.

As shown in **Scheme 1**, the synthesis of **2** commences with 2-oxazolidinone formation from **3**. Thus, treatment of **3** with trichloromethyl chloroformate and triethylamine afforded (4*R*,5*S*)-4,5-diphenyl-2-oxazolidinone (**4**). Transacetalization of **4** with 1,1-dimethoxyethane in the presence of *dl*-camphor-10-sulfonic acid smoothly took place to yield the 3-(1-methoxyethyl)-2-oxazolidinone derivative (**5**) as a 2:1 mixture of

Scheme 1



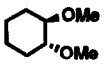
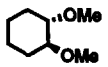
a) $ClCO_2CCl_3$, Et_3N, CH_2Cl_2, 97% b) $MeCH(OMe)_2$, cat. CSA, reflux c) 150 °C/ 15 mmHg, 79%, (two steps) d) $CHFI_2$, Et_2Zn, CH_2Cl_2, see **Table 1** e) H_2 (3 kg/ cm^2), 10% Pd-C, AcOH; HCl-MeOH, 87% (**2**•HCl) or H_2 (3 kg/ cm^2), 10% Pd-C, AcOH; TsOH, MeOH, 90% (**2**•TsOH) f) $(Boc)_2O$, Et_3N, CH_2Cl_2, 62% g) 3,5-$(NO_2)_2C_6H_3COCl$, Et_3N, THF

diastereomers. Heating of **5** under a reduced pressure effected elimination of methanol[4] to give **6**, mp 170-171 °C, $[\alpha]_D^{20}$ +21.7° (*c* 0.775, $CHCl_3$) [*lit.*,[5] $[\alpha]_D^{20}$ -22.1° (*c* 1.99, $CHCl_3$) for the enantiomer of **6**].

With **6** in hand, the reaction of **6** with zinc-monofluorocarbenoid[6] was next examined. Thus, treatments of **6** with zinc-monofluorocarbenoid generated from fluorodiiodomethane and diethylzinc gave the (4*R*,5*S*)-3-(2-fluorocyclopropyl)-4,5-diphenyl-2-oxazolidinone derivatives (**7a-d**) as mixtures of four possible diastereomers. The results collected by changing the reaction conditions are summarized in **Table 1**. The ratios of **7a-d** was definitely determined by the ^{19}F-NMR spectra.[7] Since the reactivity of **6** was found to be obviously lower than that of *N*-vinylcalbamates employed in the preceding paper, all the reactions were carried out at higher reaction temperatures than those of the previous cases.[3] Although the diastereoface selectivity concerning the C_1-position of cyclopropylamine moiety [(**7a**+**7b**):(**7c**+**7d**)] was high enough (91:9), the chemical yield and *cis*-diastereoselectivity [(**7a**+**7c**):(**7b**+**7d**)] were found to be fairly low (44% and 54:46, respectively) probably due to instability of zinc-monofluorocarbenoid at room temperature (run 1). It is well known that some sorts of ethers can coordinate with zinc-carbenoid species as ligands to form stable complexes.[8] Accordingly, in order to improve the chemical yield and *cis*-diastereoselectivity, effects of various ethers and reaction temperatures on the cyclopropanation were next studied.

After examinations, we found that more improved chemical yields and *cis*-diastereoselectivities can be realized by the combined uses of various ethers and molecular sieves 4A (MS4A) as additives. Thus, the better chemical yield of **7a-d** was found to be obtained by the use of refluxing ether (Et_2O) as a reaction solvent (run 2). Interestingly, the similar result could be obtained by employing 1.0 equivalent of Et_2O to the amounts of diethylzinc and fluorodiiodomethane in refluxing dichloromethane (run 3). Addition of tetrahydrofran (THF) which may behave as a stronger ligand to the zinc-monofluorocarbenoid gave desired **7a** as a major product in more improved yield and with slightly higher *cis*-diastereoselectivity. Following to Et_2O and THF, 1,2-dimethoxyethane (DME), 1,2-diethoxyethane (DEE), and (1*R*,2*R*)- and (1*S*,2*S*)-1,2-dimethoxycyclohexane were

