Stereoselective Synthesis of Trifluoromethylated Compounds with Controlled Adjacent Tertiary Carbons by Michael Addition to (*E*)-3-(Trifluoromethyl)acrylates

Noriyasu Shinohara,† Jiro Haga,† Takashi Yamazaki,*,† Tomoya Kitazume,*,† and Shinichiro Nakamura‡

Department of Bioengineering, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226, Japan, and Mitsubishi Chemical Corporation Research Center, 1000 Kamoshida-cho, Aoba-ku, Yokohama 227, Japan

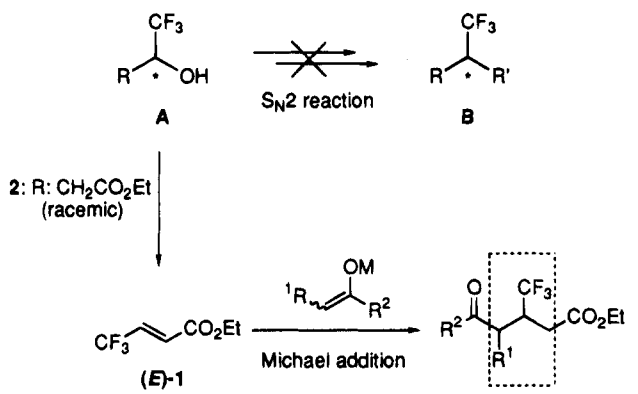
Received March 15, 1995®

Michael addition reaction of various lithium enolates to ethyl (*E*)-3-(trifluoromethyl)acrylate (***E***)-**1** was found to be one of the most effective routes to construct materials not only with a CF_3 group but also with readily distinguishable multiple functionalities by the routine chemical transformations. Particularly, employment of lithium enolates from chiral acyloxazolidinones as Michael donors resulted in the formation of 1,4-adducts, usually with a high degree of diastereoselectivity as well as with a high degree of diastereofacial selectivities only in a single step. Further, it was suggested by both the experimental results and the *ab initio* calculations that interaction between fluorine(s) and lithium strongly stabilized the present Michael intermediates, allowing for the smooth reactions even with ketone enolates under kinetically controlled conditions.

Fluorinated organic molecules have been gaining significant interest in the medicinal[1] and functional materials fields.[2] We have devoted our attention to the development of the syntheses of chiral building blocks containing a trifluoromethyl (CF_3) group[3] with the general structure **A** as shown in Scheme 1. Carbon–carbon bond formation at the stereogenic center by substitution of a hydroxyl group with retention of stereochemistry is readily expected from the analogy of the results with the nonfluorinated substrates. However, this is not the case, presumably because of the electron-withdrawing ability as well as the electronegativity of a CF_3 group leading to the shortening of the C–O bond as well as the difficult accessibility of the incoming nucleophiles to the reaction site.[4]

In recent years, while a few studies concerning the construction of chiral structure **B** (Scheme 1) have been reported,[5] the results were not satisfactory in terms of stereoselectivities or as building blocks with plural easily differentiated functional groups. For solving this problem, we planned to apply the enolate-Michael addition reaction known to be one of the powerful methods for the diastereoselective construction of a new carbon–carbon framework in an efficient manner.[6] For this purpose,

Scheme 1



ethyl 3-(trifluoromethyl)acrylate (***E***)-**1** was chosen as an acceptor (Scheme 1) because of the ready availability of its starting material **2** as well as the expectation of its high reactivity due to a strongly electron-withdrawing CF_3 group. Realization of this reaction allows us to indirectly substitute the hydroxy group in **A** located at the α-position of the trifluoromethyl group with various alkyl groups.

Prior to the experiments, we performed MOPAC[7] calculation of (***E***)-**1**, to predict its reactivity as a Michael acceptor, along with its nonfluorinated prototype, ethyl crotonate **3**, and ethyl 3,3-bis(trifluoromethyl)acrylate **4**, the latter of which has been reported to proceed via *anti*-Michael addition (Figure 1).[8] According to the result, (***E***)-**1** was revealed to have a significantly lower LUMO energy level than **3** and a similar value for the corresponding p_z orbital coefficients at the reaction sites, which demonstrated the higher reactivity of (***E***)-**1** compared to **3**. In contrast to these compounds, the α-position of **4**

† Tokyo Institute of Technology.
‡ Mitsubishi Chemical Corporation Research Center.
® Abstract published in *Advance ACS Abstracts,* June 15, 1995.

(1) (a) Welch, J. T.; Eswarakrishman, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1990. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (c) Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381.

(2) (a) Arakawa, S.; Nito, K.; Seto, J. *Mol. Cryst. Liq. Cryst.* **1991**, *204*, 15. (b) Buchecker, R.; Kelly, S. M.; Funfschilling, J. *Liq. Cryst.* **1990**, *8*, 217. (c) Doyle, T. R.; Vogol, O. *J. Am. Chem. Soc.* **1989**, *111*, 8510.

(3) Kitazume, T.; Yamazaki, T. Effect of the Fluorine Atom on Stereocontrolled Synthesis: Chemical or Biological Methods. In *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; American Chemical Society: Washington, DC, 1991; Chapter 12.

(4) Takahashi, O.; Furuhashi, K.; Fukumasa, M.; Hirai, T. *Tetrahedron Lett.* **1990**, *31*, 7031.

(5) (a) Hanzawa, Y.; Suzuki, M.; Sekine, T.; Murayama, T.; Taguchi, T. *J. Chem. Soc., Chem. Commun.* **1991**, 721. (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169.

(6) (a) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227. (b) Yamaguchi, M. *Yuki Gosei Kagaku Kyokaishi* **1986**, *44*, 405.

(7) Semiempirical molecular orbital calculation was performed by MOPAC v 6.10 (AM1) implemented in a CAChe Worksystem (SONY/Tektronix Corp.) for the conformers obtained from the rigid search method, followed by their optimization by the eigenvector following minimization (EF) method with the extra keyword "PRECISE", final gradient norm being less than 0.01 kcal/Å. Molecular mechanics were also carried out with this system.

(8) Martin, V.; Molines, H.; Wakselman, C. *J. Org. Chem.* **1992**, *57*, 5530.

0022-3263/95/1960-4363$09.00/0

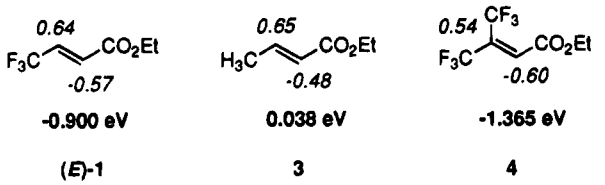
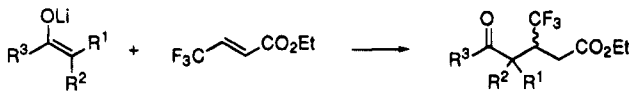


Figure 1. MOPAC calculation for Michael acceptors **(*E*)-1**, **3**, and **4**: p_z orbital coefficients are italic and LUMO energy levels are bold.

Table 1. Reaction of (*E*)-1 with Acyclic Lithium Enolates



entry	product	R^1	R^2	R^3	method[a]	yield (%)[b]	selectivity	(% de)[c]
1	**5a**	H	H	Ph	A, 1.0 h	33 (58)		
2	**5a**	H	H	Ph	B, 3.0 h	(14)		
3	**5b**	Me	H	Ph	B, 0.5 h	98	>98	(*anti*)
4	**5c**	Me	Me	Ph	B, 1.5 h	–		
5	**5d**	Me	H	Et	B, 0.5 h	97	84	(*anti*)
6[d]	**5d**	H	Me	Et	B, 0.5 h	97	>98	(*anti*)
7[d]	**5d**	Me	H	Et	B, 0.5 h	97	96	(*anti*)
8	**5e**	H	H	OEt	B, 1.5 h	87		
9	**5f**	H	Me	OEt	B, 1.0 h	54	78	(*anti*)
10	**5g**	Me	Me	OEt	B, 1.0 h	98		
11	**5i**	H	H	NMe_2	B, 1.5 h	86		
12	**5j**	H	Me	NMe_2	B, 1.5 h	89	70	(*syn*)
13	**5l**	Me	Me	NMe_2	B, 3.5 h	–		

[a] A: at −78 °C to rt. B: at −78 °C. [b] In parentheses are shown yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [c] In parentheses is shown the relative stereochemistry of the major product. [d] Lithium enolate via the corresponding enol silyl ether ((*E*):(*Z*) = 10:90 for entry 6 or (*E*):(*Z*) = 76:24 for entry 7) was employed.

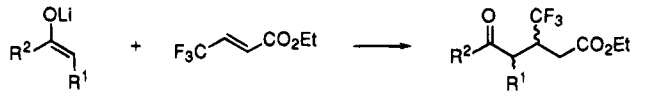
had a larger absolute value of the coefficient than the β-position, which clearly rationalizes its *anti*-Michael addition preference. These results prompted us to investigate the enolate-Michael reactions with **(*E*)-1** as an acceptor, and we describe the full details on this topics.

Results and Discussion

Reaction of (*E*)-1 with Acyclic Lithium Enolates. As was described in our previous paper,[9] the Lewis acid-mediated procedure with the corresponding enol silyl ether did not proceed and lithium enolates were found to be suitable for this reaction.

The present Michael addition with acyclic lithium enolates summarized in Table 1 can be divided into the following three types: (i) the reaction did not occur, and the acceptor was recovered (entries 4 and 13); (ii) many impurities were observed by ^{19}F NMR, and the 1,4-adduct was given only in low yield (entries 2 and 9); and (iii) the 1,4-addition proceeded smoothly in good yield (entries 3, 5–8, and 10–12). As shown in entry 1, the yield was improved by increasing the reaction temperature (compare entries 1 and 2). This result might imply that the 1,2-addition pathway caused formation of impurities in view of evidence that conjugate addition was favored over carbonyl addition at higher temperatures.[10] In the case of R^1 and/or R^2 being Me, the influence of the substitution

Table 2. Reaction of (*E*)-1 with Cyclic Enolates



entry	product	R^1 and R^2	method[a]	yield (%)[b]	selectivity	(% de)[c]
1	**6a**	$(CH_2)_4$	B, 4.0 h	(25)	>46[d]	(*anti*)
2	**6a**	$(CH_2)_4$	A, 4.0 h	80	>56[d]	(*anti*)
3	**6b**	$(CH_2)_3$	A, 4.0 h	93	20	
4	**6c**	$(CH_2)_3O$	B, 2.0 h	>98	74	(*anti*)
5	**6d**	$(CH_2)_2O$	B, 3.0 h	90	84	
6	**6e**	$(CH_2)_2N(CH_3)$	B, 3.5 h	51 [37]	88	

[a] A: at −40 °C. B: at −78 °C. [b] In parentheses is shown the yield determined by ^{19}F NMR using $PhCF_3$ as an internal standard, and in brackets is shown the yield of the corresponding 1,2-adduct **7**. [c] In parentheses is shown the stereochemistry of the major product. [d] Accurate selectivity could not be calculated due to some impurities.

pattern of the ketone enolates on their reactivity was opposed to that of the ester enolates (entries 3–7 vs entries 8–10). For the amide enolates, 1,4-adducts were obtained at −78 °C in good yields except for the disubstituted donor (entry 13). In sharp contrast to the present case, it is interesting to note that nonfluorinated ethyl crotonate did not show any significant enolate substitution effects.[6b] While dependence on R^1 and R^2 in the present reaction was interesting, the origin of the phenomenon was not clear yet.

The transition states of Michael addition can be classified as two types:[11] one is an eight-membered chelated model and the other is an open chain nonchelated model. When diethyl ketone was employed as the donor, both (*E*)- and (*Z*)-enolates exclusively gave the same *anti* diastereomer (entries 5 and 6). These results strongly suggest that the reaction proceeds via the latter transition state, at least in this instance. Yamaguchi and co-workers have reported that ethyl propionate enolate reacts with ethyl crotonate, which is a nonfluorinated prototype, in 43% de (*anti* major).[6b] For *N*,*N*-dimethyl propionamide, while they have reported the de value to be 33% (*syn* major), 80% de (*syn* major) was obtained in our hands. The results of entries 9 and 12 showed the higher *anti* selective tendency compared with that of ethyl crotonate. This difference probably stems from the different steric requirement between Me and CF_3 moieties.

Reaction of (*E*)-1 with Cyclic Enolates. In our previous reports, only acyclic enolates were employed as donors. Enolates derived from cyclic carbonyl compounds were expected to show different reactivities or selectivities because of the fixation of their geometry. Especially where the (*E*)-amide enolate is required, *N*-alkyl lactam is used since there are currently no methods available for its generation. Then we examined the reaction of **(*E*)-1** with various cyclic enolates (Table 2).

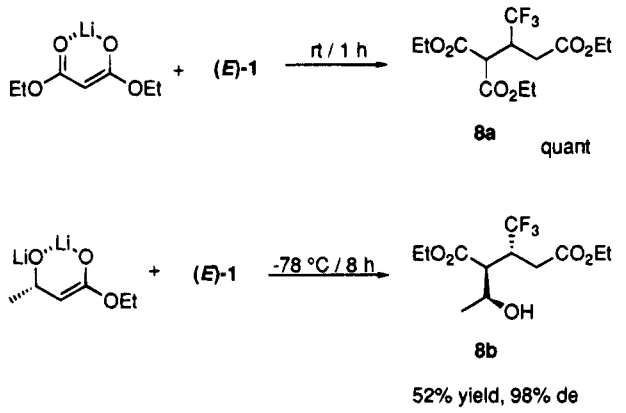
Because of the low yield of **6a** and recovery of **(*E*)-1** at −78 °C (entry 1), cyclic ketones were reacted at −40 °C (entries 2 and 3). On the other hand, lactones gave 1,4-adducts in good yields and with higher diastereoselectivities even at −78 °C (entries 4 and 5). In the case of propiophenone and ethyl propionate with one alkyl substituent, as mentioned before, the former afforded much better results than the latter. However, for cyclic ketones or lactones, such a substitution pattern affected

(9) (a) Yamazaki, T.; Haga, J.; Kitazume, T.; Nakamura, S. *Chem. Lett.* **1991**, 2171. (b) Yamazaki, T.; Haga, J.; Kitazume, T. *Chem. Lett.* **1991**, 2175.

