USE OF 1,3-DIOXIN-4-ONES AND THEIR RELATED COMPOUNDS IN SYNTHESIS. PART 35.[1] SYNTHESIS OF OPTICALLY PURE FLUOROMALONAMIC ACIDS BY MEANS OF ASYMMETRIC FLUORINATION OF CHIRAL 1,3-OXAZINE-4,6-DIONES†

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Abstruct-Fluorination of chiral 5-substituted 1,3-oxazine-4,6-dione derivatives proceeded stereoselectively to give the 5-fluorooxazinediones, which were readily transformed to optically pure fluoromalonamic acids.

Owing to their expected enhancement of biological activity, fluorinated organic compounds have attracted much attention in the field of medicinal chemistry.[2] Chiral substituted fluoromalonates are useful intermediates for construction of such compounds because of their bifunctionality and impossible racemization. However, the synthetic methods for these malonates so for reported are not satisfactory. Asymmetric hydrolysis of prochiral α-substituted α-fluoromalonate with lipase catalysis gives good results only when the α-substituent is relatively small one, such as methyl and ethyl groups.[3] Asymmetric fluorination of chiral monosubstituted

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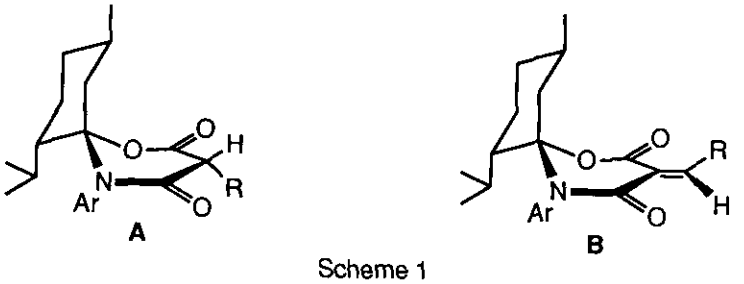
† This paper is dedicated to Emeritus Professor M. Hamana on the occasion of his 75th birthday.

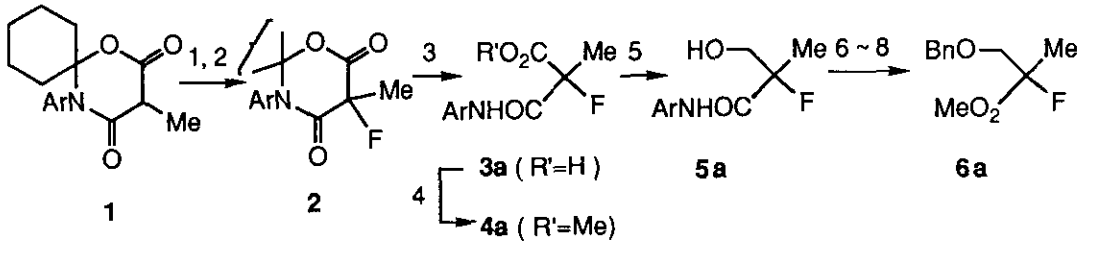
malonates results in unsatisfactory diastereo excesses (d.e.) of the products,[4] even though this method has a wider applicability to a variety of the α-substituents than enzymatic methods. We report here a general synthetic method for preparation of enantiomerically pure α-substituted α-fluoromalonamic acids and their derivatives by means of asymmetric fluorination of chiral spiro 1,3-oxazine-4,6-dione derivatives (**A**).

We have recently found a new methodology for enantiocontrol based on the characteristic conformation of six-membered heterocycles such as 1,3-dioxin-4-one,[5] 1,3-dioxane-4,6-dione,[6] and 1,3-oxazine-4,6-dione,[7] all having a spiro chiral auxiliary at the 2-position. For example, base-mediated alkylation of **A**[7a] as well as hetero-Diels-Alder reaction of **B**[7b] with electron-rich olefins proceed from the less hindered α-side with high diastereoselections.



