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A Facile and Stereocontrolled Synthesis of γ-Substituted γ-Fluoroglutamates by Conjugate Addition: Conflicting Effect between Fluorinated Enaminoester and Hinderered Michael Acceptor

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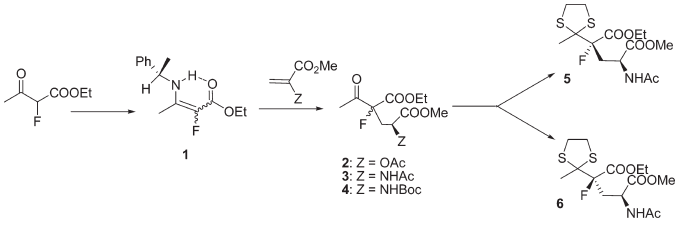

Asymmetric Michael addition of chiral 2-fluoroenaminoesters derived from (*S*)-1-phenylethylamine to α-substituted methyl acrylate leads to diastereomeric γ-substituted γ-fluoroglutamate precursors. The tertiary center bearing the amino acid function in its natural configuration is generated with a high level of stereocontrol in contrast to the quaternary carbon center. Diastereomeric γ-substituted γ-fluoroglutamates were efficiently separated and isolated as thioketal derivatives harboring very good enantioselectivity. The Michael addition diastereoselectivity was studied for the asymmetric conjugate addition of fluorinated chiral β-enaminoester to methyl α-acetamidoacrylate by ^{19}F and ^{1}H NMR experiments as well as ab initio computations. An interfering conjunction between hindrance of the electrophile and a destabilizing effect of the fluorine atom borne by the nucleophile is revealed.

Introduction

As a result of their applications in biological and medicinal chemistry, materials, enzyme mechanism studies, and asymmetric synthesis, fluoroorganic compounds draw an increasing striking interest.[1−3] The uncommon nature of fluorine, combining high electronegativity, small steric size, and low polarizability with high stability of the C−F bond,[4−6] confers a whole range of key properties to fluorinated chemicals, including modifications in physical and conformational properties, selective reactivities, enhanced binding interactions, and metabolic stability.[3,7]

These properties of the fluorine atom have been successfully exploited to elaborate potent therapeutic agents. Among the plethora of fluorinated drugs, we can mention the most famous antineoplastic agent 5-fluorouracil,[8] the antidepressant fluoxetine (Prozac),[9] and the antibacterial flurithromycin (Ritro).[3] Fluorine-containing molecules have also enjoyed widespread

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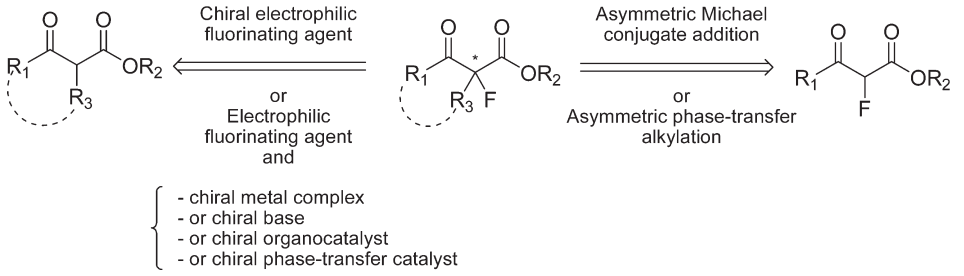
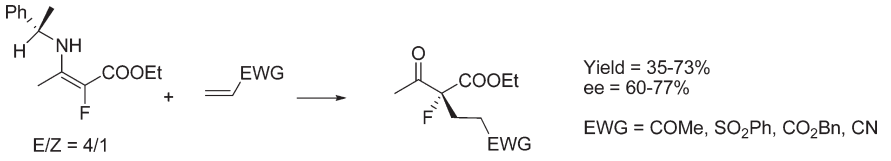
SCHEME 1. Two Main Strategies for the Synthesis of Chiral α-Alkyl-α-fluoro-β-ketoesters



SCHEME 2. Asymmetric Michael Addition of α-Fluoro-β-enaminoester to Unsubstituted Electrophilic Alkenes



applications as biological tracers or mechanistic probes such as the very well-known radiopharmaceutical 2-deoxy-2[^{18}F]fluoro-D-glucose[10] or 4-fluoro-glutamic acids,[11] respectively.

Referring to the great potential of fluorinated compounds in plentiful areas, their synthesis constitutes a challenging topic in continuing development. One of the most attractive aspects of organofluorine chemistry is the asymmetric construction of chiral fluorinated quaternary carbon centers. In this context, two main strategies have been developed: the direct fluorination strategy and the fluorinated building block strategy (Scheme 1). These two distinctive approaches have been applied to carbonyl substrates such as β-ketoesters for the construction of valuable chiral fluorinated synthons. Enantioselective electrophilic fluorination of achiral α-alkyl-β-ketoesters involves the use of a fluorinating agent associated to a chiral base or to a catalytic transition metal (Pd, Ti, Ru, Cu) chiral complex or the use of an optically active fluorinating agent.[12,13] In addition, asymmetric fluorination of α-alkyl-β-ketoesters can be achieved under phase-transfer catalysis or in the presence of a chiral organocatalyst.[12,13] Nevertheless, restricted to the synthesis of acyclic β-ketoesters, only transition-metal-catalyzed enantioselective fluorination showed a good level of enantioselectivities.[12] Alternatively, a recent advantageous approach is the challenging construction of a chiral fluorine-containing quaternary carbon by an enantioselective alkylation of racemic α-fluorinated β-ketoesters under phase-transfer conditions[14] or via an enantioselective organocatalyzed Michael reaction.[15−17] However, the latter is limited to nitroolefins as alkylating agents (Scheme 1).

We recently outlined the first stereoselective alkylation reactions of an acyclic α-fluoro-β-enaminoester using an asymmetric conjugate addition to a range of electrophilic alkenes (Scheme 2).[18] The advantage of this strategy is the ready availability of molecularly diversified chiral organofluorine compounds by the straightforward variation of the alkylating agent.

In the context of our ongoing study of the synthesis of fluorine-containing β-ketoesters, we have focused our attention on the development of a novel stereoselective access to γ-fluoro-glutamic acid. Indeed, γ-fluorinated analogues of glutamic acid are compounds of biological interest. For example, they have been used to probe the enzymatic poly-γ-glutamylation and corresponding hydrolysis of folates and antifolates and to study the role of analogous derivatives of antifolates such as methotrexate in the cytotoxic action of these drugs.[11] Their potential biological relevance has resulted in intensive synthetic demands for fluorinated glutamic acids and glutamines.[19,20]

Herein, we report the first direct access to γ-substituted γ-fluoro-glutamic acid precursors by asymmetric Michael addition. NMR analyses as well as theoretical calculations have been made in order to evaluate the combined effects of both the presence of a fluorine atom on the chiral enaminoester and the α-hindrance of the electrophilic alkenes on the stereochemical outcome.

