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A mild and efficient synthesis of a chiral pyridazinone derivative

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ABSTRACT

We found a mild and efficient reaction condition for construction of a chiral 5-methyl-4,5-dihydropyridazin-3(2*H*)-one from a chiral β-methyl γ-ketocarboxylic acid via the corresponding acid hydrazide without racemization. Furthermore, we demonstrated that this two-step reaction can be attained by *one-pot* reaction. This method could be applied to various kinds of substrates because of the mild reaction conditions.

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1. Introduction

We previously reported that (−)-6-[7-methoxy-2-(trifluoromethyl)pyrazolo[1,5-*a*]pyridin-4-yl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (**KCA-1490**) showed dual phosphodiesterase (PDE) 3/4 inhibitory activity with very potent combined bronchodilatory and anti-inflammatory activity[1] (Fig. 1). Moreover, we have reported that some racemic compounds, which have bicyclic heteroaromatic replacement subunits for the pyrazolo[1,5-*a*]pyridine core of **KCA-1490** showed as good activity as that of the racemate of **KCA-1490**.[2] The activity is quite different from that of the enantiomer in the case of **KCA-1490**. We therefore attempted to synthesize optically active compounds of the heteroaromatic analogs. To this end, we focused on the process of synthesizing optically active compound **1**, which is one of the heteroaromatic analogs.

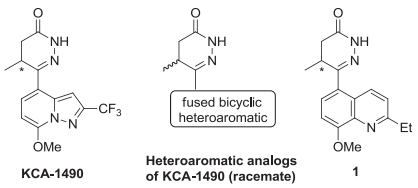

Fig. 1. Chemical structures of KCA-1490 and its analogs.

Previous reports have described the asymmetric syntheses of 6-substituted 5-methyl-4,5-dihydro-3(2*H*)-pyridazinones from optically active β-methyl γ-ketocarboxylic acids or esters and hydrazine (Table 1, entry 1–3).[3–5] According to these reports, the degree of the racemization varies according to the substituent of the 6-position of the pyridazinone ring, and the important points to prevent racemization are the pH and temperature of the reaction conditions. In the case of these compounds (**1a**–**c**), the enantiomeric excess (ee) could be increased by recrystallization.

We first tried a reaction using our substrate 2 (96% ee) with hydrazine monohydrate in EtOH, and the ee of the resulting compound **1** was reduced to 34% ee (entry 4). We therefore attempted to employ the reported reaction conditions with addition of acetic acid to regulate the pH condition. Nevertheless, the best result with an ee of **1** was 54% ee after several examinations of pH condition (entry 5). The ee of **1** could be increased to 93% ee by the recrystallization method, but the substance was obtained from the mother liquor as an amorphous form, and the ee could not be further increased. Therefore, we decided to research a new synthetic method for construction of chiral 5-methyl-4,5-dihydropyridazin-3(2*H*)-ones from optically active β-methyl γ-ketocarboxylic acids or esters without racemization.

It has not yet determined at which stage racemization occurs under the above reaction conditions. To clarify the point of racemization, we planned a two-step reaction for the synthesis of **1** from **2**, intentionally seeking conditions under which the racemization would not proceed at each step. We report here a mild and efficient reaction condition for the construction of a chiral 5-methyl-4,5-dihydropyridazin-3(2*H*)-one from a chiral β-methyl γ-

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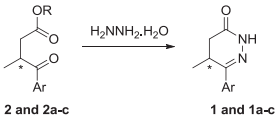
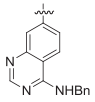
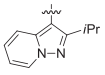
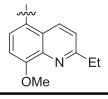
Table 1
Previous reports of asymmetric syntheses of 6-substituted 5-methyl-4,5-dihydro-3(2*H*)-pyridazinones