Scheme 1

In continuation of the above line of work, our attention was focussed on fluorination of the chiral malonate equivalents (**A**). As a model study, fluorination of the oxazine

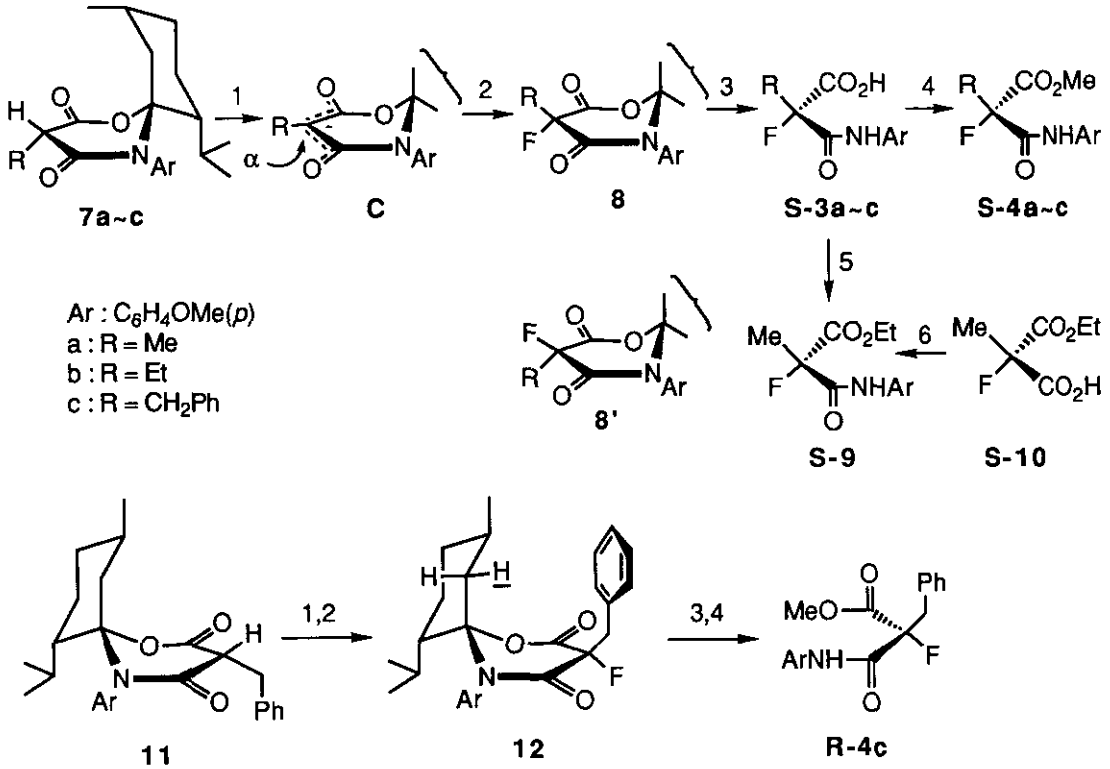


Reagents and conditions 1: NaH, DMF, 0 °C ; 2: FTT, - 78 °C ; 3: KOH, MeOH ; 4: CH_2N_2, ether (73%, overall yield from **1**) ; 5: $Ca(BH_4)_2$, MeOH (56%) ; 6: NaH, benzyl bromide, DMF ; 7: KOH, ethylene glycol, 150 °C ; 8: CH_2N_2, ether (76% from **5a**).

Scheme 2

(1)[8,9] was examined. When the sodium salt of **1** was treated with 1-fluoro-2,4,6-trimethylpyridinium triflate (FTT)[10] in THF-HMPA at -78 °C,[11] the fluorinated compound (**2**) was obtained in a quantitative yield. Compound (**2**) was readily transformed to the methyl malonamate (**4a**) *via* the acid (**3a**). On reduction with calcium borohydride, compound (**4a**) gave the alcohol (**5a**), which was converted to the ester (**6a**) by the series of the reactions shown in Scheme 2.

When the chiral 5-methyloxazinedione (**7a**)[7] was fluorinated with FTT at -78 °C, the product (a mixture of **8** and **8'**) was obtained in a high yield. Basic hydrolysis of the product gave the acid (**3a**) and *l*-menthone both in quantitative yields.



Reagents and conditions 1: NaH, DMF, 0 °C ; 2 : FTT, -78 °C ; 3 : KOH, MeOH, room temperature ; 4 : CH_2N_2, ether ; 5 : N,N'-dicyclohexylcarbodiimide, EtOH, DMAP, CH_2Cl_2, 0 °C ; 6 : N,N'-dicyclohexylcarbodiimide, *p*-anisidine, CH_2Cl_2.