Results

Fluoro-enaminoester **1** was prepared quantitatively by condensation between ethyl 2-fluoroacetoacetate and (*S*)-1-phenylethylamine either under refluxing azeotropic conditions[18] or at room temperature in the presence of sodium sulfate as drying agent in dichloromethane or THF. Independently of the reaction conditions (reaction temperature and nature of the solvent), the two fluoro-enaminoester isomers were obtained in a 4:1 *E*/*Z* ratio, and the major chelated *E s-cis* configuration was established in our previous work by a 2D HOESY NMR ^{1}H−^{19}F.[18] Note that the imine tautomer was never observed (Scheme 3).

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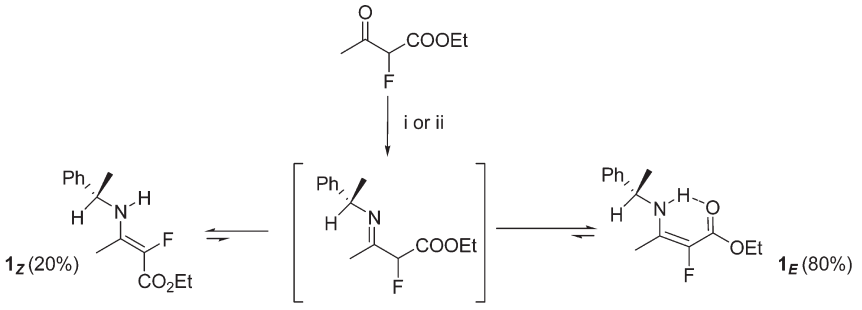
SCHEME 3. Preparation of α-Fluoro-β-enaminoester 1



SCHEME 4. Synthesis of Michael Adducts 2-4

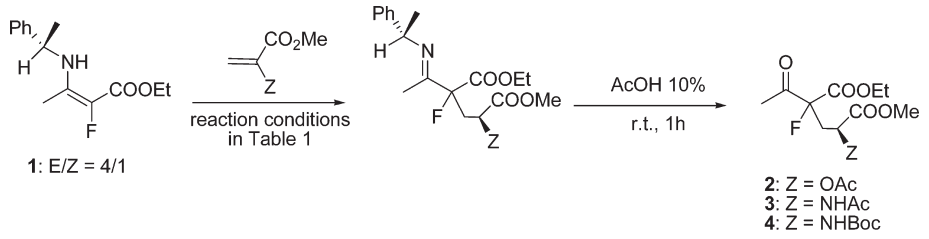


TABLE 1. Reaction Conditions, Yields, and Diastereomeric and Enantiomeric Excesses for Compounds 2−4

entry	compd	CH_2=C(Z)−CO_2Me (equiv)	reaction conditions	Lewis acid (equiv)	isolated yield (%)	ee (%)[a]	de (%)[b]
1	**2**	OAc (1.2)	THF (0.2 M) reflux, 2 days		86	>95	10
2	**3**	NHAc (1.4)	THF (0.2 M), reflux, 7 days		78	>95	15
3	**3**	NHAc (1.2)	THF (0.8 M) reflux, 3 days		60	>95	10
4	**3**	NHAc (1.4)	THF (0.2 M) reflux, 20 h	$ZnCl_2$ (0.1)	82	82	15
5	**3**	NHAc (1.4)	THF (0.2 M) reflux, 20 h	$ZnCl_2$ (1)	76	55	20
6	**3**	NHAc (1.4)	benzene (0.2 M) 66 °C, 7 days.		60	>95	15
7	**3**	NHAc (1.4)	benzene (0.1 M) μW, 150 °C, 150 W, 9 h		80	>95	15
8	**3**	NHAc (1.2)	benzene (0.5 M) μW, 150 °C, 150 W, 2 h		48	66	40
9	**3**	NHAc (1.2)	THF (0.5 M), μW 150 °C, 150 W, 2 h		59	82	40
10	**3**	NHAc (1.2)	THF (2 M), μW 150 °C, 150 W, 1 h		65	78	40
11	**3**	NHAc (1.2)	neat, μW, 150 °C 150 W, 1 h		38	70	50
12	**4**	NHBoc (1.2)	THF (0.2 M) reflux, 15 days		0		
13	**4**	NHBoc (1.2)	THF (0.2 M), reflux, 15 days	$ZnCl_2$ (1.2)	0		

[a]Determined by ^{1}H NMR with Eu(hfc)$_3$ chiral shift reagent. Equivalent ee values have been measured for both diastereomers. [b]Determined by ^{1}H NMR.

Addition of the α-fluoro-enaminoester **1** to α-substituted Michael acceptors, such as methyl α-acetoxyacrylate, methyl α-acetamidoacrylate, and methyl α-(*tert*-butyloxycarbonyl)-aminoacrylate, was carried out in various reaction conditions. The reaction was followed by ^{19}F NMR until complete consumption of the fluoroenaminoester starting material **1**. Michael adducts were obtained after hydrolytic workup (10% aqueous AcOH, room temperature, 1 h) of the intermediary imines (Scheme 4). Diastereomeric and enantiomeric excesses (de and ee) were both determined by ^{1}H NMR experiments. Enantiomeric excesses were determined using Eu(hfc)$_3$ as chiral shift agent. Results are summarized in Table 1.

Under thermal activation (entries 1, 2, 3, and 6), alkylated α-fluoro β-ketoesters **2** and **3** were isolated in 60−86% yield, but a relatively long reaction time of 2−7 days was necessary; ee values were excellent (>95%) (see Figure 1 in the Supporting Information). Surprisingly, de values were disappointing (around 10−20%) (see Figure 1 in the Supporting Information) compared to the excellent excesses obtained starting from the α-methylated enaminoester analogue.[21] These results suggest that the presence of a fluorine atom instead of a methyl group disfavors the concomitant control of the two stereogenic carbon centers. Moreover, compared to the excellent results obtained in the reaction between α-fluoro enaminoester and unsubstituted electrophilic olefins,[18] this dramatic drop of diastereoselectivity could find an explanation not only in the presence of a fluorine atom on the nucleophilic imine but also in the α-substitution of the Michael acceptor.