(10) Oare, D. A.; Henderson, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132.

(11) (a) Bernardi, A.; Capelli, A. M.; Cassinari, A.; Cometti, A.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1992**, *57*, 7029. (b) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.

Scheme 2

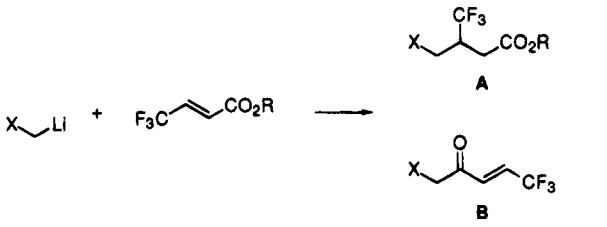


the reactivity in an opposite sense. A Michael adduct from lactam **6f** was obtained in moderate yield with concomitant formation of 1,2-adduct **7** in 37% yield (entry 6).

It is well-accepted that lithium enolates from β-carbonyl or β-hydroxy esters such as diethyl malonate or 3-hydroxybutyrate possess the intermolecular chelation structure, which might give the more rigid conformations like cyclic enolates.[12] When diethyl malonate was subjected to the reaction at room temperature, 1,4-adduct **8a** was obtained in good yield. The requirement of raising the reaction temperature might be derived from the significant stability of its lithium enolate. It was reported that dianion from (*S*)-3-hydroxybutyrate was alkylated by electrophiles with high stereoselectivities, allowing for the preferential reaction from the less hindered *si*-face. Furthermore, considering that (*S*)-3-hydroxybutyrate could be obtained easily in high optical purity by bakers' yeast reduction,[13] the corresponding enolate would realize highly stereoselective asymmetric Michael addition. The results led us to expect excellent diastereoselectivity (Scheme 2).

Reaction of (*E*)-1 with Compounds with Anion-Stabilizing Functionalities. Next, we planned the employment of donors with other anion-stabilizing functionalities like nitromethane. When ethyl ester was used as the Michael acceptor, methyl phenyl sulfoxide[14] and dimethyl methylphosphonate[15] mainly produced 1,2-adducts in contrast to nitromethane (Table 3, entries 1–3). Then we employed 2,6-di-*tert*-butyl-4-methylphenyl ester **10** (BHT ester)[16] for exerting the steric hindrance around the carbonyl group, which might lead to the preferential formation of the desired 1,4-adduct. As expected, methyl phenyl sulfoxide with this acceptor gave 1,4-adduct in good yield, while dimethyl methylphosphonate did not furnish any product at all (entries 4 and 5). This BHT ester acceptor was also reacted with the same γ-lactam of entry 6 in Table 2 to improve the yield of the 1,4-addition product

Table 3. Reaction of (*E*)-1 with a Donor with Anion-Stabilizing Functionalities



entry	product	X	R	method[a]	yield A (%)[b]	yield B (%)[b]
1	**9a**	O_2N	Et	B, 6.0 h	83	–
2	**9b**	PhS(O)	Et	A, 2.0 h	(20)	78
3	**9c**	$(MeO)_2P(O)$	Et	A, 2.0 h	–	90
4	**9d**	PhS(O)	BHT[c]	A, 2.0 h	80	(10)
5	**9e**	$(MeO)_2P(O)$	BHT[c]	B, overnight	–	–

[a] A: at −78 °C. B: at −78 °C to rt. [b] In parentheses are shown yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [c] BHT: 2,6-di-*tert*-butyl-4-methylphenyl.

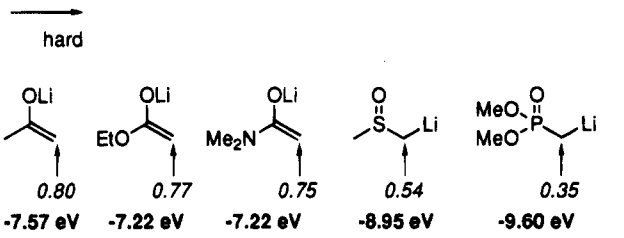


Figure 2. MOPAC calculation for lithium enolates or their equivalents: p_z orbital coefficients are italic and HOMO energy levels are bold.

11 but with lower diastereoselectivity. The above result suggests the possible control of stereochemistries of the products by the ester moiety of the Michael acceptor.

In general, softer enolates have a greater propensity for the conjugate addition than harder ones on the basis of the frontier orbital theory.[17] It was also reported that hard enolates had a low HOMO level and a small coefficient at the reaction site.[18] For obtaining quantum chemical information, semiempirical MO calculations were carried out. The results are shown in Figure 2. MOPAC results demonstrated that sulfoxide and phosphonate were particularly harder than the others, phosphonate being the hardest. This calculation conveniently and, at least, qualitatively explained two experimental results; one was the boundary of 1,4- or 1,2-addition with (*E*)-**1** between amide and sulfoxide, and another was acceptor **10** reacted in a 1,4-manner with various donors except for phosphonate.

Reaction of (*E*)-1 with Enolates from Acyloxazolidinones. As described above, the present conjugate addition could be extended to its asymmetric version, but our example has the apparent limitation toward the donor employed. Then, for obtaining the easily transformable structure, chiral acyloxazolidinones were employed. Their lithium enolates yielded the products, usually with a high degree of diastereoselectivity and diastereofacial selectivity (Table 4). Reaction with acetylated oxazolidinone was the special case, which furnished

(12) (a) Tomioka, K.; Ando, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 715. (b) Züger, M.; Weller, T.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2005. (c) György, F. *Helv. Chim. Acta* **1979**, *62*, 2825. (d) György, F. *Helv. Chim. Acta* **1979**, *62*, 2829. (e) Fráter, G.; Muellar, U.; Guenther, W. *Tetrahedron* **1984**, *40*, 1269.

(13) Seebach, D.; Sutter, M. A.; Weher, R. H.; Züger, M. F. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 215.

(14) Casey, M.; Manage, A. C.; Gairns, R. S. *Tetrahedron Lett.* **1989**, *30*, 6919.

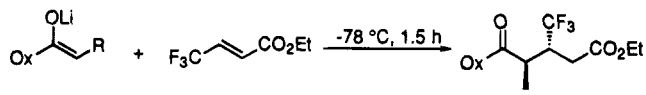
(15) Deschamps, B.; Anh, N. T.; Penne, J. S. *Tetrahedron Lett.* **1973**, 527.

(16) (a) Häner, R.; Laube, T.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 5396. (b) Schore, N. E.; Rowley, E. G. *J. Am. Chem. Soc.* **1988**, *110*, 5224.

(17) Ho, T.-L. In *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic: New York, 1977; Chapter 7.

(18) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: Chichester, U.K., 1976.

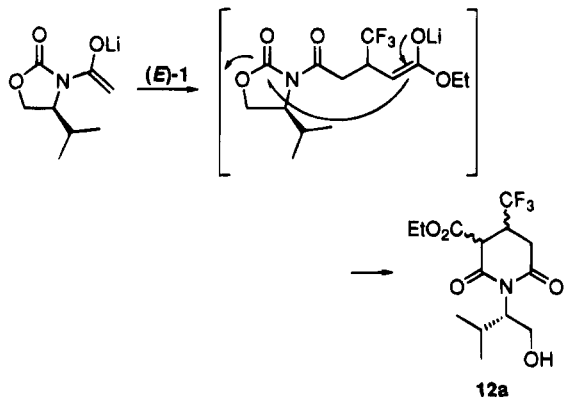
Table 4. Reaction of (*E*)-1 with enolates from Acyloxazolidinones[a]



entry	product	R	yield (%)[b]	selectivity	(% de)[c]
1	**12a**	H	93	78	(*anti*)
2	**12b**	Me	88	>98	(*anti*)
3	**12c**	Et	52 (74)[d]	>98	(*anti*)
4	**12d**	*i*-Pr	97	97	(*anti*)
5[e]	**12e**	Ph	62	30	
6	**12f**	$PhCH_2O$	36	>98	(*anti*)
7	**12g,h**	Cl	96	34	
8[f]	**12g,h**	Br	98	36	

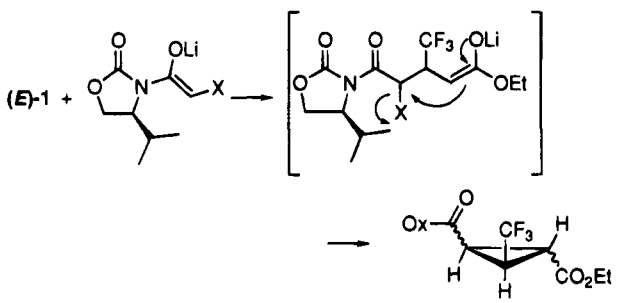
[a] Ox: (4*S*)-4-(prop-2-yl)oxazolidinon-3-yl. [b] In parentheses is shown a yield determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [c] Unless otherwise noted, these diastereomers resulted from the two contiguous carbon atoms, $CF_3-C^*-C^*-R$, which were proven by removal of the chiral auxiliary. [d] This gap is due to the close R_f values of the product and the starting material. [e] Potassium hexamethyldisilazide (KHMDS) was employed for the generation of the enolate. [f] **12g**:**12h** = 68:32.

Scheme 3



12a

Scheme 4

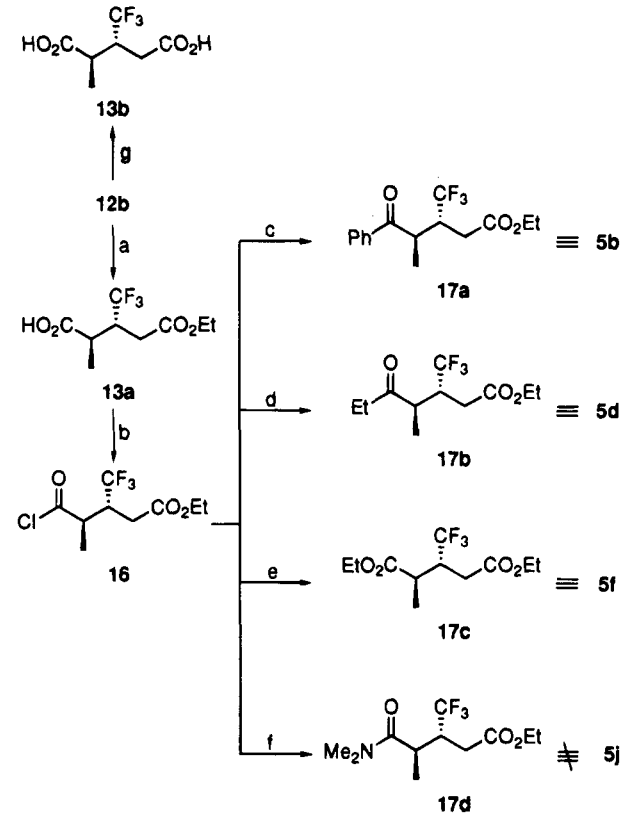


12g, 12h

X = Br or Cl

the cyclic product **12a** presumably via the intramolecular nucleophilic attack of the resulting ester enolate to the carbonyl moiety of the oxazolidinone ring (Scheme 3). In this case, only two diastereomers were obtained in 78% de out of four possible diastereomers. Oxazolidinone with a phenylacetyl moiety did not give any adduct via the corresponding lithium enolate, while the use of potassium hexamethyldisilazide (KHMDS) affected the reaction to afford the desired product but with lower diastereoselectivity (30% de). For α-haloacyloxazolidinones (entries 7 and 8), chiral cyclopropanes **12g,h** were formed in a one-pot procedure (Scheme 4). These results were explained by the intramolecular nucleophilic reaction after the conjugate addition, and it is interesting to note that

Scheme 5[a]