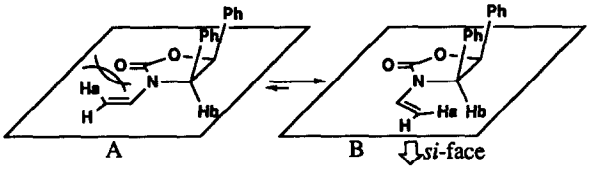
Table 1 Cycropropanation of **6** with fluorodiiodomethane and diethylzinc.[a)]

Run	Conditions		Yield (%)[b)]	Ratio[c)]
	Additives	Temp.		**7a:7b:7c:7d**
1	------[d)]	rt	44 (88)	50 : 41 : 4 : 5
2	Et_2O,[e)] MS4A	reflux	69 (83)	50 : 41 : 4 : 5
3	Et_2O, MS4A	reflux	64 (87)	53 : 36 : 5 : 6
4	THF, MS4A	reflux	73 (85)	56 : 33 : 5 : 7
5	DME,[f)] MS4A	reflux	68 (77)	63 : 27 : 5 : 5
6	DME, MS4A	reflux[g)]	85 (94)	59 : 28 : 5 : 8
7	DME, MS4A	rt[g)]	76 (83)	65 : 25 : 5 : 5
8	DEE,[h)] MS4A	reflux	88 (92)	59 : 30 : 5 : 6
9	 MS4A	reflux	67 (84)	65 : 25 : 6 : 4
10	 MS4A	reflux	67 (84)	65 : 25 : 6 : 4

a) Otherwise noted, all the reaction were carried out in dichloromethane by employing fluorodiiodomethane (3 eq.), diethylzinc (1M solution in hexane, 3 eq.), ethers (3 eq.), and MS4A (equal weight to **6**). b) The yields in parentheses were corrected for the recovery of **6**. c) Determined by ^{19}F-NMR spectrum.[7] d) No additive was used. e) Diethylether was used as a solvent. f) 1,2-Dimethoxyethane. g) A 1M solution of diethylzinc in dichloromethane was used. h) 1,2-Diethoxyethane.

employed as bidentate ligands (runs 5-10). The best results in terms of chemical yield [88%, (run 8)] and diastereoselectivity [(**7a**+**7b**):(**7c**+**7d**)=90:10 (runs 5, 9, and 10); (**7a**+**7c**):(**7b**+**7d**)= 71:29 (runs 9 and 10)] were realized by the uses of these ethers as additives in refluxing dichloromethane. In runs 6 and 8, **7a** was isolated in *ca.* 50% yield after separation by column chromatography. Enantiomeric (1*R*,2*R*)- and (1*S*,2*S*)-dimethoxycyclohexane were not found to give different effect on diastereoselectivty of the reaction (runs 9 and 10). The two major products **7a**, mp 173-177.5 °C (decomp.), $[\alpha]_D^{20}$ +73.6° (*c* 0.451, $CHCl_3$) and **7b**, mp 171-173.5 °C (decomp.), $[\alpha]_D^{20}$ +55.4° (*c* 0.523, $CHCl_3$), were readily isolated by column chromatography and their stereochemistries were assigned by their ^{1}H-NMR spectra[9] and single crystal x-ray analysis of **7b**, and later confirmed by successful synthesis of **2** from **7a** (*vide infra*).

The remarkable diastereoface selectivity [(**7a**+**7b**):(**7c**+**7d**)=max. 90:10] may be explained by considering the following conformations (**A** and **B**) of **6** in which the exocyclic olefin has a maximum conjugation with the lone pair of nitrogen. Since **A** would have a severe steric interaction between the oxygen atom of carbamate group and the vinyl proton (Ha), **B** seems to be more favorable. Indeed, the NOE was observed between Ha and Hb of the 2-oxazolidinone ring in the ^{1}H-NMR spectrum of **6**. Accordingly, the diastereoface selectivity may arise from the *si*-face attack of the zinc-monofluorocarbenoid from the less hindered side of **B**. The moderate *cis*-diastereoselectivity [(**7a**+**7c**):