Replacement of THF as the solvent by the noncoordinating benzene modified neither efficiency nor stereoselectivities (entries 2 and 6). As expected in the asymmetric Michael conjugate addition, reaction time was shortened using more concentrated reactive medium without affecting either rate or selectivities (entries 2 and 3).

As the Michael addition reaction needed a prolonged time under thermal conditions to afford the adduct **3** in reasonable yields, we have investigated the effect of activation

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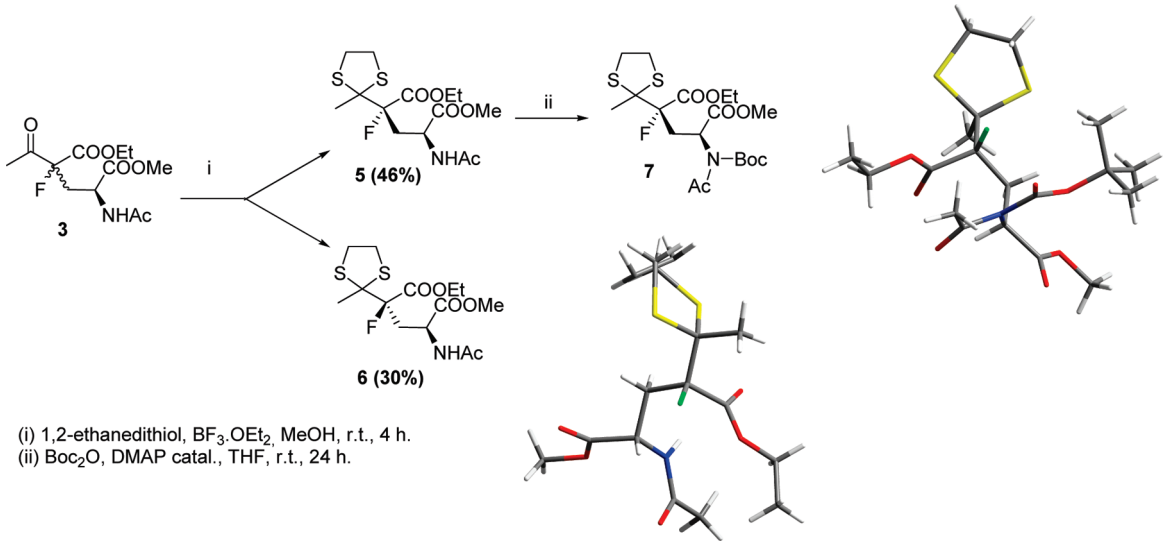
SCHEME 5. Thioketalization of Adduct 3 and X-ray Crystal Structures of Compounds 6 and 7



agents such as a Lewis acid and microwave irradiation. As expected, the presence of $ZnCl_2$ made a positive contribution to the reaction duration. Unfortunately, its use had no beneficial effect on the stereoselectivity and furthermore caused erosion of enantioselectivity (entries 4 and 5 vs entry 2) with only 55% ee when the Lewis acid was added in a stoichiometric amount (entry 5). Otherwise, in a similar reaction dilution, microwave irradiation improved reaction time without upsetting either ee or de (entry 7). The microwave irradiation associated with the increase of the reaction concentration allowed a notable reduction in reaction time combined with an enhancement of the diastereoselectivity. Regrettably, we observed a concomitant loss of both enantioselectivity and yield (entries 8, 9, 10 vs entry 7). To recapitulate, the results were concentration-dependent (diluted to neat) but independent of the solvent (polar vs aprotic apolar one) (entries 7−11); these observations were in accordance with what was commonly observed in asymmetric Michael reaction involving an "aza-ene-synthesis-like" transition state.[22]

In parallel, in order to investigate the impact of the Michael acceptor steric hindrance on stereoselectivity, the Boc-protected Michael acceptor has been engaged in the conjugate addition. Nevetherless, replacement of the acetamido moiety by Boc protective group has dramatic consequences: Michael adduct **4** was never observed whatever the reaction conditions used (entries 12 and 13). Steric hindrance by the Boc protective group may disfavor the Michael acceptor's approach to the fluoroenaminoester **1**.

Gratifyingly, the thioketalization by 1,2-ethanedithiol of the diastereomic mixture of **3** allowed efficient separation of the thioketal diastereomers **5** and **6** by flash chromatography on silica gel (Scheme 5). Same strategy has been applied starting from compound **2**, but unfortunately, the resultant thioketal diastereomers could not be separated. Only the minor diastereomer **6** crystallized in a satisfying manner authorizing the direct determination of its absolute configuration by means of a single-crystal X-ray analysis, on the basis of the anomalous diffusion of the sulfur atom.[23,24] For the major diastereomer **5**, a prior *N*-Boc-protection into derivative **7** was crucial to realize X-ray structure elucidation (Scheme 5). The assignments of the (2*R*,4*S*) and (2*S*,4*S*) absolute configurations of the respective compounds **6** and **5** (through its Boc derivative **7**) led us to elucidate that only the tertiary carbon center was stereocontrolled in compound **3**. Because of the similar results obtained in the synthesis of compound **2**, assignments of the absolute configurations of compounds **6** and **5** can be transposed to compound **2**.

In summary, α-substitution of the acrylate partner combined with the presence of a fluorine atom on the chiral enaminoester α-position has a dramatic effect on the stereocontrol of the Michael adduct quaternary center. In our previous work implying an unsubstituted Michael acceptor, we have proposed that the mechanism operated through a highly ordered transition state only in the case of the *E* enaminoester diastereomer.[18] Nevertheless, excellent stereocontrol of the tertiary carbon center contradicts this hypothesis and could be justified by the more or less concerted proton transfer of the enaminoester to the acrylate α-carbon center in a highly ordered transition state not only in *E* enaminoester diastereomer but also in the *Z* one (Scheme 6).[25] Indeed, according to the adopted "aza-ene-synthesis-like" mechanism, the 4*S* absolute configuration of this tertiary carbon center can be justified by a "*syn*-periplanar" approach of the two reactants on the less hindered π-face of each enaminoester diastereoisomer with the "*endo*-arrangement" of the acrylate ester group (Scheme 6).

Nevertheless, this proposal does not explain the weak control of the Michael adduct quarternary center because the expected de should be roughly of 60%. In an attempt of understanding the origin of this lack of selectivity in Michael adducts formation, NMR experiments and theoretical calculations have been conducted.