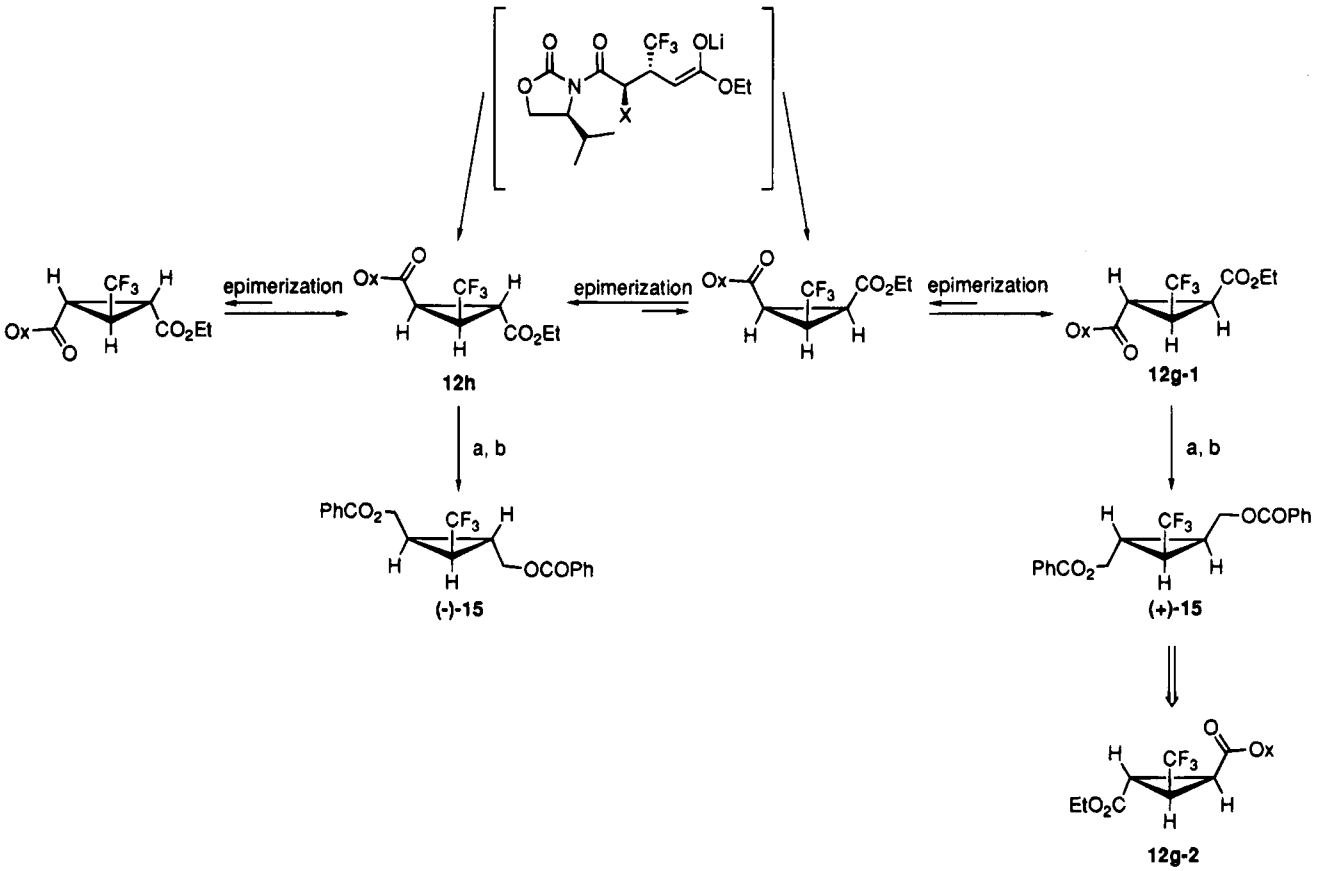
[a] (a) LiOOH for 0.3 h; (b) $SOCl_2$; (c) $PhAlEt_2$; (d) EtMnI; (e) EtOH, pyridine; (f) aqueous $HNMe_2$; (g) LiOOH for 4 h.

only two diastereomers were yielded out of eight possible stereoisomers.

Clarification of the Relative Stereochemistry. Recently, Evans and co-workers have reported on the excellent ability of chiral acyloxazolidinones for asymmetric synthesis.[19] From their literature, two inherent natures of acyloxazolidinones' lithium enolates were noted: (i) exclusive formation of (*Z*)-enolate and (ii) reaction with electrophiles at its *si*-face without any exception. Both of these are of course very important factors for controlling the stereochemistry of the products. In our hands, Michael adduct **12b** from propionyloxazolidinone was treated with LiOOH for 4 h to furnish dicarboxylic acid **13b**, whose X-ray crystallographic analysis established the absolute stereochemistry as (*R*) for both C-2 and C-3 positions (Scheme 5). Thus, it was revealed that (*S*)-propionyloxazolidinone reacted at its *si*-face, consistent with the preceding studies, and 1,4-addition proceeded with *anti* selectivity. Other enolates in Table 4 would react with the acceptor in the same manner, possibly leading to the formation of the resultant Michael adducts with the same stereochemical relationship. When potassium enolate from phenylacetyloxazolidinone was employed, the desired product was afforded with lower diastereoselectivity (30% de). In this instance, evidence that removal of the chiral auxiliary from **12e** furnished the corresponding monoacid **14** with basically

(19) (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 1. (b) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (c) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (d) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (e) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141. (f) Evans, D. A.; Bilodean, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750.

Scheme 6[a]



[a] (a) $LiAlH_4$, 0 °C/1.5 h, 85%; (b) PhCOCl, pyridine, rt, overnight, 98%.

the same de value (36% de) would be interpreted as being the result of the predominant reaction at the *si*-face like other acyl oxazolidinone cases but with poor face matching with **(*E*)-1**.

The absolute configuration of cyclopropane **12h** (minor diastereomer) was determined as (1′*S*), (2′*S*), and (3′*S*) by X-ray crystallographic analysis. In order to determine the configuration of the major isomer **12g**, **12h** was treated with $LiAlH_4$ and then the corresponding diol was transformed to **(−)-15**. Its enantiomer **(+)-15** was obtained from **12g** by the same procedure (Scheme 6). While the result still leaves the possibility that the absolute configuration of cyclopropane **12g** is **12g-1** or **12g-2**, the correct structure would be the former on the basis of the aforementioned *si*-face selectivity of acyloxazolidinones.

Chiral acid chloride **16** with an *anti* configuration was derived from monoacid **13a** with complete retention of stereochemistry, the latter of which was obtained by treatment of Michael adduct **12b** with LiOOH for 0.3 h (Scheme 5). While the reaction with the corresponding Grignard reagent or alkyl cuprate did not furnish the desired **17a** or **17b**, they were prepared in 42 or 33% yields by the reaction with $PhAlEt_2$[20] or EtMnI,[21] respectively. On the other hand, acid chloride **16** was independently allowed to be reacted with EtOH or aqueous dimethylamine, giving **17c** or **17d**, respectively, without any evidence of epimerization by ^{19}F NMR in each case. Comparison of their ^1H and ^{13}C NMR data with those of racemic materials **5b**, **5d**, and **5f** obtained by the Michael process has led us to unambiguously correlate their structures (major isomer) as *anti*. The spectroscopic information of the minor isomer from *N*,*N*-dimethylpropionamide agreed with that of **17d**. Thus, it was revealed that major isomer **5j** had a *syn* configuration.

The relative stereochemistry of **6a** was determined by X-ray crystallographic analysis of the corresponding diol **18** (major isomer) derived from reduction of the major isomer of **6a** (Scheme 7). According to the result, it was revealed that Michael addition with cyclohexanone occurred in an *anti* selective fashion. Elucidation of the stereochemistry of Michael adduct **20** from δ-valerolactone enolate and benzyl 3-(trifluoromethyl)acrylate was carried out via the corresponding carboxylic acid **19**. X-ray analysis of the latter clarified the *anti* relationship, which allowed us to determine the same *anti* configuration of **6d**.

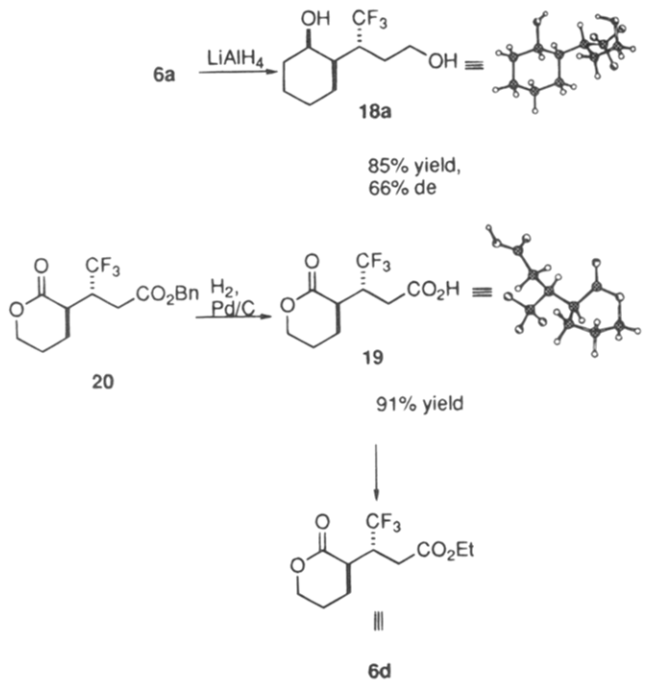
The relative stereochemistry of Michael adduct **8b** was determined by ^1H NMR analysis of the corresponding lactone **21** (Figure 3). For obtaining information on the conformational preference, we calculated its four possible stereoisomers by MM2.[7] The results on the dihedral angles $H_a-C-C-H_b$ and $H_b-C-C-H_c$ for the conformers within 2 kcal/mol of the most stable one permitted us to calculate the expected coupling constants. Comparison of these values with the observed data led us to assume that the relative stereochemistry of **21** is 3,4-*trans*, 4,5-*cis*.

Mechanism

It was revealed that 3-(trifluoromethyl)acrylate reacted with various lithium enolates, while Michael adducts

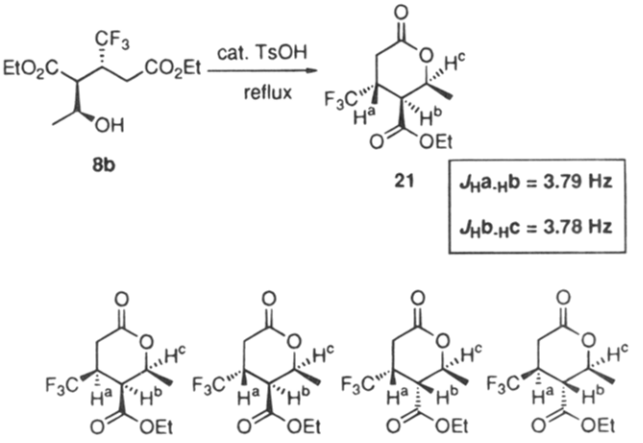
(20) Mole, T.; Jeffery, E. A. In *Organoaluminium compounds*; Elsevier: Amsterdam, 1972; Chapter 12.

Scheme 7



from ketones were not usually obtained under kinetically controlled conditions when nonfluorinated α,β-unsaturated esters were employed as the acceptors. As the Michael addition is formally reversible,[6a] the progress of this reaction is dependent on the relative stability of the starting and produced enolates.[22] Thus, conjugate addition of a ketone enolate to a nonfluorinated acceptor usually follows the retro-Michael process because the starting enolate is more stable than the resulting ester enolate.[23] On the other hand, ketone enolates smoothly reacted with our acceptor **(*E*)-1** in good yields. Although this sharp difference could be conceptually explained by isomerization of the first intermediate **22** to the more stable enolate **23** as shown in Scheme 8, a D_2O trapping experiment clearly demonstrated no such isomerization for the intermediary ester enolate. Therefore, the fact that **(*E*)-1** was the good Michael acceptor even toward ketone enolates suggests the existence of some special driving force.

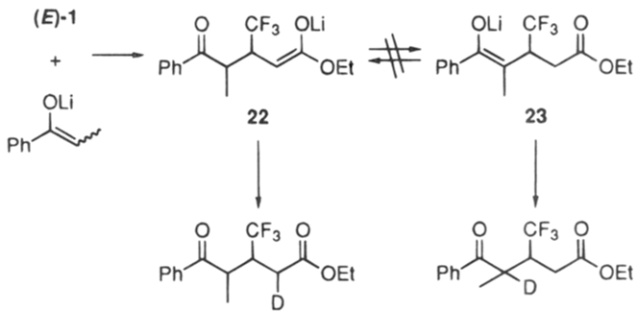
Recent X-ray analysis of fluorine-containing metals has demonstrated the coordination of fluorine atom(s) to metal,[24] which was also supported by molecular orbital calculations.[25] Thus, Dixon and co-workers reported the monofluoroacetaldehyde enol calculation wherein the alkali metals were substituted for H at the enol hydroxyl



	trans-cis	cis-cis	cis-trans	trans-trans
$J_{Ha.Hb}$	4.83	1.83	2.43	8.87
$J_{Hb.Hc}$	3.19	3.04	1.77	9.04

Figure 3. Comparison of the observed coupling constants of **21** with the calculated values of its four possible stereoisomers.

Scheme 8



group, and they found a more than 10 kcal/mol stabilization by interaction of such metals as lithium, sodium, or potassium with a fluorine atom. On the basis of this strong five-membered intramolecular stabilization, we also assumed that the interaction between fluorine and lithium was the stabilizing factor for the intermediate enolate. Then, for the verification of this hypothesis, *ab initio*[26] calculations (6-31G*)[27] were carried out for the conformationally isomeric model molecules, **24a**−**d** (Figure 4). Only considering the steric repulsion between fluorine(s) and lithium, comformers **24c,d** should be more stable, while **24a** was calculated to be the most stable of all. Two specific features were observed for this isomer, especially the fluorine atoms closer to the lithium; one was the short F−Li distance of 2.01 Å, and the other was the C−F bond elongation of 0.038 Å. These points clearly supported the concurrent coordination of two fluorine atoms to lithium. The same trend was found for **24b**, while there was a significant energy difference (10.35 kcal/mol) between these conformers. This stems from not only the decrease of the number of fluorine atoms

(21) (a) Tarbell, D. S.; Leister, N. A. *J. Org. Chem.* **1958**, *23*, 1150. (b) Cahiez, G.; Alexakis, A.; Normant, J. F. *Synth. Commun.* **1979**, 639.

(22) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152.

(23) The α,β-unsaturated esters with an additional activating group at the α-position react with ketone enolates under kinetic conditions: Corey, E. J.; Houpis, I. N. *Tetrahedron Lett.* **1993**, *34*, 2421.

(24) (a) Stalke, D.; Whitmire, K. H. *J. Chem. Soc., Chem. Commun.* **1990**, 833. (b) Murray-Rust, P.; Stallings, W. C.; Monti, C. T.; Preston, R. K.; Glusker, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 3206. (c) Carrell, H. L.; Glusker, J. P.; Pieroy, E. A.; Stallings, W. C.; Zaeharias, D. E.; Davis, R. L.; Astbury, C.; Kennard, C. H. L. *J. Am. Chem. Soc.* **1987**, *109*, 8067.