(**7b**+**7d**)=max. 71:29] may be explained by the "bent" transition state in a similar manner to that described for the preparation of *dl*-**2**.[3]

Elaboration of **7a** to **2** was effectively achieved in one step. Thus, reductive removal of the 4,5-diphenyl-2-oxazolidinone moiety of **7a** was readily accomplished by hydrogenolysis in the presence of 10% palladium on charcoal, affording **2**•HCl, mp 154-156 °C (decomp.), $[\alpha]_D^{20}$ -20.6° (*c* 0.781, EtOH), after treatment with methanolic hydrogen chloride. In a similar manner, **2**•TsOH, mp 178-179 °C (decomp.), $[\alpha]_D^{20}$ -10.7° (*c* 1.08, MeOH), was also produced by hydrogenolysis of **7a** followed by treatment with *p*-toluenesulfonic acid (TsOH). Definite identification of **2** was achieved by transforming **2**•HCl to known *tert*-butyl *N*-[(1*R*,2*S*)-2-fluorocyclopropyl]carbamate (**8**).[2c] Thus, treatment of **2**•HCl with di-*tert*-butyl dicarbonate in the presence of triethylamine furnished **8**, mp 77.5-78.5 °C, $[\alpha]_D^{25}$ -66.5° (*c* 0.840, $CHCl_3$) [*lit.*,[2c] mp 63 °C, $[\alpha]_D$ -60.27° (*c* 0.740, $CHCl_3$) for **8**; mp 73 °C, $[\alpha]_D$ +65.57° (*c* 0.610, $CHCl_3$) for the enantiomer of **8**], whose ^{1}H-NMR and IR spectra were identical with those of authentic **8**.[2c,10] The optical purity of **2** was determined as 98% ee by converting **2**•TsOH to the corresponding *N*-[(1*R*,2*S*)-2-fluorocyclopropyl]-3,5-dinitrobenzamide (**9**) followed by by chiral HPLC analysis.[11]

As mentioned above, we have succeeded in exploring the novel asymmetric synthesis which can afford (1*R*,2*S*)-2-fluorocyclopropylamine (**2**), 98% ee, in 35% overall yield, by employing diastereoface selective cyclopropanation of the chiral and conformationally rigid *N*-vinylcarbamate (**6**) with zinc-monofluorocarbenoid.

References and Notes

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6. Only one example has been reported for the reaction of zinc-monofluorocarbenoid. See, Nishimura, J.; Furukawa, J. *Chem. Commun.* **1971**, 1375.
7. In the ^{19}F-NMR spectrum ($CDCl_3$, CCl_3F as an internal standard), the signals of C_2-fluorine atoms of (1*R*,2*S*)-, (1*R*,2*R*)-, (1*S*,2*R*)-, and (1*S*,2*S*)-isomers (**7a**-**d**) were found at δ −223.92, -209.11, -228.45, and -211.48 ppm, respectively.
8. Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 723 and references sited therein.
9. In the ^{1}H-NMR spectra, the coupling constants between C_1- and C_2-protons of the cyclopropane moieties of **7a** and **7b** were found at 3.1 and 1.0 Hz, respectively. Since *cis*-substituted cyclopropane derivative always exhibits a larger coupling constant than *trans*-substituted one, this spectral characteristic clearly suggests that **7a** and **7b** bear the *cis*- and *trans*-stereochemistries, respectively.
10. Similar hydrogenolysis of **7b** followed by treatment of methanolic hydrogen chloride gave (1*R*,2*R*)-2-fluorocyclopropylamine hydrochloride, mp 131-134 °C, $[\alpha]_D^{20}$ -14.2° (*c* 0.604, EtOH) in 65% yield. This was allowed to react with di-*tert*-butyl dicarbonate in the presence of triethylamine, affording *tert*-butyl *N*-[(1*R*,2*R*)-2-fluorocyclopropyl]carbamate, mp 59.5-61 °C, $[\alpha]_D^{25}$ -23.9° (*c* 0.999, $CHCl_3$), in 44% yield.
11. The conditions for the analysis were the same as previously reported.[3]

(Received in Japan 5 March 1992)