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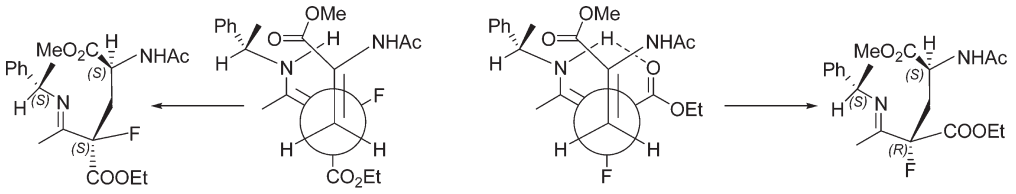
SCHEME 6



NMR Experiments

Conjugate addition of fluoro-enaminoester **1** to a slight excess of methyl α-acetamidoacrylate was carried out at 60 °C in benzene-d_6, and the reaction was monitored periodically by ^{1}H and ^{19}F{^{1}H} NMR spectroscopy. ^{1}H and ^{19}F{^{1}H} NMR spectra revealed that reaction began after 1 day of warming at 60 °C. After a prolonged heating of 9 days, chiral enaminoester **1** was completely consumed, as indicated by the absence of its characteristic signals by ^{1}H and ^{19}F{^{1}H} NMR spectroscopy. ^{19}F{^{1}H} NMR spectra for this sample showed that the *E* enaminoester isomer (δ −178,7 ppm; see Figure 2 in the Supporting Information) was consumed faster than the *Z* one (δ −163,8 ppm; see Figure 2 in the Supporting Information). In the same time, expected diastereomeric Michael adducts were formed as the major species together with several unidentified minor species. No effort was made to identify other unknown ^{19}F-containing products.

Appearance of the proton resonances of the two diastereomeric imine intermediates at δ 0.83 and 0.98 (triplet, CH_3 of the ethyl ester moiety) and at δ 1.27 and 1.36 (doublet, CH_3 of chiral inductor) were observed at an equal intensity concomitantly with disappearance of the corresponding signals of fluoroenaminoester **1** at δ 1.07 (t) and 1.15 (d) (see Figures 3 and 4 in the Supporting Information). These results indicated that both diastereomers were simultaneously formed and proved that the poor de values were not a result of epimerization of the Michael adduct during acidic hydrolysis step.

Comparatively, we have previously shown that conjugate addition of chiral α-fluoro enaminoester **1** to unsubstituted electrophilic alkenes gave the corresponding Michael adducts with fairly good enantioselectivities in more shortened reaction times than those required for an α-substituted acceptor (approximately 1 day versus 7 days, respectively).[18] That is why reaction of fluoroenaminoester **1** to benzylacrylate was reexamined under the same thermal condition reaction as those employed for the α-substituted acceptor. Interestingly, neither rate nor enantioselectivity were affected after 7 days in refluxing THF and were similar to those previously described.[18] According to this result, epimerization of the quaternary center, which might be favored by heating the fluorinated imine adduct under prolonged reaction time, can be excluded. It is, therefore, abundantly clear that electrophilic acceptor α-substitution decreases the conjugate addition kinetic.

In parallel, tautomerization of the chiral enaminoester **1** was studied by ^{19}F NMR experiments. At 60 °C, in benzene-d_6, ^{19}F NMR spectra showed that the *E*/*Z* ratio was stable even after 7 days of heating. In addition, ^{19}F NMR experiment was carried out in DMSO-d_6 at variable temperature over the range of 25−150 °C (see Figure 5 in the Supporting Information). At 110 °C, the isomeric enamines proportions began to equilibrate, furnishing an irreversible and stable 55:45 *E*:*Z* ratio without detecting an imine intermediate (see Figure 6 in the Supporting Information). Moreover, when the similar ^{19}F NMR experiment was performed in the presence of a slight excess of electrophilic alkene (1.2 equiv) in a 0.2 M DMSO-d_6 solution, the equilibrating temperature fell to 60 °C also without detection of an imine intermediate (see Figure 7 in the Supporting Information). In these conditions, the stable 55:45 *E*:*Z* ratio is obtained at 70 °C. At this temperature, we can also observe the formation of imine adducts. This NMR-measured *E*:*Z* ratio is in accordance with de measurements of the slow thermally activated Michael addition (Table 1; entries 1−7). These monitored ^{19}F NMR experiments show that the electrophilic alkene facilitates the enaminoesters' equilibration. Under piezoprocess activation, the conjugate addition reaction could be accelerated at the expense of the thermodynamic equilibrium of enamines justifying the best de obtained (entries 8−11). In these attempts, the erosion of ee can be explained by the destabilization of the intramolecular hydrogen bonding in the chelate β-enaminoester not only by the presence of the fluorine atom but also by the drastic heating.

It is manifest that the stereochemical outcomes can be interpreted by the combined destabilizing effects of (1) the disfavored steric interaction between the acetamido substituent of the acceptor and the ester group of the enamine in the compact approach and (2) the destabilizing electron-withdrawing effect of the fluorine atom in the chelate β-enaminoester (Scheme 7). Only kinetic control of the asymmetric conjugate addition can give an explanation of the reported diastereoselectivities. Indeed, the steric interaction of the acetamido group of the electrophilic olefin is more unfavorable with the ester substituent of the enamine (**TS1**, Scheme 7) than with the fluorine one (**TS2**, Scheme 7), implying that the asymmetric conjugate addition of the fluoro-enaminoester nucleophile $\mathbf{1}_{\boldsymbol{Z}}$ is more rapid than one of the diastereomer $\mathbf{1}_{\boldsymbol{E}}$ ($k_2 > k_1$, Scheme 7). In the same time, the 60 °C requisite reaction temperature authorizes the *E*/*Z* interconversion.

To validate this hypothesis of kinetic control ab initio calculations have been done.

Theoretical Calculations

Geometry optimizations of the diastereomeric (*R*)-fluoro-enaminoesters reactants as well as the corresponding transition states were performed with the Hartree−Fock (HF), HF/6-311G(d,p) basis set[26−28] using the Gaussian 03

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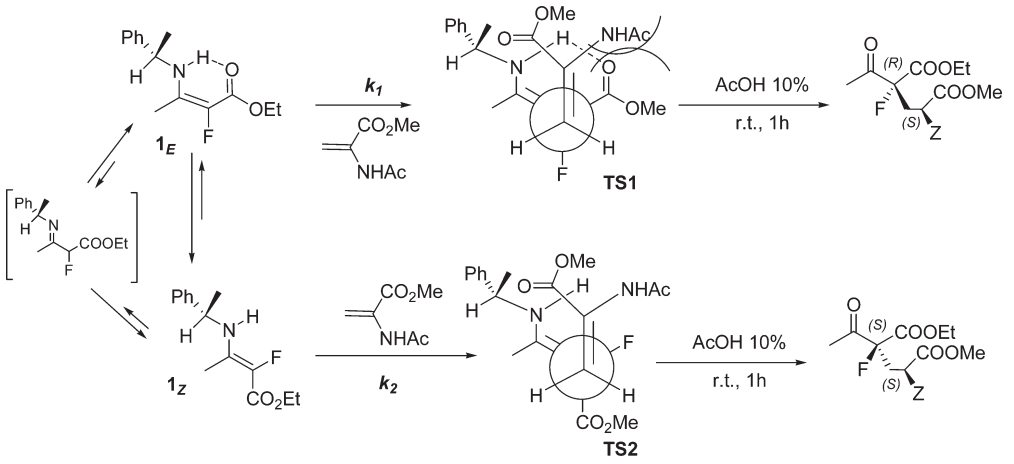
SCHEME 7. Kinetic Control Hypothesis of Asymmetric Michael Addition of Fluoro-enaminoester 1 to Methyl α-Acetamidoacrylate



program.[29] Force calculations were carried out to ensure that each transition structure had one negative eigenvalue in the Hessian matrix as required.