(25) (a) Dixon, D. A.; Smart, B. E. In *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; American Chemical Society: Washington, DC, 1991; Chapter 2. (b) van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 755. (c) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327. (d) Iwata, S.; Qian, C.-P.; Tanaka, K. *Chem. Lett.* **1992**, 357.

(26) Frisch, M. J.; Head-Gordon, M.; Schlegel, H. B.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Fluder, E. M.; Topiol, S.; Pople, J. A. *Gaussian 88*; Gaussian, Inc.: Pittsburgh, PA.

(27) The calculation was done by the Gaussian 88 program, and geometries were fully optimized with C_s symmetry for the closed shell ground state configuration by the RHF level energy gradient method of the 3-21G basis set. To obtain a more accurate relative stability, the RHF energy by the 6-31G* basis set was calculated on the above optimized geometries.

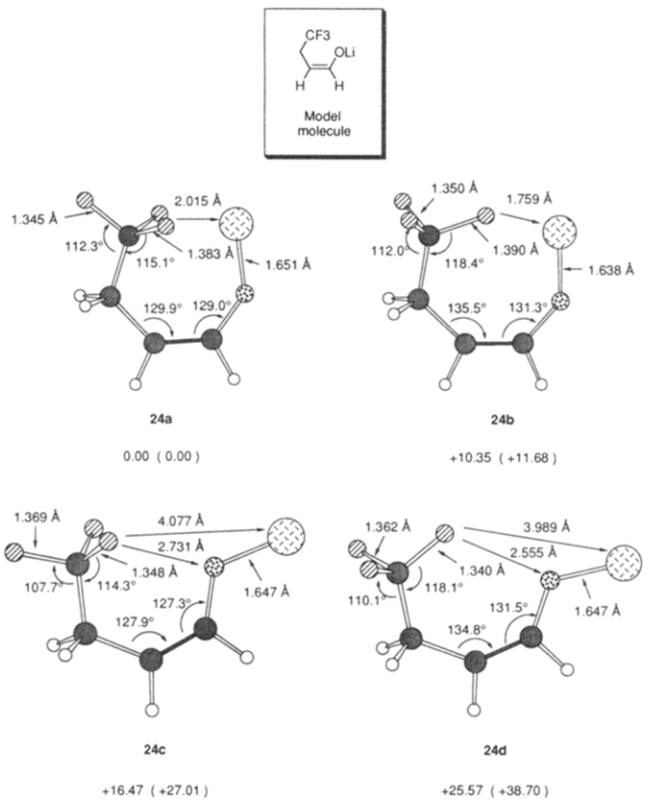


Figure 4. Results of 6-31G* calculation for the conformationally isomeric model molecules **24a**−**d** (in kcal/mol). In the parentheses are shown the results of 3-21G calculation.

interacting with lithium but also the structural strain in **24b** apparent from the C=C−O and C−C=C angles of 131.3 and 135.5°, respectively (for **24a**, 129.0 and 129.9°, respectively). These calculations might be overestimated since monomers or no solvation are assumed; however, they unambiguously revealed the interesting property of fluorine atoms, which might play an important role in the present Michael addition reactions.

Conclusion

It has been demonstrated that Michael addition reaction to **(*E*)-1** is the efficient method for stereoselectively constructing β-trifluoromethylated carbonyl compounds. When the 1,2-adduct preferentially occurred for **(*E*)-1**, use of BHT ester acceptor **10** was sometimes effective. Employment of chiral acyloxazolidinones as donors afforded the corresponding 1,4-products, usually with a high degree of diastereoselectivity and a high degree of diastereofacial selectivity. It was also suggested from the result of *ab initio* calculations that interaction between fluorine(s) and lithium was some special driving force in the present reaction.

Experimental Section

General Methods.[28] Gas liquid chromatography (GLC) was performed using silicone GE XE-60 or ULBON HR-20M on Chromosorb W, 30 m × 3 mm.

(*E*)-2,6-Di-*tert*-butyl-4-methylphenyl 4,4,4-Trifluoro-2-butenoate (10). To a solution of 2,6-di-*tert*-butyl-4-methylphenol (2.6 g, 12 mmol) in methylene chloride (50 mL) was added *n*-butyllithium (4.8 mL, 12 mmol) under an atmosphere of nitrogen at 0 °C. After 30 min, this solution was treated with 1.6 g (10 mmol) of 3-(trifluoromethyl)acryloyl chloride. After the mixture was stirred overnight at room temperature, 1 N HCl was added to the reaction mixture, which was extracted with methylene chloride, washed with 1 N HCl and diluted $NaHCO_3$, dried over anhydrous $MgSO_4$, and purified by silica gel column chromatography (AcOEt:*n*-hexane = 1:4). Yield: 67%. R_f = 0.62 (AcOEt:*n*-hexane = 1:4). ^{1}H NMR: δ 1.31 (18 H, s), 2.33 (3 H, t, J = 0.42 Hz), 6.76 (1 H, dq, J = 9.47, 1.03 Hz), 6.98 (1 H, dq, J = 9.45, 3.71 Hz), 7.14 (2 H, q, J = 0.42 Hz). ^{13}C NMR: δ 21.54, 31.57, 35.29, 122.05 (q, J = 287.7 Hz), 127.27, 129.09 (q, J = 6.0 Hz), 133.17 (q, J = 35.8 Hz), 135.26, 141.79, 145.03, 164.47. ^{19}F NMR: δ 13.6 (d, J = 4.2 Hz). IR (neat): ν 2950, 2900, 2850, 1750 cm^{-1}. HRMS calcd for $C_{19}H_{25}F_3O_2$ *m/e* 342.1807, found 342.1795.

General Procedure for Michael Addition of Enolates to Ethyl 3-(Trifluoromethyl)acrylate. A dry two-necked flask equipped with a rubber septum was placed under a nitrogen atmosphere and charged with freshly distilled THF (5 mL) and 0.34 mL (2.4 mmol) of diisopropylamine. This solution was cooled to −78 °C with a dry ice−acetone bath and treated with 0.98 mL (2.4 mmol) of a 2.5 M solution of *n*-butyllithium in hexane which was stirred for 15 min. To this solution was added 2.4 mmol of carbonyl compound, and the resulting solution was stirred for 30 min. The reaction mixture was then treated with 0.29 mL (2.0 mmol) of ethyl 3-(trifluoromethyl)acrylate, which was further stirred at −78 °C. The reaction was quenched with aqueous 3 N HCl, the mixture was diluted with ether, and the resulting organic layer was separated. The aqueous layer was extracted with ether twice, and the combined ethereal layers were washed with brine, dried ($MgSO_4$), and evaporated. The resulting crude material was purified by silica gel column chromatography and/or distillation. When the enol silyl ether was employed, generation of the lithium enolate was realized by the treatment of this material with 1 equiv of MeLi in THF at room temperature for 1 h, which was used in a same manner as described above.

Ethyl 3-(Trifluoromethyl)-5-oxo-5-phenylvalerate (5a). Yield: 33%. Bp: 145−150 °C/0.2 mmHg (bath temperature). R_f = 0.29 (*n*-hexane:AcOEt = 10:1). ^{1}H NMR: δ 1.23 (3 H, t, J = 7.12 Hz), 2.53 (1 H, dd, J = 15.97, 6.91 Hz), 2.70 (1 H, dd, J = 15.89, 6.05 Hz), 3.24 (1 H, dd, J = 17.82, 7.67 Hz), 3.35 (1 H, dd, J = 17.86, 4.90 Hz), 3.58 (1 H, m), 4.14 (2 H, q, J = 7.14 Hz), 7.52 and 7.93 (5 H, m). ^{13}C NMR: δ 14.10, 33.38 (q, J = 2.6 Hz), 35.94 (q, J = 27.5 Hz), 36.76 (q, J = 2.0 Hz), 61.30, 127.88 (q, J = 280.2 Hz), 128.50, 129.19 , 134.04, 136.64, 170.88, 196.30. ^{19}F NMR: δ 6.2 (d, J = 8.5 Hz). IR (neat): ν 3075, 3000, 2950, 1740, 1695, 1600, 1580 cm^{-1}. HRMS calcd for $C_{14}H_{15}F_3O_3$ *m/e* 288.0973, found 288.0958.

(3*R,4*R**)-Ethyl 3-(Trifluoromethyl)-4-methyl-5-oxo-5-phenylpentanoate (5b).** Yield: 98%. De: >98%. R_f = 0.30 (*n*-hexane:AcOEt = 10:1). ^{1}H NMR: δ 1.24 (3 H, dq, J = 7.04, 0.78 Hz), 1.24 (3 H, t, J = 7.14 Hz), 2.57 (1 H, dd, J = 16.77, 6.94 Hz), 2.67 (1 H, dd, J = 16.77, 5.54 Hz), 3.44 (1 H, dddq, J = 9.40, 6.95, 5.61, 4.88 Hz), 3.94 (1 H, dq, J = 7.00, 4.85 Hz), 4.13 (1 H, dq, J = 10.68, 7.07 Hz), 4.17 (1 H, dq, J = 10.82, 7.08 Hz), 7.49, 7.59, 7.94 (5 H, m). ^{13}C NMR: δ 12.88, 14.05, 29.80 (q, J = 2.5 Hz), 37.88 (q, J = 1.9 Hz), 40.68 (q, J = 26.0 Hz), 61.13, 127.50 (q, J = 280.8 Hz), 128.37, 128.89, 133.48, 135.35, 170.58, 200.75. ^{19}F NMR: δ 8.2 (d, J = 9.2 Hz). IR (neat): ν 3050, 3000, 2925, 1740, 1690, 1600, 1580 cm^{-1}. HRMS calcd for $C_{15}H_{17}F_3O_3$ *m/e* 302.1130, found 302.1141.

(3*R,4*R**)-Ethyl 3-(Trifluoromethyl)-4-methyl-5-oxoheptanoate (5d).** Yield: 98%. De: 84%. Bp: 115 °C/0.8 mmHg (bath temperature). R_f = 0.40 (*n*-hexane:AcOEt = 7:1). ^{1}H NMR: δ 1.07 (3 H, t, J = 7.23 Hz), 1.14 (3 H, dq, J = 7.16, 0.77 Hz), 1.27 (3 H, t, J = 7.15 Hz), 2.51 (2 H, d, J = 6.25 Hz), 2.56 (2 H, dq, J = 7.18, 1.19 Hz), 2.96 (1 H, dq, J = 7.20, 5.10 Hz), 3.36 (1 H, dtq, J = 9.42, 6.29, 5.09 Hz), 4.14 (1 H, dq, J = 10.85, 7.11 Hz), 4.17 (1 H, dq, J = 10.76, 7.20 Hz). ^{13}C NMR: δ 7.72, 12.16, 14.08, 29.85 (q, J = 2.5 Hz), 34.44, 40.22 (q, J = 26.2 Hz), 43.17 (q, J = 1.9 Hz), 61.19, 127.43 (q, J = 280.6 Hz), 170.74, 211.23. ^{19}F NMR: δ 8.2 (d, J = 9.0 Hz). IR

(28) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 4346.

(neat): ν 2975, 2950, 1740, 1720 cm^{-1}. HRMS calcd for $C_{11}H_{17}F_3O_3$ *m/e* 254.1130, found 254.1142.

Diethyl 3-(Trifluoromethyl)glutarate (5e). Yield: 82%. Bp: 94.5 °C/5.5 mmHg. R_f = 0.63 (*n*-hexane:AcOEt = 10:1). ^{1}H NMR: δ 1.27 (6 H, t, J = 7.14 Hz), 2.51 (2 H, dd, J = 16.30, 7.51 Hz), 2.68 (2 H, dd, J = 16.30, 5.81 Hz), 3.30 (1 H, m), 4.17 (4 H, q, J = 7.14 Hz). ^{13}C NMR: δ 13.66, 32.66 (q, J = 2.6 Hz), 36.71 (q, J = 27.7 Hz), 60.89, 127.04 (q, J = 280.2 Hz), 170.29. ^{19}F NMR: δ 4.9 (d, J = 8.8 Hz). IR (neat): ν 2975, 2950, 2925, 1740 cm^{-1}. HRMS calcd for $C_{10}H_{15}F_3O_4$ *m/e* 256.0923, found 256.0906.

(2*R,3*R**)-Diethyl 3-(Trifluoromethyl)-2-methylglutarate (5f).** Yield: 29% (determined by ^{19}F NMR using $PhCF_3$ as an internal standard). De: 78%. Bp: 95–100 °C/0.09 mmHg (bath temperature). R_f = 0.40 (*n*-hexane:AcOEt = 10:1). ^{1}H NMR: δ 1.22 (3 H, dq, J = 7.16, 0.87 Hz), 1.27 and 1.28 (3 H each, t, J = 7.15, 7.14 Hz), 2.57 (2 H, d, J = 6.27 Hz), 2.90 (1 H, dq, J = 7.18, 4.43 Hz), 3.38 (1 H, dtq, J = 9.47, 6.36, 4.46 Hz), 4.17 (4 H, q, J = 7.13 Hz). ^{13}C NMR: δ 12.51 (q, J = 1.2 Hz), 14.13, 14.15, 30.15 (q, J = 2.5 Hz), 37.72 (q, J = 2.1 Hz), 41.40 (q, J = 26.4 Hz), 61.39, 61.43, 127.64 (q, J = 281.3 Hz), 171.16, 174.11. ^{19}F NMR ($CDCl_3$): δ 8.6 (d, J = 8.8 Hz). IR (neat): ν 3000, 2900, 2850, 1740 cm^{-1}. HRMS calcd for $C_{11}H_{17}F_3O_4$ *m/e* 270.1079, found 270.1090.