Scheme 3

Methylation of **3a** gave the methyl ester (**4a:** 91% overall yield from **7a**) whose enantiomeric excess (e.e.) was determined as 89% by hplc analysis with chiral column.[12] The absolute configuration of the fluorinated product was determined as **8a** by the comparison of the specific rotation of the corresponding ethyl ester [**S-9**, $[\alpha]_D^{26}$ +4.4° (*c* 1.09, $CHCl_3$)] with that of the authentic sample [$[\alpha]_D^{24}$ +3.7° (*c* 2.12, $CHCl_3$)] obtained from the known half ester (**S-10**).[3,13]

The fluorination of ethyl and benzyl analogues (**7b, c**)[7] also proceeded with high d.e. (*ca.* 90%) as determined by hplc analysis of the corresponding methyl esters (**S-4b, c**). Due to the high diastereoselection (**8/8'**= *ca.* 20), enantiomerically pure **S-3** has become readily available, so long as it is crystalline. Thus, recrystallization of the fluorinated oxazines gave diastereomerically pure **8a** (mp 137-139 °C), **8b** (mp 125-127 °C), and **8c** (mp 137-138 °C), which afforded optically pure **S-4a** [mp 95-97 °C, $[\alpha]_D^{23}$ -8.6° (*c* 1.09)], **S-4b** [mp 85-86 °C, $[\alpha]_D^{22}$ -31.0° (*c* 1.05)], and **S-4c** [mp 130-132 °C, $[\alpha]_D^{21}$ -150.9° (*c* 1.06)][14] through the reaction sequence shown in Scheme 3.

The diastereoisomeric oxazines (e.g. **11**) also show the similar stereoselectivity in the same fluorination reactions. For example, the major product obtained from fluorination of **11** was the α-fluorooxazine (**12**). The fluorinated product was converted to the methyl ester (**R-4c**) by hydrolysis followed by methylation (overall yield, 90% from **11**). The e.e. value (67%)[15] of **R-4c** indicates that the d.e. of the fluorination was lower than that of **7c**. However, enantiomerically pure **R-4c** [mp 130-132 °C, $[\alpha]_D^{19}$ +149.4° (*c* 1.04)][14] was again prepared from pure **12** (mp 165-167 °C) which could be obtained by direct recrystallization of the fluorinated product. The stereochemistry of the fluorinated product (**12**) was assigned definitely based on the ^{1}H-nmr spectrum which showed the equatorial proton (H in formura **12**) in 6-potion of **12** at an extremely high field (broad doublet, 0.05 ppm) due to the shielding effect of the benzene ring.

In conclusion, the chiral spiro 1,3-oxazinediones were found to serve as chiral malonate equivalents and provide a general method for enantioselective synthesis of fluoromalonamates (**S-** and **R-4**) as well as the derivatives such as **5** and **6**. The high

diastereoselectivity in the fluorination associated with the ready isolation of the major diastereoisomer by recrystallization made this method very convenient for preparation of the enantiomerically pure compounds. The high diastereoselectivity is well explained, just like as in the alkylation reactions[7a] of **A** as well as in the cycloaddition reactions[7b] of **B**, by assuming the sofa conformation of the much delocalized anion **C** whose α-side is less hindered than the β-side.

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8. Compound **1** (mp 169-171 °C) was prepared by the reported method: E. Ziegler, K. Belegratis, and G. Brus, *Monatsh. Chem.*, 1967, **98**, 555.
9. All new compounds were characterized by full spectroscopic (^{1}H-nmr, ir, ms) data and elemental analyses. Yields refer to spectroscopically and chromatographically homogeneous (>98%) materials.

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11. Typical procedure for the fluorination: Compound **1** (10 mmol) was stirred with sodium hydride (11 mmol) in DMF (20 ml) at 0 °C for 10 min. FTT (11 mmol) was added to the solution at -78 °C and the whole was stirred for 2 h at the same temperature. The reaction mixture was treated with phosphate buffer solution (pH 6.8) and then extracted with ether. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to give essentially pure **2** in a quantitative yield. Chiral oxazines **7** and **12** were fluorinated similarly.

12. The e. e. was determined with Chiralcel OJ (mobile phase: hexane-isopropanol, 4 : 1) using the racemic sample **4a** as the standerd.

13. The e. e. of this sample was 89% based on hplc analysis with Chiralpak AD (mobile phase, hexane-isopropanol, 9 : 1).

14. The specific rotations of **R-** and **S-4** were determined in MeOH.

15. Chiralpak AD, mobile phase, hexane-isopropanol, 9 : 1.

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