The experimental results have shown that the stereocontrol of the tertiary center can be justified by a cyclic transition state invoking (1) the attack on the less hindered face of the chiral fluoroenaminoester, (2) the *endo*-approach in which the ester group of the acceptor faced the nitrogen atom of the enamine partner to the fluoroenaminoester, and (3) the internal concerted transfer of the hydrogen borne by the chiral enaminoester nitrogen. Moreover, NMR study performed in DMSO at various temperature conditions put in evidence the possible and irreversible isomeric fluoro-enaminoester equilibrium. The transition structures for the calculations have been built taking into account these experimental data. Note that the calculations have been done starting from the fluoroenaminoester *R* enantiomer.

Calculations revealed that for the fluoroenaminoester, the *E* configuration is preferred by 2.23 kcal/mol over the *Z* one: this result confirms that internal hydrogen bonding between the H atom of the amino group and the oxygen of the carboxyl ester function stabilizes the chelate β-enaminoester *E*. This difference between the enthalpies of formation justifies the experimentally observed *E:Z* ratio. In both diastereomeric enaminoesters, the methyl group, borne by the chiral carbon (C*) of the *R* configuration, is practically in the plane of the enamine while the H atom is located in one face and the phenyl group hinders the opposite face, creating a facial discrimination (Table 2).

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Transition Structures

The related six-membered "aza-ene-synthesis-like" transition state structures were built with the *endo* approach of the acetamidoacrylate ester group to (*R*)-fluoro-enaminoester. Analysis of their energies and their geometries revealed that, in the case of the *E* isomer, the most stable transition state corresponds to the approach of methyl acetamidoacrylate on the *re* π-face of the *E* enaminoster, which adopts a conformation where the phenyl dihedral angle θ is nearly equal to 76° (Figure 1). This dihedral angle θ is comparable to its most stable position 67° (close to the corresponding angle value found in the crystal structure of enaminoester, 72°).[30] Conversely, when methyl acetamidoacrylate is approaching the *si* π-face, the *E* enaminoester adopts a conformation where the phenyl dihedral angle θ is about 166° (Figure 1). In the *si* π-face, hence, for minimizing steric effects, the phenyl group is pushed away from its most stable position at 67°. This observation explains the difference of the enthalpies of formation (4.0 kcal/mol) of the two possible transition states *SR* and *RS* (Table 3).

The same analysis applied to the transition structures involving the *Z*-(*R*)-fluoroenaminoester put in evidence that the most stable transition state *RR* corresponds to an approach of the methyl acetamidoacrylate on the *Si* π-face of the *Z* enaminoester. The later adopts a conformation where the phenyl dihedral angle θ is roughly equal to 77° (Figure 1). This dihedral angle θ is comparable to its most stable position at 66°. In opposition, when the methyl acetamidoacrylate is approaching by the *re* π-face, the fluoroenaminoester *Z* adopts a conformation where the phenyl dihedral angle θ is about 163°. In the *re* π-face, hence, for minimizing steric effects, the phenyl group is pushed away from its most stable position at 66°, justifying the difference of the enthalpies of formation (2.0 kcal/mol) of the two possible transition states *RR* and *SS* from the enaminoester *Z* (Table 3).

The computational data gathered in Table 3 allow several conclusions with regard to experimental observations. In all cases, the lowest energy for the transition states *SR* and *RR* show that the alkylation is thermodynamically favored on the less hindered π-face, *anti* to the bulky phenyl substituent

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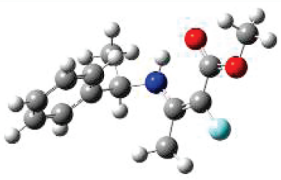
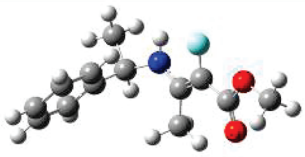
TABLE 2. Parameters for the Low Energy (*R*)-Fluoroenaminoester Conformers

	(*R*)-Fluoroenaminoester *E*	(*R*)-Fluoroenaminoester *Z*
		
Ph-C*-N-$C_{(3)}$ dihedral angle	67°2	66°0
Me-C*-N-$C_{(3)}$ dihedral angle	-168°9	-170°0
H-C*-N-$C_{(3)}$ dihedral angle	-52°7	-53°9
ΔΔH in kcal/mol	0.	2.23

of the chiral amine group. This explains and confirms the experimentally observed stereochemistries of the concomitantly created tertiary and quaternary carbon centers starting from the *E* and *Z* isomeric fluoroenaminoesters independently. In this context, the populations of the Michael adducts can only be affected by the respective population of the *E* and *Z* fluoroenaminoester isomers. Moreover, compared to other already studied enaminoesters, presence of the fluorine atom weakens stabilizing intramolecular hydrogen bonding and favors isomeric fluoroenaminoester equilibrium, the existence of which has been demonstrated by NMR studies. Consequently, the relative population of the two Michel adducts can be interpreted as an interplay of steric, electronic, and kinetic factors.