Diethyl 2,2-Dimethyl-3-(trifluoromethyl)glutarate (5g). Yield: 98%. R_f = 0.49 (AcOEt:*n*-hexane = 1:4). ^{1}H NMR: δ 1.21 (3 H, brs), 1.25 (3 H, q, J = 1.49 Hz), 1.27 (3 H, t, J = 7.13 Hz), 1.28 (3 H, t, J = 7.14 Hz), 2.43 (1 H, ddq, J = 17.15, 5.31, 0.71 Hz), 2.58 (1 H, dd, J = 17.14, 6.36 Hz), 3.54 (1 H, ddq, J = 6.36, 5.31, 9.80 Hz), 4.17 (2 H, q, J = 7.12 Hz), 4.19 (2 H, q, J = 7.14 Hz). ^{13}C NMR: δ 13.99, 14.10, 21.10 (q, J = 1.9 Hz), 23.89, 30.65 (q, J = 2.7 Hz), 43.18, 45.49 (q, J = 25.0 Hz), 61.27, 127.34 (q, J = 281.8 Hz), 171.16, 175.66. ^{19}F NMR: δ 13.1 (d, J = 9.7 Hz). IR (neat): ν 3000, 2900, 1740 cm^{-1}. HRMS calcd for $C_{12}H_{19}F_3O_4$ *m/e* 284.1235, found 284.1235.

Ethyl *N,N*-Dimethyl-3-(trifluoromethyl)glutamate (5i). Yield: 86%. R_f = 0.25 (*n*-hexane:AcOEt = 1:1). ^{1}H NMR: δ 1.26 (3 H, t, J = 7.15 Hz), 2.55 (1 H, dd, J = 16.28, 8.95 Hz), 2.60 (2 H, d, J = 6.23 Hz), 2.69 (1 H, dd, J = 16.32, 4.56 Hz), 2.97 and 3.04 (3 H each, s), 3.43 (1 H, m), 4.16 (2 H, q, J = 7.15 Hz). ^{13}C NMR: δ 14.14, 31.33 (q, J = 2.2 Hz), 33.34 (q, J = 2.5 Hz), 35.76, 37.27, 37.02 (q, J = 27.2 Hz), 61.17, 127.92 (q, J = 280.1 Hz), 169.45, 171.08. ^{19}F NMR: δ 5.8 (d, J = 9.0 Hz). IR (neat): ν 3000, 2950, 1740, 1655 cm^{-1}. HRMS calcd for $C_{10}H_{16}F_3NO_3$ *m/e* 255.1082, found 255.1090.

(3*R,4*S**)-Ethyl *N,N*-Dimethyl-3-(trifluoromethyl)-4-methylglutamate (5j).** Yield: 89%. De: 70%. R_f = 0.36 (*n*-hexane:AcOEt = 1:1). ^{1}H NMR: δ 1.25 (3 H, dq, J = 6.86, 0.74 Hz), 1.26 (3 H, t, J = 7.13 Hz), 1.27 (1 H, t, J = 7.15 Hz, minor diastereomer), 2.52 (1 H, dd, J = 16.93, 7.41 Hz), 2.73 (1 H, ddq, J = 16.93, 4.50, 0.69 Hz), 2.95 (3 H, s, minor diastereomer), 2.97 (3 H, s), 3.09 (3 H, s, minor diastereomer), 3.10 (3 H, s), 3.15 (1 H, m), 3.25 (1 H, dq, J = 7.53, 6.77 Hz), 4.16 (2 H, dq, J = 7.17, 0.93 Hz). ^{13}C NMR: δ 14.15, 16.37 (q, J = 1.7 Hz), 31.71 (q, J = 2.9 Hz), 33.93 (q, J = 1.7 Hz), 36.00, 37.51, 43.26 (q, J = 25.9 Hz), 61.16, 127.99 (q, J = 281.5 Hz), 171.77, 173.98. ^{19}F NMR: δ 7.9 (d, J = 8.7 Hz, minor diastereomer), 10.7 (d, J = 8.7 Hz). IR (neat, as a diastereomeric mixture): ν 2750, 2950, 1740, 1650 cm^{-1}. HRMS calcd for $C_{11}H_{18}F_3NO_3$ *m/e* 269.1239, found 269.1255.

(3*S,1′*S**)-Ethyl 3-(2′-Oxocyclohexyl)-3-(trifluoromethyl)propionate (6a).** Yield: 80%. De: >46%. R_f = 0.43 (AcOEt:*n*-hexane = 1:4). ^{1}H NMR: δ 1.28 (3 H, t, J = 7.16 Hz), 1.51–2.29 (8 H, m), 2.34 (1 H, dd, J = 15.94, 10.08 Hz), 2.45 (1 H, dd, J = 15.88, 7.68 Hz), 3.54–3.78 (1 H, m), 4.18 (2 H, q, J = 7.14 Hz). ^{13}C NMR: δ 14.10, 24.93, 27.02, 28.41 (q, J = 1.5 Hz), 30.36 (q, J = 2.5 Hz), 37.53 (q, J = 26.1 Hz), 41.90, 48.52 (q, J = 1.7 Hz), 61.07, 129.14 (q, J = 280.1 Hz), 170.71, 208.41. ^{19}F NMR: δ 9.1 (d, J = 10.3 Hz). IR (neat): ν 2950, 2850, 1740, 1720 cm^{-1}. HRMS calcd for $C_{12}H_{18}F_3O_3$ *m/e* (M + H) 267.1208, found 267.1238.

Ethyl 3-(2′-Oxocyclopentyl)-3-(trifluoromethyl)propionate (6b). Yield: 93% (3:2 diastereomeric mixture). R_f = 0.50 (AcOEt:*n*-hexane = 1:5). ^{1}H NMR: δ 1.26 (3 H, t, J = 7.41 Hz, major isomer), 1.27 (3 H, t, J = 7.14 Hz, minor isomer), 1.62–2.80 (9 H, m), 3.20–3.50 (1 H, m), 4.12 (2 H, q, J = 7.45 Hz, major isomer), 4.17 (2 H, q, J = 7.28 Hz, minor isomer). ^{13}C NMR: δ 14.03 (major isomer), 14.14, 20.50 (major isomer), 20.56, 24.74 (major isomer), 26.57 (q, J = 1.9 Hz, minor isomer), 30.22 (q, J = 2.4 Hz, major isomer), 32.00 (q, J = 3.0 Hz, minor isomer), 37.22, 38.00 (q, J = 27.1 Hz, major isomer), 39.07 (q, J = 26.0 Hz, minor isomer), 47.85 (q, J = 1.7 Hz, minor isomer), 48.11 (q, J = 1.7 Hz, major isomer), 61.16 (minor isomer), 61.25 (major isomer), 126.99 (q, J = 280.9 Hz, minor isomer), 127.49 (q, J = 283.5 Hz, major isomer), 170.31 (major isomer), 170.69 (minor isomer), 216.28 (major isomer), 216.35 (minor isomer). ^{19}F NMR: δ 7.9 (d, J = 9.4 Hz, major isomer), 10.8 (d, J = 8.5 Hz, minor isomer). IR (neat, as a diastereomeric mixture): ν 2980, 2890, 1750 cm^{-1}. HRMS calcd for $C_{11}H_{15}F_3O_3$ *m/e* 252.0973, found 252.0977.

(3*S,2′*S**)-Ethyl 3-Pentan-5′-olid-2′-yl-3-(trifluoromethyl)propionate (6c).** Yield: quantitative. De: 74%. R_f = 0.72 (AcOEt:*n*-hexane = 1:2). ^{1}H NMR: δ 1.27 (3 H, t, J = 7.14 Hz), 1.69–2.19 (4 H, m), 2.50 (1 H, dd, J = 15.47, 7.69 Hz), 2.64 (1 H, dd, J = 15.41, 6.72 Hz), 2.97 (1 H, ddd, J = 11.87, 7.40, 2.31 Hz), 3.76 (1 H, dddq, J = 7.13, 6.60, 2.19, 9.87 Hz), 4.16 (2 H, q, J = 7.17 Hz), 4.27–4.47 (2 H, m). ^{13}C NMR: δ 14.04, 20.74, 22.48, 30.10 (q, J = 2.5 Hz), 39.28 (q, J = 2.2 Hz), 39.95 (q, J = 26.6 Hz), 61.36, 69.05, 127.24 (q, J = 280.0 Hz), 170.28, 170.84. ^{19}F NMR: δ 8.4 (d, J = 9.4 Hz). IR (neat): ν 3000, 2600, 1740 cm^{-1}. HRMS calcd for $C_{11}H_{16}F_3O_4$ *m/e* (M + H) 269.1000, found 269.0977.

Ethyl 3-Butan-4′-olid-2′-yl-3-(trifluoromethyl)propionate (6d). Yield: 90%. De: 84%. R_f = 0.64 (AcOEt:*n*-hexane = 1:1). ^{1}H NMR: δ 1.27 (3 H, t, J = 7.16 Hz), 2.17–2.30 (1 H, m), 2.32–2.43 (1 H, m), 2.37 (1 H, dd, J = 15.81, 6.06 Hz), 2.64 (1 H, dd, J = 15.81, 7.57 Hz), 3.07 (1 H, ddd, J = 11.94, 9.13, 2.81 Hz), 3.53 (1H, dddq, J = 7.52, 6.28, 2.76, 9.17 Hz), 4.17 (2 H, q, J = 7.17 Hz), 4.24 (1 H, ddd, J = 10.66, 9.15, 6.49 Hz), 4.45 (1 H, ddd, J = 8.90, 8.86, 2.61 Hz). ^{13}C NMR: δ 14.00, 24.19, 29.94 (q, J = 2.5 Hz), 38.57 (q, J = 2.3 Hz), 34.00 (q, J = 28.7 Hz), 61.50, 66.56, 126.91 (q, J = 279.8 Hz), 169.61, 175.79. ^{19}F NMR: δ 7.4 (d, J = 9.4 Hz). IR (neat): ν 2980, 2920, 1760, 1740 cm^{-1}. HRMS calcd for $C_{10}H_{14}F_3O_4$ *m/e* (M + H) 255.0844, found 255.0851.

Ethyl 3-(*N*-Methyl-2′-pyrrolidinon-3′-yl)-3-(trifluoromethyl)propionate (6e). Yield: 51%. De: 88%. R_f = 0.18 (AcOEt:*n*-hexane = 1:1). ^{1}H NMR: δ 1.26 (3 H, t, J = 7.15 Hz), 1.8–2.3 (2 H, m), 2.27 (1H, dd, J = 15.90, 4.58 Hz), 2.55 (1 H, dd, J = 15.90, 8.65 Hz), 2.87 (3 H, s), 2.75–2.95 (1 H, m), 3.24–3.35 (2 H, m), 3.45–3.70 (1 H, m), 4.15 (2 H, q, J = 7.14 Hz). ^{13}C NMR: δ 14.05, 20.43, 29.97, 39.21, 40.66 (q, J = 2.17 Hz), 47.40, 61.19, 127.58 (q, J = 280.0 Hz), 170.01, 172.61. ^{19}F NMR: δ 8.5 (d, J = 9.0 Hz). IR (neat): ν 3000, 2950, 1740, 1690 cm^{-1}. HRMS calcd for $C_{11}H_{17}F_3NO_3$ *m/e* (M + H) 268.1161, found 268.1189.

(3*Z*,2′*E*)-*N*-Methyl-3-(4′-hydroxy-1′,1′,1′-trifluorobut-2′-enyl-4′-idene)-2-pyrrolidinone (7). Yield: 37%. R_f = 0.35 (AcOEt:*n*-hexane = 1:1). Mp: 84–85 °C. ^{1}H NMR: δ 2.82 (2 H, t, J = 7.03 Hz), 2.92 (3 H, s), 3.49 (2 H, dd, J = 7.62, 6.30 Hz), 6.37 (1 H, dq, J = 15.65, 6.69 Hz), 6.57 (1 H, dq, J = 15.48, 1.56 Hz), 11.5 (1 H, br). ^{13}C NMR: δ 20.19, 29.55, 47.50, 107.88, 120.88 (q, J = 34.4 Hz), 123.27 (q, J = 269.2 Hz), 129.09 (q, J = 6.8 Hz), 152.40, 172.31. ^{19}F NMR: δ 14.0 (d, J = 5.5 Hz). IR (KBr): ν 2950, 1650 cm^{-1}. HRMS calcd for $C_9H_{11}F_3NO_2$ *m/e* (M + H) 222.0742, found 222.0727.

Diethyl 2-(Ethoxycarbonyl)-3-(trifluoromethyl)glutarate (8a). Yield: 99%. R_f = 0.63 (AcOEt:*n*-hexane = 1:3). ^{1}H NMR: δ 1.27 (3 H, t, J = 7.16 Hz), 1.28 (3 H, t, J = 7.17 Hz), 1.29 (3 H, t, J = 7.17 Hz), 2.72 (1 H, dd, J = 17.47, 7.51 Hz), 2.86 (1 H, dd, J = 17.31, 4.31 Hz), 3.67 (1 H, dddq, J = 4.37, 5.70, 7.77, 8.88 Hz), 3.78 (1 H, d, J = 5.69 Hz), 4.19 (2 H, q, J = 7.14 Hz), 4.23 (2 H, q, J = 7.14 Hz), 4.24 (2 H, q, J = 7.14 Hz). ^{13}C NMR: δ 13.93, 14.12, 30.89 (q, J = 2.3 Hz), 39.72 (q, J = 27.4 Hz), 49.75, 61.22, 62.07, 62.38, 126.53 (q, J = 280.4 Hz), 166.71, 170.43. ^{19}F NMR: δ 7.6 (d, J = 7.5 Hz). IR (neat): ν 3000, 2950, 2925, 1760, 1745 cm^{-1}. HRMS calcd for $C_{13}H_{20}F_3O_6$ *m/e* (M + H) 329.1212, found 329.1198.