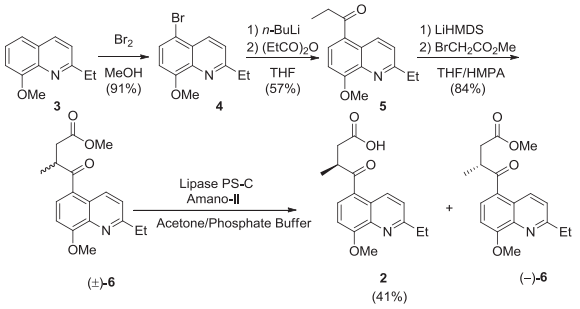
2 and 2a-c 1 and 1a-c

Entry	Substrate	Ar	R	Conditions	Result	Recrystallization
1	**2a** (86% ee) (Ref. 3)		Me	+AcOH (pH 6.5) refl. in EtOH/H_2O	**1a**, 91% (84% ee)	98% ee
2	**2b** (>99% de) (Ref. 4)		*l*-Menthyl	+AcOH ($H_2NNH_2 \cdot H_2O$/AcOH=1/2) in EtOH, rt	**1b**, 51% (>99% ee) after recrystallization	(>99% ee)
3	**2c** (90% ee) (Ref. 5)		Me	+AcOH (pH 6.5) refl. in EtOH/H_2O	**1c**, 69% (90% ee)	99.6% ee
4	**2** (96% ee)		H	80 °C in EtOH	**1**, 77% (34% ee)	Not tested
5				+AcOH (pH 6.5) 80 °C in EtOH	**1**, 68% (54% ee)	93% ee

ketocarboxylic acid via the corresponding acid hydrazide without racemization.

2. Results and discussions

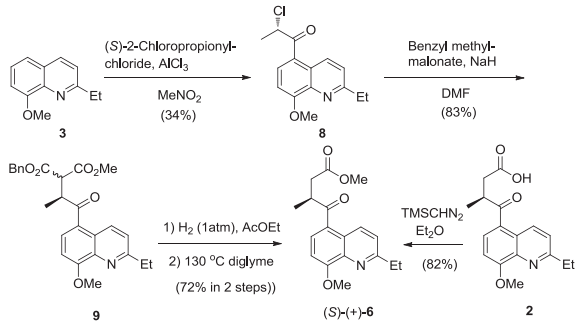
Our substrate compound **2** was prepared as follows (Scheme 1). 2-Ethyl-8-methoxyquinoline[6] (**3**) was brominated with bromine, and the resulting bromide **4** was treated with *n*-butyl lithium followed by the reaction of propionic anhydride to give a ketone **5**. Treatment of compound **5** with LiHMDS, and then with methyl bromoacetate afforded racemic γ-ketoester **6**. The racemate was hydrolyzed with lipase (lipase PS-C Amano-II) to give optically active carboxylic acid 2[7] (96% ee) in 41% yield and remaining ester (−)-6 (Scheme 2).



Scheme 1. Preparation of substrate **2**.

Toward the two-step reaction for synthesis of **1** from **2**, we planned acid hydrazidation of **2** followed by dehydrative intramolecular cyclization.

Although several methods have been reported for the preparation of acid hydrazides, surprisingly, there has been no report to prepare of acid hydrazides of γ-ketoacids to our knowledge. Therefore, we carefully examined various reaction conditions for the preparation of the acid hydrazide. The results are summarized in Table 2. We first tried one of the most general methods for the preparation of peptides, i.e., using EDC·HCl (*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride) and an equal amount of triethylamine with



Scheme 2. Determination of absolute configuration of **2**.

HOBT (1-hydroxybenzotriazole) in dichloromethane at room temperature (run 1). The corresponding acid hydrazide **7** was obtained in moderate yield, but the ee of **7** was decreased to 45% ee. Subsequent attempts using CDI (1,1′-carbonyldiimidazole) or DMTMM (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride) as other types of condensation methods were not effective for preparing the acid hydrazide of the γ-ketoacid because of the low yields (run 2, 3). On the other hand, the DCC (*N*,*N*'-dicyclohexylcarbodiimide) with HOBT method was effective for yielding **7** without racemization and in moderate yield (run 4). Furthermore, the EDC·HCl with HOBT method (without triethylamine) was more effective for preparing **7** without racemization (run 5). These results suggest that racemization proceeded easily in the presence of an excessive base.

Next we examined the dehydrative intramolecular cyclization of **7** (Table 3). We tried various kinds of acid for the reaction at room temperature. TFA, TsOH·H_2O or PPTS was effective to give **1** with almost no racemization in good yield. In the run using acetic acid, racemization was prevented but the yield was moderate. The cyclization reaction proceeded smoothly when using $KHSO_4$, but a low level of racemization occurred. On the other hand, montmorillonite K-10, and $MgSO_4$ were ineffective because there was almost no reaction using these reagents.

As described above, we succeeded in producing the chiral compound without racemization by a two-step reaction in 46% total yield (Table 2; run 5 and Table 3; run 1).

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