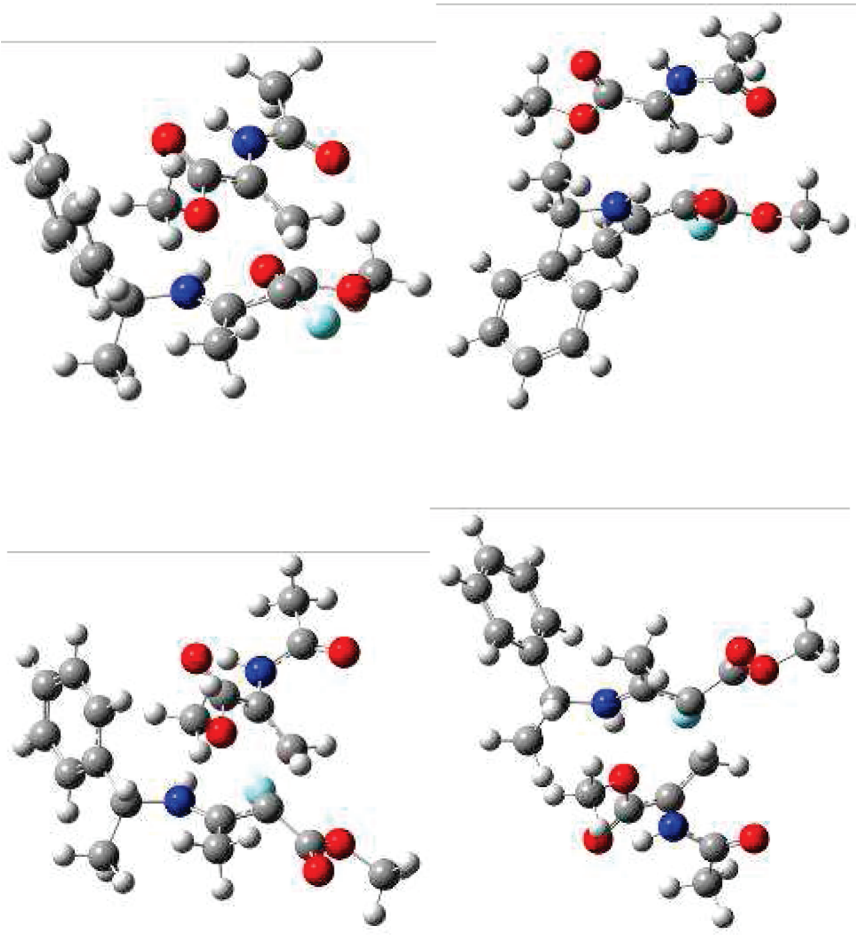


FIGURE 1. Ab initio optimized transition state geometries for (*R*)-fluoroenaminoester *E* and methyl acetamidoacrylate: (top left) *RS* transition state/disfavored hindered *si*-approach; (top right) *SR* transition state/favored *re*-approach; (bottom left) *SS* transition state/disfavored hindered *re*-approach; (bottom right) *RR* transition state/favored *si*-approach.

TABLE 3. Difference of Formation Enthalpies of Transition States for Addition of Isomeric (*R*)-Fluoroenaminoesters to Methyl Acetamidoacrylate

	(*R*)-Fluoroenaminoester *E*		(*R*)-Fluoroenaminoester *Z*	
	si-face *RS*	*re*-face *SR* (expected major)	*re*-face *SS*	*si*-face *RR* (expected minor)
Φ−C*−N−C dihedral angle	165°5	75°8	163°3	76°7
Me−C*−N−C dihedral angle	−69°6	−160°5	−71°1	−159°2
H−C*−N−C dihedral angle	49°8	−44°1	48°0	−43°2
ΔΔ*H* in kcal/mol	4.0	0	1.96	0

Conclusion

Through this work, we have reported a step-economical and efficient access to γ-substituted γ-fluoro-glutamic acid precursors by asymmetric Michael addition. A very high level of stereocontrol of the tertiary center bearing the amino-acid function in its natural configuration was obtained. The NMR studies as well as ab initio calculations have shown that the absence of stereocontrol of the quaternary carbon center is due to the interfering conjunction of the hindered α-substitution of the electrophilic alkene combined to the destabilizing effect of the electronegative fluorine atom borne by the nucleophilic enaminoester. The presence of the fluorine atom favors the diastereomeric *E*:*Z* equilibrium by destabilization of the hydrogen bonding in the chelate enaminoester. The formation of both diastereomeric glutamate precursors is attributed to kinetic control of the asymmetric Michael addition starting from the diastereomeric fluoroenaminoesters. The lack of diastereocontrol has been elegantly circumvented by the straightforward separation and isolation of both diastereo- and enantiopure spirothioketal diastereomeric derivatives. This synthetic pathway offers a direct access to each γ-substituted γ-fluoroglutamate diastereomer, which is of great interest for structure−activity relationships studies.

Experimental Section

Commercial reagents were used without purification. Fluoroenaminoester **1**, methyl acetoxyacrylate, methyl (*tert*-butyloxycarbonyl)aminoacrylate, and methyl acetamidoacrylate were synthesized according classical procedures.[18,31,32] Prior to use, THF was freshly distilled from sodium−benzophenone and toluene from CaH_2. All anhydrous reactions were carried out under an argon atmosphere. Microwave experiments were carried out in a CEM Discover Labmate microwave oven using 10-mL pressurized vials. Analytical thin layer chromatography was performed using glass plates precoated with silica gel 40 F_{254} purchased from a supplier and was revealed by UV light or Kägi-Misher reagent. All flash chromatography separations were performed on silica gel (40−63 μm). Melting points were recorded on a melting point apparatus (Dr Totoli) and are uncorrected. Infrared (IR) spectra were obtained as neat films. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded at 400, 188 and 100 MHz, respectively, unless otherwise specified. $CDCl_3$ was used as internal reference. NMR peak assignments have been made on the basis of HMBC, HMQC, NOESY, and ^{1}H−^{1}H COSY spectra. Specific rotations $[\alpha]^{20}_D$ were measured with a sodium (589 nm) lamp at 20 °C in a 1-dm cell. Diastereomeric excesses (de) were evaluated by ^{1}H NMR spectroscopy. Enantiomeric excesses (ee) were evaluated by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as chiral shift reagent.

General Procedure for the Michael Reaction between Enaminoester 1 and α-substituted Electrophilic Alkenes. To a solution of compound **1** (1 equiv) in THF (0.2 M) were added dropwise, under inert atmosphere, a catalytic amount of hydroquinone and a solution of electrophilic alkene (1.4 equiv) in a minimum of THF. After the mixture was stirred at reflux (evolution reaction was monitored by ^{19}F NMR) and was cooled, a solution of 10% AcOH was added. After further stirring at room temperature for 1 h, THF was evaporated, and the aqueous layer was extracted 3 times with dichloromethane. The organic layers were then combined, washed with 1 M HCl and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (cyclohexane/EtOAc, 3/7) to yield the desired compound.