(3*R*,4*S*,5*S*)-Ethyl 4-(Ethoxycarbonyl)-5-hydroxy-3-(trifluoromethyl)hexanoate (8b). Yield: 52%. *Rf* = 0.61

(AcOEt:*n*-hexane = 1:1). $[\alpha]^{24.0}_D$: +5.27 (*c* 0.97, $CHCl_3$). ^1H NMR: δ 1.27 (3 H, t, J = 7.14 Hz), 1.28 (3 H, d, J = 6.47 Hz), 1.31 (3 H, t, J = 7.17 Hz), 2.66–2.94 (1 H, br), 2.70 (1 H, dd, J = 16.74, 6.03 Hz), 2.74 (1 H, dd, J = 8.61, 3.80 Hz), 2.82 (1 H, dd, J = 16.76, 5.67 Hz), 3.32 (1 H, dtq, J = 9.01, 5.92, 8.81 Hz), 4.18 (2 H, dq, J = 1.40, 7.15 Hz), 4.09–4.20 (1 H, m), 4.24 (2 H, dq, J = 1.09, 7.15 Hz). ^{13}C NMR: δ 14.07, 21.70, 30.89 (q, J = 2.6 Hz), 40.55 (q, J = 26.4 Hz), 49.01, 61.23, 61.42, 65.40, 127.09 (q, J = 280.4 Hz), 170.71, 172.86. ^{19}F NMR: δ 8.8 (d, J = 8.5 Hz). IR (neat): ν 3540, 3000, 2950, 1740 cm^{-1}. HRMS calcd for $C_{12}H_{20}F_3O_5$ *m/e* (M + H) 301.1263, found 301.1254.

Ethyl 4-Nitro-3-(trifluoromethyl)butanoate (9a). Yield: 83%. *Rf* = 0.68 (AcOEt:*n*-hexane = 1:1). ^1H NMR: δ 1.29 (3 H, t, J = 7.16 Hz), 2.60 (1 H, dd, J = 17.13, 8.63 Hz), 2.82 (1 H, dd, J = 17.13, 4.97 Hz), 3.55–3.80 (1 H, m), 4.21 (2 H, q, J = 7.14 Hz), 4.62 (1 H, dd, J = 14.12, 5.55 Hz), 4.71 (1 H, dd, J = 14.16, 6.39 Hz). ^{13}C NMR: δ 14.03, 30.66 (q, J = 2.3 Hz), 38.91 (q, J = 28.6 Hz), 61.80, 72.28, 125.57 (q, J = 279.8 Hz), 169.27. ^{19}F NMR: δ 7.3 (d, J = 8.3 Hz). IR (neat): ν 3000, 2950, 1740, 1570, 1380 cm^{-1}. HRMS calcd for $C_7H_{11}F_3NO_4$ *m/e* (M + H) 230.0640, found 230.0530.

(*E*)-1-(Phenylsulfinyl)-5,5,5-trifluoropent-3-en-2-one (9b). Yield: 78%. *Rf* = 0.62 (AcOEt). Mp: 95.0–96.5 °C. ^1H NMR: δ 4.00 (1 H, d, J = 14.31 Hz), 4.07 (1 H, d, J = 14.30 Hz), 6.55 (1 H, dq, J = 15.93, 5.64 Hz), 6.68 (1 H, dq, J = 15.91, 1.06 Hz), 7.52–7.68 (5 H, m). ^{13}C NMR: δ 60.31, 124.00, 129.64, 132.04, 141.88, 130.84 (q, J = 35.5 Hz), 133.79 (q, J = 5.7 Hz), 189.19. ^{19}F NMR: δ 13.1. IR (KBr): ν 3100, 2950, 2900, 1700, 1660 cm^{-1}.

(*E*)-Dimethyl 2-Oxo-5,5,5-trifluoro-3-pentenylphosphonate (9c). Yield: 90%. ^1H NMR: δ 3.31 (2 H, d, J = 22.87 Hz), 3.78 (3 H, s), 3.84 (3 H, s), 6.69 (1H, dq, J = 15.85, 6.06 Hz), 6.88 (1 H, dq, J = 15.87, 1.55 Hz). ^{13}C NMR: δ 40.75 (d, J = 128.4 Hz), 52.66, 52.73, 122.10 (q, J = 270.6 Hz), 130.18 (q, J = 35.5 Hz), 133.59 (q, J = 5.3 Hz), 169.83. ^{19}F NMR: δ 13.3. IR (neat): ν 2950, 1740, 1300, 1260, 1140, 1040 cm^{-1}.

2,6-Di-*tert*-butyl-4-methylphenyl 4-(Phenylsulfinyl)-3-(trifluoromethyl)butanoate (9d). Yield: 80% (1:1 diastereomeric mixture). *Rf* = 0.33 (AcOEt:*n*-hexane = 1:4). ^1H NMR: δ 1.31, 1.32, 1.32, 1.36 (9 H each, s each), 2.32 (3 H, s), 2.98–3.47 (5 H, m), 7.12–7.14 (2 H, m), 7.49–7.72 (5 H, m). ^{13}C NMR: δ 21.49, 31.46, 31.53, 31.56, 32.96, 33.99, 35.18, 35.64 (q, J = 28.3 Hz), 35.71 (q, J = 28.7 Hz), 54.56, 56.25, 124.00, 124.12, 126.68 (q, J = 251.1 Hz), 126.79 (q, J = 250.2 Hz), 127.17, 127.23, 129.53, 131.79, 134.96, 135.39, 141.87, 141.93, 142.03, 142.78, 143.70, 145.25, 145.31, 170.3, 170.4. ^{19}F NMR: δ 8.1 (d, J = 8.3 Hz), 8.5 (d, J = 6.7 Hz). IR (KBr): ν 2950, 1760, 1050, 745, 735 cm^{-1}. HRMS calcd for $C_{26}H_{34}F_3O_4S$ *m/e* (M + H) 483.2181, found 483.2187.

2,6-Di-*tert*-butyl-4-methylphenyl 3-(*N*-methyl-2′-pyrrolidinon-3′-yl)-3-(trifluoromethyl)propionate (11). Yield: 80% (63:37 diastereomeric mixture). R_f = 0.43 and 0.52 (AcOEt:*n*-hexane = 1:1). ^1H NMR: δ 1.30 and 1.30 (9 H each, s each, minor diastereomer), 1.32 and 1.33 (9 H each, s each, major diastereomer), 1.95–2.32 (2 H, m), 2.31 (3 H, s), 2.67–3.06 (5 H, m), 3.18–3.56 (4 H, m), 7.05–7.15 (2 H, m). ^{13}C NMR: δ 21.49, 22.59 (q, J = 1.7 Hz), 29.95, 31.35–31.52 (m), 32.31 (q, J = 2.6 Hz), 35.12–35.22 (m), 39.65 (q, J = 26.1 Hz), 39.77 (q, J = 1.8 Hz), 46.98 (major diastereomer), 47.33 (minor diastereomer), 127.03, 127.06, 127.15 (q, J = 281.0 Hz), 127.18, 127.22, 134.66, 134.73, 141.94, 142.05, 145.49, 170.27 (minor diastereomer), 171.11 (major diastereomer), 172.40 (minor diastereomer), 172.96 (major diastereomer). ^{19}F NMR: δ 9.1 (d, J = 9.0 Hz, minor diastereomer), 10.9 (d, J = 8.2 Hz, major diastereomer). IR (neat, as a diastereomeric mixture): ν 2950, 2850, 1760, 1680 cm^{-1}. HRMS calcd for $C_{24}H_{34}F_3NO_3$ *m/e* 441.2490, found 441.2470.

(3S*,2′S*)-Benzyl 3-Pentan-5′-olid-2′-yl-3-(trifluoromethyl)propionate (20). Yield: quantitative. R_f = 0.39 (AcOEt:*n*-hexane = 1:1). ^1H NMR: δ 1.75–2.15 (4 H, m), 2.55 (1 H, dd, J = 15.32, 7.82 Hz), 2.71 (1 H, dd, J = 15.50, 6.46 Hz), 2.96 (1 H, ddd, J = 11.49, 7.22, 2.17 Hz), 3.65–3.90 (1 H, m), 4.15–4.42 (2 H, m), 5.12 (2 H, s), 7.30–7.40 (5 H, m). ^{13}C NMR: δ 20.67 (q, J = 1.8 Hz), 22.42, 30.05 (q, J = 2.4 Hz), 39.22 (q, J = 1.9 Hz), 39.92 (q, J = 26.6 Hz), 67.24, 68.95, 127.13 (q, J = 280 Hz), 128.42, 128.46, 128.56, 128.60, 135.31, 170.13, 170.80. ^{19}F NMR: δ 9.5 (d, J = 9.7 Hz). IR (neat): ν 2950, 1740, 750, 700 cm^{-1}. HRMS calcd for $C_{16}H_{18}F_3O_4$ *m/e* (M + H) 331.1157, found 331.1174.

(3*R*,4*R*,1′*S*)-*N*-[1′-(1″-Methylethyl)-2′-hydroxyethyl]-3-(ethoxycarbonyl)-4-(trifluoromethyl)piperidine-2,6-dione (12a). Yield: 93%. De: 89%. R_f = 0.28 (*n*-hexane:AcOEt = 2:1). $[\alpha]^{27.0}_D$: +2.59 (*c* 0.83, MeOH). ^1H NMR: δ 0.79 (3 H, d, J = 6.68 Hz), 1.02 (3 H, d, J = 6.59 Hz), 1.32 (3 H, t, J = 7.15 Hz), 2.39 (1 H, dsep, J = 10.80, 6.59 Hz), 2.65 (1 H, s), 2.86 (1 H, dd, J = 17.66, 8.25 Hz), 3.06 (1 H, dd, J = 17.65, 5.80 Hz), 3.29 (1 H, m), 3.78 (1 H, dd, J = 11.94, 3.43 Hz), 3.86 (1 H, d, J = 7.55 Hz), 4.02 (1 H, dd, J = 11.94, 8.52 Hz), 4.30 (2 H, q, J = 7.12 Hz), 4.53 (1 H, ddd, J = 10.80, 8.52, 3.43 Hz). ^{13}C NMR: δ 13.95, 19.64, 20.33, 25.96, 29.94 (q, J = 2.3 Hz), 37.13 (q, J = 29.4 Hz), 49.35, 61.99, 62.40, 63.28, 125.72 (q, J = 280.2 Hz), 167.30, 168.08, 169.88. ^{19}F NMR: δ 5.7 (d, J = 7.5 Hz), 6.9 (d, J = 7.5 Hz, minor diastereomer). IR (neat): ν 3450, 2975, 2950, 2875, 1735, 1680 cm^{-1}. HRMS calcd for $C_{14}H_{20}F_3NO_5$ *m/e* 339.1294, found 339.1266.

(3*R*,4*R*,4′*S*)-Ethyl 3-(Trifluoromethyl)-4-methyl-5-[4′-(1″-methylethyl)-2′-oxazolidinon-3′-yl]-5-oxopentanoate (12b). Yield: 88%. De: >98%. R_f = 0.27 (*n*-hexane:AcOEt = 3:1). $[\alpha]^{22.0}_D$: +44.04 (*c* 1.10, MeOH). ^1H NMR: δ 0.89 (3 H, d, J = 6.88 Hz), 0.92 (3 H, d, J = 7.05 Hz), 1.18 (3 H, d, J = 6.96 Hz), 1.27 (3 H, dt, J = 7.15, 0.26 Hz), 2.34 (1 H, dsep, J = 7.01, 3.50 Hz), 2.57 (2 H, d, J = 6.22 Hz), 3.48 (1 H, m), 4.17 (2 H, q, J = 7.15 Hz), 4.25 (1 H, dd, J = 9.17, 3.12 Hz), 4.29 (1 H, dd, J = 9.18, 8.09 Hz), 4.29 (1 H, q, J = 6.80 Hz), 4.44 (1 H, ddd, J = 8.17, 3.36, 3.25 Hz). ^{13}C NMR: δ 13.13, 14.13, 14.28, 18.06, 28.19, 29.98 (q, J = 2.4 Hz), 35.81 (q, J = 2.0 Hz), 41.04 (q, J = 26.2 Hz), 58.90, 61.39, 63.42, 127.64 (q, J = 279.9 Hz), 154.07, 171.28, 174.65. ^{19}F NMR: δ 8.8 (d, J = 8.7 Hz). IR (neat): ν 2975, 2925, 2875, 1785, 1740, 1700 cm^{-1}. HRMS calcd for $C_{15}H_{22}F_3NO_5$ *m/e* 353.1450, found 353.1423.