(2*R*,4*S*)- and (2*S*,4*S*)-1-Ethyl-5-methyl 2-Acetyl-4-acetyloxy-2-fluoro-pentanedioate (2). Yellowish oil (86% yield); ee > 95%; de = 10%; R_f 0.60 (cyclohexane/EtOAc 5/5); ^{1}H NMR ($CDCl_3$, 300 MHz) M/m 55/45 δ 1.31 (t, ^3J = 7.2 Hz, 3H, COOCH$_2$*CH*$_3$), 2.07 + 2.08 (2s, 3H, *CH*$_3$COO M + m), 2.31 (d, ^4J_F = 4.8 Hz, 3H, *CH*$_3$CO M), 2.35 (d, ^4J_F = 4.8 Hz, 3H, *CH*$_3$CO m), 2.70−2.90 (m, 2H, CH$_2$), 3.76 (s, 3H, COOCH$_3$), 4.27 + 4.28 (2q, ^3J = 7.2 Hz, 2H, COO*CH*$_2$CH$_3$ m + M), 5.10−5.30 (m, 1H, CH); ^{19}F NMR ($CDCl_3$) δ −166.28 (M), −166.31 (m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.88 (COOCH$_2$*C*H$_3$), 20.25 (*C*H$_3$CO), 25.26 (*C*H$_3$CO), 34.48 + 34.62 (d, ^2J_F = 20.3 Hz, *C*H$_2$ M + m), 52.63 (COO*CH*$_3$), 62.84 + 63.02 (COO*C*H$_2$CH$_3$ m + M), 66.94 + 67.35 (CH M + m), 97.14 + 97.47 (d, ^1J_F = 200 Hz, *C*qF M + m), 165.20 + 165.52 (d, ^2J_F = 24.8 Hz, *C*OOEt M + m), 169.25 (COOMe), 169.47 (O*C*OCH$_3$), 200.69 + 201.10 (d, ^2J_F = 28.5 Hz, *C*O M + m); IR (cm^{-1}) ν max 2959, 1748, 1438, 1372, 1283, 1214, 1149, 1091, 1014. Anal. Calcd for $C_{12}H_{17}FO_7$ C, 49.32; H, 5.86. Found: C, 49.79; H, 6.09.

(2*R*,4*S*)- and (2*S*,4*S*)-1-Ethyl-5-methyl 2-Acetyl-4-acetylamino-2-fluoro-pentanedioate (3). Yellowish oil (80% yield); ee > 95%; de = 15%; R_f 0.25 (cyclohexane/EtOAc 5/5); ^{1}H NMR ($CDCl_3$) M/m 6/4 δ 1.25 + 1.26 (2t, ^3J = 7.1 Hz, 3H, COOCH$_2$*CH*$_3$ m + M), 1.93 (s, 3H, *CH*$_3$CONH m + M), 2.25 (d, ^4J_F = 5.1 Hz, 3H, *CH*$_3$CO M), 2.27 (d, ^4J_F = 4.8 Hz, 3H, *CH*$_3$CO m), 2.50−2.80 (m, 2H, CH$_2$ m + M), 3.68 + 3.69 (2s, 3H, COOCH$_3$ m + M), 4.20 (q, ^3J = 7.1 Hz, 2H, COO*CH*$_2$CH$_3$ m + M), 4.69 (m, 1H, CH m), 4.76 (m, 1H, CH M), 6.30 (d, ^3J = 8.1 Hz, 1H, CONH M), 6.42 (d, ^3J = 8.1 Hz, 1H, CONH m); ^{19}F NMR ($CDCl_3$) δ −164.90 (M), −164.94 (m); ^{13}C NMR ($CDCl_3$) δ 13.71 + 13.81 (COOCH$_2$*C*H$_3$ m + M), 22.64 (NHCO*CH*$_3$ m + M), 25.14 + 25.24 (*C*H$_3$CO m + M), 34.95 (d, ^2J_F = 20.7 Hz, *C*H$_2$ M + m), 47.63 (d, ^3J_F = 2.4 Hz, CH m + M), 52.52 (COO*CH*$_3$ m), 52.55 (COO*CH*$_3$ M), 62.94 (COO*C*H$_2$CH$_3$ m + M), 98.19 (d, ^1J_F = 188 Hz, *C*qF m), 98.20 (d, ^1J_F = 210 Hz, *C*qF M), 165.37 (d, ^2J_F = 25.2 Hz, *C*OOEt M), 165.49 (d, ^2J_F = 25.1 Hz, *C*OOEt m), 169.93 (CONH m), 170.06 (CONH M), 171.47 (COOMe M), 171.54 (COOMe m), 200.93 (d, ^2J_F = 28.6 Hz, *C*O M), 201.62 (d, ^2J_F = 28.9 Hz, *C*O m); IR (cm^{-1}) ν max 3288, 2957, 1735, 1660, 1535, 1436, 1371, 1232, 1146, 1080. Anal. Calcd for $C_{12}H_{18}FNO_6$ C, 49.48; H, 6.23; N, 4.81. Found: C, 49.35; H, 6.40; N, 4.75.

Thioketalization of Compound 3. To a solution of compound **3** (500 mg, 1.7 mmol, 1 equiv) in anhydrous MeOH (5 mL) were added dropwise, under inert atmosphere, at 0 °C, 1,2-ethanedithiol (750 μL, 8.1 mmol, 4.5 equiv) and BF_3 etherate (1.7 mL). After the mixture was stirred at room temperature for 4 h, MeOH was evaporated, and the residue was dissolved in EtOAc. The organic layer was then washed with 5% NaOH and brine, dried over Na_2SO_4, filtered, and concentrated. The residue required two successive purifications by column chromatography (cyclohexane/EtOAc 5/5) to yield separately the two desired diastereomers **5** and **6**.

(2*S*,4*S*)-1-Ethyl-5-methyl 4-Acetylamino-2-fluoro-2-(2-methyl-[1,3]dithiolan-2-yl)-pentanedioate (5). White solid (46% yield); ee > 95%; de > 95%; R_f 0.17 (cyclohexane/EtOAc 5/5); mp = 95−98 °C;

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(32) Yokoyama, Y.; Takahashi, M.; Takashima, M.; Kohno, Y.; Kobayashi, H.; Kataoka, K.; Shidori, K.; Murakami, Y. *Chem. Pharm. Bull.* **1994**, *42*, 832–838.