(3*R*,4*R*,4′*S*)-Ethyl 4-Ethyl-3-(trifluoromethyl)-5-[4′-(1″-methylethyl)-2′-oxazolidinon-3′-yl]-5-oxopentanoate (12c). Yield: 52% (74% by ^{19}F NMR). De: >98%. R_f = 0.42 (*n*-hexane:AcOEt = 3:1). $[\alpha]^{29.0}_D$: +66.17 (*c* 1.00, MeOH). ^1H NMR: δ 0.87 (3 H, t, J = 7.33 Hz), 0.90 (3 H, d, J = 6.88 Hz), 0.93 (3 H, d, J = 7.08 Hz), 1.26 (3 H, t, J = 7.14 Hz), 1.64 (1 H, m), 1.73 (1 H, m), 2.36 (1 H, dsep, J = 6.99, 3.42 Hz), 2.55 (1 H, dd, J = 16.85, 6.75 Hz), 2.60 (1 H, dd, J = 16.88, 5.62 Hz), 3.36 (1 H, dddq, J = 8.84, 6.75, 6.62, 6.52 Hz), 4.16 (2 H, q, J = 7.14 Hz), 4.25 (1 H, dd, J = 9.17, 3.46 Hz), 4.27 (1 H, dd, J = 9.33, 7.44 Hz), 4.29 (1 H, ddd, J = 10.66, 6.52, 3.78 Hz), 4.47 (1 H, dt, J = 7.60, 3.37 Hz). ^{13}C NMR: δ 11.32, 14.13, 14.30, 18.14, 21.09, 28.22, 30.18 (q, J = 2.4 Hz), 41.54 (q, J = 26.3 Hz), 42.00 (q, J = 1.9 Hz), 58.92, 61.36, 63.33, 127.53 (q, J = 280.3 Hz), 154.09, 171.24, 173.92. ^{19}F NMR: δ 9.2 (d, J = 8.8 Hz). IR (neat): ν 2975, 2925, 2875, 1785, 1740, 1700 cm^{-1}. HRMS calcd for $C_{16}H_{24}F_3NO_5$ *m/e* 367.1607, found 367.1635.

(3*R*,4*R*,4″*S*)-Ethyl 3-(Trifluoromethyl)-4-(1′-methylethyl)-5-[4″-(1‴-methylethyl)-2″-oxazolidinon-3″-yl]-5-oxopentanoate (12d). Yield: 61%. De: 97%. Mp: 79.5–80.0 °C. R_f = 0.53 (*n*-hexane:AcOEt = 5:1). $[\alpha]^{27.0}_D$: +62.70 (*c* 1.13, MeOH). ^1H NMR: δ 0.87, 0.93, 0.94, and 1.00 (3 H each, d, J = 6.89, 7.37, 7.08, and 6.85 Hz, respectively), 1.28 (3 H, dt, J = 7.11, 0.31 Hz), 2.15 (1 H, dsep, J = 7.00, 5.68 Hz), 2.39 (1 H, dsep, J = 6.97, 3.30 Hz), 2.55 (1 H, dd, J = 16.59, 7.07 Hz), 2.60 (1 H, dd, J = 16.59, 5.15 Hz), 3.44 (1 H, dddq, J = 9.91, 8.38, 6.92, 5.49 Hz), 4.19 (2 H, q, J = 7.13 Hz), 4.22 (1 H, dd, J = 11.61, 4.06 Hz), 4.23 (1 H, dd, J = 11.61, 3.23 Hz), 4.46 (1 H, dd, J = 9.82, 5.63 Hz), 4.49 (1 H, ddd, J = 6.72, 3.85, 3.44 Hz). ^{13}C NMR: δ 14.14, 14.14, 14.27, 17.50, 18.15, 28.25, 28.39, 31.35 (q, J = 2.8 Hz), 41.09 (q, J = 25.7 Hz), 43.81 (q, J = 1.5 Hz), 59.09, 61.45, 63.05, 127.90 (q, J = 282.6 Hz), 154.35, 171.09, 172.60. ^{19}F NMR: δ 9.7 (d, J = 8.1 Hz). IR (neat): ν 2975, 2925, 2880, 1785, 1740, 1700 cm^{-1}. HRMS calcd for $C_{17}H_{26}F_3NO_5$ *m/e* 381.1763, found 381.1755.

Ethyl 3-(trifluoromethyl)-5-[4′-(1″-methylethyl)-2′-oxazolidinon-3′-yl]-5-oxo-4-phenylpentanoate (12e). Combined yield: 62%. De: 30%. R_f = 0.63 (*n*-hexane:AcOEt = 3:1). Major diastereomer. ^1H NMR: δ 0.88 and 0.91 (3 H each,

d, J = 6.84 Hz), 1.12 (3 H, t, J = 7.08 Hz), 2.11 (1 H, dd, J = 16.60, 5.62 Hz), 2.38 (1 H, dd, J = 16.60, 6.59 Hz), 2.45 (1 H, dsep, J = 7.08, 3.42 Hz), 3.87 and 3.95 (1 H each, dq, J = 10.74 and 7.08 and 10.74 and 7.32 Hz, respectively), 4.05 (1 H, m), 4.12 (2 H, m), 4.36 (1 H, m), 5.50 (1 H, d, J = 10.99 Hz), 7.28 (5 H, m). ^{13}C NMR: δ 13.96, 13.96, 18.00, 27.89, 31.91 (q, J = 2.5 Hz), 42.33 (q, J = 25.8 Hz), 46.70 (q, J = 2.0 Hz), 59.09, 61.14, 62.99, 127.67 (q, J = 282.3 Hz), 128.95, 129.33, 130.55, 133.93, 153.88, 170.80, 171.78. ^{19}F NMR: δ 8.3 (d, J = 8.5 Hz). Minor diastereomer. ^{1}H NMR: δ 0.90 and 0.93 (3 H each, d, J = 6.84 Hz), 1.24 (3 H, t, J = 7.08 Hz), 2.45 (1 H, dsep, J = 17.08, 3.42 Hz), 2.62 (1 H, dd, J = 16.60, 3.66 Hz), 2.81 (1 H, dd, J = 16.61, 7.57 Hz), 3.57 (1 H, dsex, J = 8.79, 3.66 Hz), 4.13 (4 H, m), 4.35 (1 H, m), 5.66 (1 H, d, J = 8.54 Hz), 7.42 (5 H, m). ^{13}C NMR: (peaks of this isomer could not be fully identified): δ 28.33, 32.32 (q, J = 2.4 Hz), 59.23, 61.10, 63.03, 128.64, 129.18, 129.58, 134.91, 171.03, 171.42. ^{19}F NMR: δ 10.8 (d, J = 8.5 Hz). IR (neat, as a diastereomeric mixture): ν 2975, 2900, 2875, 1785, 1740, 1700 cm^{-1}. HRMS calcd for $C_{20}H_{24}F_3NO_5$ m/e 415.1607, found 446.1779.

(3*R*,4*R*,4′*S*)-Ethyl 4-(Benzyloxy)-3-(trifluoromethyl)-5-[4′-(1″-methylethyl)-2′-oxazolidinon-3′-yl]-5-oxopentanoate (12f). Yield: 36%. De: 30%. R_f = 0.34 (*n*-hexane:AcOEt = 3:1). $[\alpha]^{27.0}_D$: +51.44 (*c* 0.85, MeOH). ^{1}H NMR: δ 0.89 and 0.90 (3 H each, d, J = 7.12 and 6.92 Hz, respectively), 1.23 (3 H, dt, J = 7.12, 0.40 Hz), 2.26 (1 H, dsep, J = 6.99, 3.47 Hz), 2.61 (1 H, dd, J = 17.57, 6.05 Hz), 2.89 (1 H, dd, J = 17.57, 5.79 Hz), 3.43 (1 H, dtq, J = 8.72, 5.92, 2.79 Hz), 4.08 (1 H, dq, J = 10.78, 7.12 Hz), 4.12 (1 H, dq, J = 10.78, 7.13 Hz), 4.18 (1 H, t, J = 8.69 Hz), 4.22 (1 H, dd, J = 9.05, 2.73 Hz), 4.25 (1 H, ddd, J = 8.25, 3.26, 2.93 Hz), 4.51 (1 H, d, J = 11.44 Hz), 4.54 (1 H, d, J = 11.38 Hz), 5.51 (1 H, d, J = 2.73 Hz), 7.33 (5 H, m). ^{13}C NMR: δ 14.12, 14.50, 18.05, 27.95 (q, J = 2.2 Hz), 28.26, 42.37 (q, J = 27.3 Hz), 58.77, 61.21, 64.26, 73.23, 73.52, 126.70 (q, J = 281.8 Hz), 128.46, 128.71, 128.74, 137.23, 154.02, 170.41, 171.46. ^{19}F NMR: δ 9.0 (d, J = 8.7 Hz). IR (neat): ν 2975, 2925, 2875, 1785, 1740, 1715 cm^{-1}. HRMS calcd for $C_{21}H_{26}F_3NO_6$ m/e (M + H) 446.1790, found 446.1779.

(4*S*,1″*R*,2″*R*,3″*S*)- and (4*S*,1″*S*,2″*S*,3″*S*)-3-[1′-[2″-(ethoxycarbonyl)-3″-(trifluoromethyl)cyclopropyl]-1′-oxomethyl]-4-(1‴-methylethyl)-2-oxazolidinone (12g and 12h). (4*S*,1″*R*,2″*R*,3″*S*)-Isomer. Yield: 63%. R_f = 0.46 (*n*-hexane:AcOEt = 3:1). $[\alpha]^{29.5}_D$: +14.66 (*c* 1.21, MeOH). ^{1}H NMR: δ 0.91 and 0.94 (3 H each, d, J = 6.93 and 7.02 Hz, respectively), 1.31 (3 H, t, J = 7.16 Hz), 2.38 (1 H, dsep, J = 6.97, 4.07 Hz), 2.64 (1 H, ddq, J = 10.42, 7.34, 5.85 Hz), 2.92 (1 H, t, J = 6.03 Hz), 3.50 (1 H, dd, J = 10.42, 6.21 Hz), 4.22 (2 H, q, J = 7.17 Hz), 4.25 (1 H, dd, J = 9.15, 3.17 Hz), 4.31 (1 H, dd, J = 9.15, 8.19 Hz), 4.43 (1 H, ddd, J = 8.20, 4.03, 3.21 Hz). ^{13}C NMR: δ 14.14, 14.83, 17.94, 22.49 and 27.94 (q each, J = 2.7 and 2.0 Hz, respectively), 28.56, 28.84 (q, J = 38.5 Hz), 58.99, 62.16, 64.03, 124.37 (q, J = 274.4 Hz), 154.12, 164.99, 169.78. ^{19}F NMR: δ 15.8 (d, J = 6.0 Hz). IR (neat): ν 3075, 2975, 2925, 2875, 1780, 1735, 1705 cm^{-1}. HRMS calcd for $C_{14}H_{18}F_3NO_5$ m/e 337.1137, found 337.1117. (4*S*,1″*S*,2″*S*,3″*S*) Isomer. Yield: 30%. R_f = 0.23 (*n*-hexane:AcOEt = 3:1). $[\alpha]^{28.5}_D$: +134.06 (*c* 1.13, MeOH). ^{1}H NMR: δ 0.85 and 0.92 (3 H each, d, J = 6.89 and 7.07 Hz, respectively), 1.30 (3 H, t, J = 7.16 Hz), 2.34 (1 H, dsep, J = 6.99, 3.39 Hz), 2.67 (1 H, ddq, J = 10.43, 7.36, 5.91 Hz), 2.93 (1 H, t, J = 6.05 Hz), 3.43 (1 H, dd, J = 10.39, 6.16 Hz), 4.21 (2 H, q, J = 7.16 Hz), 4.27 (1 H, dd, J = 9.18, 2.96 Hz), 4.32 (1 H, dd, J = 9.15, 8.17 Hz), 4.44 (1 H, dt, J = 8.24, 3.19 Hz). ^{13}C NMR: δ 13.95, 14.13, 18.03, 22.28, 28.17 (q each, J = 2.5 and 2.0 Hz, respectively), 28.07, 28.99 (q, J = 38.8 Hz), 59.01, 62.11, 63.97, 124.40 (q, J = 274.4 Hz), 154.11, 164.64, 169.81. ^{19}F NMR: δ 16.1 (d, J = 6.0 Hz). IR (neat): ν 3075, 2975, 2925, 2875, 1790, 1740, 1705 cm^{-1}. HRMS calcd for $C_{14}H_{18}F_3NO_5$ m/e 337.1137, found 337.1152. Anal. Calcd for $C_{14}H_{18}F_3NO_5$: C, 49.85; H, 5.38; N, 4.15. Found: C, 49.94; H, 5.44; N, 4.21.

General Procedure for Selective Removal of Oxazolidinone. A stirred solution of 1,4-adduct (1.0 mmol) dissolved in 20 mL of THF−H_2O (3:1, v/v) was treated at 0 °C with 0.35 mL (4.0 mmol, 4.0 equiv) of 35% H_2O_2, followed by 84 mg (2.0 mmol, 2.0 equiv) of solid LiOH·H_2O, and the whole mixture was stirred at the same temperature. The solution was treated with 0.55 g (4.4 mmol) of Na_2SO_3 in 3 mL of H_2O, followed by 10 mL of 0.5 N $NaHCO_3$ when TLC analysis showed the disappearance of the 1,4-adduct. After removal of THF in vacuo, the residue was diluted with H_2O and extracted twice with CH_2Cl_2. The aqueous phase was acidified to pH = 1−2 with 3 N HCl and extracted three times with EtOAc. The latter extracts were combined, dried ($MgSO_4$), and evaporated to yield the desired monoacid. No further purification was performed at this stage, but the obtained product was found to be almost pure by its spectroscopic properties.

(2*R*,3*R*)-4-Carbethoxy-3-(trifluoromethyl)-2-methylbutyric Acid (13a). Yield: 96%. $[\alpha]^{27.5}_D$: −7.25 (*c* 1.02, $CHCl_3$). ^{1}H NMR: δ 1.26 (3 H, dq, J = 7.22, 0.85 Hz), 1.27 (3 H, t, J = 7.14 Hz), 2.55 (1 H, dd, J = 16.67, 6.63 Hz), 2.64 (1 H, dd, J = 16.67, 6.47 Hz), 2.96 (1 H, dq, J = 7.15, 4.22 Hz), 3.41 (1 H, dtq, J = 9.38, 6.62, 4.19 Hz), 4.17 (2 H, q, J = 7.14 Hz), 8.3 (1 H, br). ^{13}C NMR: δ 12.30, 14.06, 30.15 (q, J = 2.4 Hz), 37.55 (q, J = 2.0 Hz), 41.18 (q, J = 26.6 Hz), 61.59, 127.51 (q, J = 281.2 Hz), 171.33, 179.84. ^{19}F NMR: δ 7.8 (d, J = 8.8 Hz). IR (neat): ν 3300, 3000, 1745, 1720 cm^{-1}. HRMS calcd for $C_9H_{14}F_3O_4$ m/e (M + H) 243.0844, found 243.0855.