^{1}H NMR ($CDCl_3$) δ 1.33 (t, ^3J = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.81 (s, 3H, CH_3CS_2), 1.97 (s, 3H, CH_3CONH), 2.80−2.90 (m, 1H, 1/2 CH_2), 2.95−3.10 (m, 1H, 1/2 CH_2), 3.33 (s, 4H, $S(CH_2)_2S$), 3.76 (s, 3H, $COOCH_3$), 4.25 (m, 2H, $COOCH_2CH_3$), 4.66 (m, 1H, CH), 6.15 (d, ^3J = 6.3 Hz, 1H, CONH); ^{19}F NMR ($CDCl_3$) δ −153.95; ^{13}C NMR ($CDCl_3$) δ 13.99 ($COOCH_2CH_3$), 22.90 ($NHCOCH_3$), 28.97 (CH_3CS_2), 35.90 (d, ^2J_F = 19.4 Hz, CH_2CH), 40.20 + 40.72 (SCH_2CH_2S), 49.13 (*C*H), 52.54 ($COOCH_3$), 62.27 ($COOCH_2CH_3$), 70.98 (d, ^3J_F = 22.3 Hz, CH_3CS_2), 100.98 (d, ^1J_F = 196.8 Hz, *Cq*F), 168.94 (d, ^2J_F = 27.2 Hz, *C*OOEt), 169.68 ($NHCOCH_3$), 171.68 (*C*OOMe); IR (cm^{-1}) ν max 3292, 2928, 1745, 1213; $[\alpha]^{20}_D$ = +47 (*c* 0.52 in CH_2Cl_2). Anal. Calcd for $C_{14}H_{22}FNO_5S_2 \cdot H_2O$: C, 43.62; H, 6.28; N, 3.63. Found: C, 43.51; H, 6.18; N, 3.52.

(2*R*,4*S*)-1-Ethyl-5-methyl 4-Acetylamino-2-fluoro-2-(2-methyl-[1,3]dithiolan-2-yl)-pentanedioate (6). White solid (30% yield); ee > 95%; de > 95%; R_f 0.13 (cyclohexane/EtOAc 5/5); mp = 92−96 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, ^3J = 7.3 Hz, 3H, $COOCH_2CH_3$), 1.77 (s, 3H, CH_3CS_2), 1.91 (s, 3H, CH_3CONH), 2.65−2.80 (m, 2H, CH_2), 3.29 (s, 4H, $S(CH_2)_2S$), 3.66 (s, 3H, $COOCH_3$), 4.21 + 4.23 (2q, ^3J = 7.2 Hz, 2H, $COOCH_2CH_3$), 4.68 (m, 1H, CH), 6.17 (d, ^3J = 8.6 Hz, 1H, CONH); ^{19}F NMR ($CDCl_3$) δ −156.20; ^{13}C NMR ($CDCl_3$) δ 13.83 ($COOCH_2CH_3$), 22.75 ($NHCOCH_3$), 28.67 (CH_3CS_2), 36.18 (d, ^2J_F = 21.0 Hz, CH_2CH), 40.11+40.64 (SCH_2CH_2S), 48.18 (d, ^3J_F = 5.2 Hz, *C*H), 52.38 ($COOCH_3$), 62.11 ($COOCH_2CH_3$), 71.05 (d, ^3J_F = 22.3 Hz, CH_3CS_2), 100.01 (d, ^1J_F = 199.5 Hz, *Cq*F), 169.22 (d, ^2J_F = 26.6 Hz, *C*OOEt), 169.73 (*C*OOMe), 171.68 ($NHCOCH_3$); IR (cm^{-1}) ν max 3276, 2929, 2359, 1735, 1223; $[\alpha]^{20}_D$ = +14 (*c* 0.51 in CH_2Cl_2). Anal. Calcd for $C_{14}H_{22}FNO_5S_2 \cdot H_2O$: C, 43.62; H, 6.28; N, 3.63. Found: C, 43.79; H, 6.15; N, 3.42.

(2*S*,4*S*)-1-Ethyl-5-methyl 4-(*N*-Acetyl-*N*-*tert*-butyloxycarbonyl-amino)-2-fluoro-2-(2-methyl-[1,3]dithiolan-2-yl)-pentanedioate (7). A solution of compound **5** (300 mg, 0.81 mmol, 1 equiv) in dry THF (8 mL) was treated with di-*tert*-butyldicarbonate (800 mg, 3.6 mmol, 4.5 equiv) and a catalytic amount of DMAP and stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo, and the residue was taken in dichloromethane (10 mL) and washed extensively with aqueous 1 M HCl (2 × 15 mL). The organic layer was dried over magnesium sulfate, filtered, concentrated in vacuo, and then purified by column chromatography (cyclohexane/EtOAc 85/15) to yield the desired product **7** as a white solid (270 mg, 71%); ee > 95%; de > 95%; R_f 0.57 (cyclohexane/EtOAc 6.5/3.5); mp = 63−70 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.33 (t, ^3J = 7.0 Hz, 3H, $COOCH_2CH_3$), 1.50 (s, 9H, $(CH_3)_3$), 1.85 (s, 3H, CH_3CS_2), 2.51 (s, 3H, CH_3CONH), 2.93−3.28 (m, 2H, CH_2), 3.33 (s, 4H, $S(CH_2)_2S$), 3.68 (s, 3H, $COOCH_3$), 4.18−4.33 (m, 2H, $COOCH_2CH_3$), 5.53 (m, 1H, CH); ^{19}F NMR ($CDCl_3$, 400 MHz) δ −158.57; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.97 ($COOCH_2CH_3$), 26.51 ($NCOCH_3$), 27.84 ($(CH_3)_3$), 29.24 (CH_3CS_2), 34.10 (d, ^2J_F = 18.9 Hz, CH_2CH), 40.34 + 40.86 (SCH_2CH_2S), 51.40 (*C*H), 52.44 ($COOCH_3$), 62.41 ($COOCH_2CH_3$), 71.33 (d, ^3J_F = 22.6 Hz, CH_3CS_2), 83.93 ($C(CH_3)_3$), 101.35 (d, ^1J_F = 197.6 Hz, *Cq*F), 151.71 (*C*OO*t*-Bu), 168.45 (d, ^2J_F = 25.8 Hz, *C*OOEt), 170.56 (*C*OOMe), 172.83 ($NCOCH_3$); IR (cm^{-1}) ν max 2978, 2930, 1737, 1702, 1369; $[\alpha]^{20}_D$ = −20 (*c* 2.1 in CH_2Cl_2). Anal. Calcd for $C_{19}H_{30}FNO_7S_2$: C, 48.81; H, 6.47; N, 3.00. Found: C, 48.91; H, 6.17; N, 2.88.

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Supporting Information Available: X-ray analysis and crystallographic information files in CIF format of compounds **6** and **7**; ^{1}H, ^{19}F, and ^{13}C NMR spectra of the new compounds **2**, **3**, **5**, **6**, and **7**; molecular modeling coordinates for enaminoesters **1*Z*** and **1*E*** as well as for the four transition states. This material is available free of charge via the Internet at http://pubs.acs.org.