(2*R*,3*R*)-3-(Trifluoromethyl)-2-methylglutalic Acid (13b). The same procedure for the preparation of (2*R*,3*R*)-4-carbethoxy-3-(trifluoromethyl)-2-methylbutyric acid was employed, except for the reaction time (4 h), and the same workup afforded the desired diacid. Purification was performed by recrystallization from CH_2Cl_2 to afford pure diacid in 86% yield. Mp: 90.0−91.5 °C. $[\alpha]^{24.5}_D$: −15.83 (*c* 1.03, $CHCl_3$). ^{1}H NMR: δ 1.23 (3 H, dq, J = 7.24, 0.83 Hz), 2.59 (2 H, d, J = 6.39 Hz), 2.95 (1 H, dq, J = 7.15, 3.67 Hz), 3.40 (1 H, dtq, J = 9.68, 6.59, 3.64 Hz), 7.65 (2 H, brs). ^{13}C NMR: δ 11.75, 29.61 (q, J = 2.5 Hz), 37.28 (q, J = 2.0 Hz), 41.02 (q, J = 26.6 Hz), 127.56 (q, J = 281.2 Hz), 175.02, 178.03. ^{19}F NMR: δ 7.7 (d, J = 9.8 Hz). IR (KBr): ν 3060, 2990, 1725 cm^{-1}. HRMS calcd for $C_7H_9F_3O_4$ m/e 214.0453, found 214.0453. Anal. Calcd for $C_7H_9F_3O_4$: C, 39.26; H, 4.24; N, 0.00. Found: C, 39.09; H, 4.33; N, −0.03.

4-Carbethoxy-3-(trifluoromethyl)-2-phenylbutyric Acid (14). Combined yield: 85%. De: >98%. Major diastereomer. ^{1}H NMR: δ 1.13 (3 H, t, J = 7.16 Hz), 2.16 (1 H, dd, J = 16.80, 4.09 Hz), 2.36 (1 H, dd, J = 16.80, 6.47 Hz), 3.79 (2 H, m), 3.92 (1 H, dq, J = 10.82, 7.16 Hz), 3.98 (1 H, dq, J = 10.82, 7.16 Hz), 7.33 (5 H, m), 10.30 (1 H, brs). ^{13}C NMR: δ 13.91, 31.53 (q, J = 2.4 Hz), 42.09 (q, J = 26.1 Hz), 50.25, 61.12, 126.93 (q, J = 280.7 Hz), 128.57, 129.15, 129.29, 133.40, 170.27, 177.34. ^{19}F NMR: δ 7.3 (d, J = 7.2 Hz). Minor diastereomer. ^{1}H NMR: δ 1.23 (3 H, t, J = 7.16 Hz), 2.64 (1 H, dd, J = 17.13, 4.26 Hz), 2.76 (1 H, dd, J = 17.05, 7.41 Hz), 3.54 (1 H, m), 4.01 (1 H, d, J = 4.69 Hz), 4.11 (1 H, dq, J = 10.57, 7.16 Hz), 4.14 (1 H, dq, J = 10.57, 7.16 Hz), 7.33 (5 H, m), 10.30 (1 H, bs). ^{13}C NMR: δ 14.02, 31.83 (q, J = 2.6 Hz), 43.29 (q, J = 25.9 Hz), 50.25, 61.26, 126.54 (q, J = 281.2 Hz), 128.40, 128.74, 128.89, 134.26, 170.54, 176.79. ^{19}F NMR: δ 9.8 (d, J = 7.5 Hz). IR (neat, as a diastereomeric mixture): ν 3065, 2990, 1740, 1720 cm^{-1}. HRMS calcd for $C_{14}H_{16}F_3O_4$ m/e 305.1001, found 305.0981.

(1*R*,3*R*)-1,3-Bis[(benzoyloxy)methyl]-2-(trifluoromethyl)cyclopropane (+)-(15)) and (1′*S*,3*S*)-1,3-Bis[(benzoyloxy)methyl]-2-(trifluoromethyl)cyclopropane ((−)-(15)). To a stirred solution of lithium aluminum hydride (0.15 g, 4.0 mmol) in 10 mL of freshly distilled THF was added a solution of 0.68 g (2.0 mmol) of **9g** or **9h** in 10 mL of freshly distilled THF at 0 °C under a nitrogen atmosphere. After the mixture was stirred for 1.5 h at 0 °C, the reaction was quenched by cautious addition of 4 N aqueous KOH. The supernatant was separated by decantation, and the resulting precipitates were washed twice with THF. The combined supernatants were dried ($MgSO_4$) and evaporated. To a solution of 0.86 mL (6.0 mmol) of benzoyl chloride and the crude product in methylene chloride (6 mL) was carefully added pyridine (0.36 mL, 6 mmol) under an atmosphere of nitrogen at 0 °C. After the mixture was stirred overnight at room temperature, 1 N HCl was added to the reaction mixture, which was extracted with methylene chloride, washed with 1 N HCl and diluted $NaHCO_3$, dried

over anhydrous $MgSO_4$, and purified by silica gel column chromatography (AcOEt:*n*-hexane = 3:1) to give pure **15** in 85% yield. **(+)-15.** R_f = 0.42 (*n*-hexane:AcOEt = 3:1). $[\alpha]^{21.0}_D$: +3.91 (*c* 1.08, $CHCl_3$). ^1H NMR: δ 1.75–2.05 (3 H, m), 4.20–4.45 (3 H, m), 4.55–4.70 (1 H, m), 7.30–7.80 (6 H, m), 7.90–8.20 (4 H, m). ^{13}C NMR: δ 20.70, 20.75, 23.13 (q, J = 37.1 Hz), 62.32 (q, J = 2.2 Hz), 65.09, 125.95 (q, J = 290.9 Hz), 128.38, 128.44, 128.89, 129.60, 133.08, 133.20, 134.55, 166.27, 166.34. ^{19}F NMR: δ 18.9. IR (neat): ν 3060, 1790, 1720, 1600, 1450, 1210, 700 cm^{-1}. HRMS calcd for $C_{20}H_{17}F_3O_4$ *m/e* 378.1079, found 378.1075. **(−)-15.** $[\alpha]^{20.0}_D$: −3.17 (*c* 0.55, $CHCl_3$). ^1H NMR: δ 1.74–2.05 (3 H, m), 4.20–4.45 (3 H, m), 4.52–4.65 (1 H, m), 7.32–7.74 (6 H, m), 7.94–8.20 (4 H, m). ^{13}C NMR: δ 20.69, 20.74, 23.12 (q, J = 37.4 Hz), 62.33 (q, J = 2.2 Hz), 65.10, 125.86 (q, J = 281.4 Hz), 128.38, 128.44, 128.89, 129.60, 133.58, 133.08, 133.20, 134.55, 166.25, 166.35. ^{19}F NMR: δ 18.9.

(2*R*,3*R*)-4-Carbethoxy-3-(trifluoromethyl)-2-methylbutyroyl Chloride (16). To a stirred solution of 0.242 g (1.0 mmol) of monoacid, prepared from Michael adduct with *N*-propionyloxazolidinone, in 5 mL of benzene was added 0.37 mL (5.0 mmol) of distilled $SOCl_2$ at 0 °C under a N_2 atmosphere. After 3.5 h reflux and the removal of the volatiles in vacuo, the residue was distilled under reduced pressure to afford the desired acid chloride in 90% yield (0.235 g, 0.90 mmol). Bp: 85–90 °C/1.0 mmHg (bath temperature). ^1H NMR: δ 1.28 (3 H, t, J = 7.15 Hz), 1.35 (3 H, dq, J = 7.14, 0.77 Hz), 2.50 (1 H, dd, J = 16.99, 7.00 Hz), 2.66 (1 H, dd, J = 16.89, 6.05 Hz), 3.32 (1 H, dq, J = 7.14, 4.39 Hz), 3.57 (1 H, dddq, J = 9.09, 6.98, 6.06, 4.35 Hz), 4.19 (1 H, dq, J = 7.12, 0.96 Hz), 4.19 (1 H, dq, J = 7.19, 0.96 Hz). ^{13}C NMR: δ 12.84 (q, J = 1.3 Hz), 14.08, 29.73 (q, J = 2.5 Hz), 41.14 (q, J = 27.1 Hz), 49.39 (q, J = 2.1 Hz), 61.79, 127.01 (q, J = 281.2 Hz), 170.39, 175.87. ^{19}F NMR: δ 8.4 (d, J = 8.1 Hz).

(3*R*,4*R*)-Ethyl 3-(Trifluoromethyl)-4-methyl-5-oxo-5-phenylpentanoate (17a). To a solution of phenyllithium (0.58 mL, 1.05 mmol, 1.8 M in cyclohexane and ether) in 5 mL of freshly distilled THF was added Et_2AlCl (1.1 mL, 1.1 mmol, 1.0 M in hexanes) at −78 °C under a N_2 atmosphere. After the mixture was stirred for 30 min at −78 °C, the above acid chloride (0.261 g, 1.0 mmol) was added with removal of a cooling bath. The solution was further stirred for 2 h at room temperature, quenched with water, and filtered through Celite-545. The filtrate was separated, and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Purification with silica gel column chromatography (*n*-hexane:AcOEt = 7:1) afforded the desired keto ester (0.127 g, 0.42 mmol, 42% yield). R_f = 0.30 (*n*-hexane:AcOEt = 10:1). $[\alpha]^{23.0}_D$: −15.81 (*c* 0.66, MeOH). ^1H NMR: δ 1.24 (3 H, dq, J = 7.08, 0.73 Hz), 1.24 (3 H, t, J = 7.14 Hz), 2.57 (1 H, dd, J = 16.72, 6.84 Hz), 2.67 (1 H, dd, J = 16.72, 5.50 Hz), 3.44 (1 H, dddq, J = 9.40, 6.95, 5.61, 4.88 Hz), 3.94 (1 H, dq, J = 7.08, 4.77 Hz), 4.13 (1 H, dq, J = 10.75, 7.08 Hz), 4.17 (1 H, dq, J = 10.86, 7.08 Hz), 7.49, 7.59, 7.94 (5 H, m). ^{13}C NMR: δ 12.88, 14.06, 29.80 (q, J = 2.5 Hz), 37.89 (q, J = 1.9 Hz), 40.69 (q, J = 26.0 Hz), 61.14, 127.51 (q, J = 280.8 Hz), 128.38, 128.90, 133.49, 135.36, 170.58, 200.75. ^{19}F NMR: δ 8.2 (d, J = 9.2 Hz). IR (neat): ν 3050, 3000, 2925, 1740, 1690, 1600, 1580 cm^{-1}.

(3*R*,4*R*)-Ethyl 3-(Trifluoromethyl)-4-methyl-5-oxoheptanoate (17b). To a stirred suspension of 0.509 g (1.6 mmol) of manganous iodide in 7 mL of freshly distilled ether was added 3.2 mL (1.6 mmol) of ethylmagnesium bromide (0.5 M in ether) at 0 °C under a N_2 atmosphere. After stirring for 10 min at 0 °C, the solution was allowed to warm to ambient temperature and stirred for another 30 min to afford EtMnI. In a separate flask, a solution of ethyl chloroformate (0.15 mL, 1.6 mmol) in 3 mL of freshly distilled ether was added to a stirred solution of the above acid chloride (0.363 g, 1.5 mmol) and Et_3N (0.22 mL, 1.6 mmol) in 7 mL of freshly distilled ether at 0 °C under a N_2 atmosphere. After the mixture was stirred for 1 h at room temperature, the amine salt was filtered off and the residue was washed with ether. The combined filtrate was washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated. The resulting crude mixed anhydride was then added via syringe to the suspension of EtMnI in ether at −40 °C. The resulting slurry was stirred for 2 h at room temperature. The reaction was quenched with aqueous 1 N HCl, the mixture was diluted with ether, and the resulting organic layer was separated. The aqueous layer was extracted with ether twice, and the combined ethereal layers were washed with brine, dried ($MgSO_4$), and evaporated. Purification with silica gel column chromatography (*n*-hexane:AcOEt = 7:1) followed by distillation (bp 115 °C/0.8 mmHg (bath temperature)) afforded the desired keto ester (0.133 g, 0.52 mmol, 35% total yield). R_f = 0.40 (*n*-hexane:AcOEt = 7:1). $[\alpha]^{16.0}_D$: −1.30 (*c* 0.99, MeOH). ^1H NMR: δ 1.07 (3 H, t, J = 7.24 Hz), 1.14 (3 H, dq, J = 7.16, 0.77 Hz), 1.27 (3 H, t, J = 7.15 Hz), 2.51 (2 H, d, J = 6.32 Hz), 2.56 (2 H, dq, J = 7.18, 1.19 Hz), 2.96 (1 H, dq, J = 7.17, 5.11 Hz), 3.36 (1 H, dtq, J = 9.42, 6.29, 5.09 Hz), 4.14 (1 H, dq, J = 10.75, 7.13 Hz), 4.17 (1 H, dq, J = 10.82, 7.17 Hz). ^{13}C NMR: δ 7.73, 12.17, 14.09, 29.86 (q, J = 2.4 Hz), 34.45, 40.23 (q, J = 26.2 Hz), 43.18 (q, J = 1.9 Hz), 61.21, 127.44 (q, J = 281.2 Hz), 170.74, 211.23. ^{19}F NMR: δ 8.2 (d, J = 9.0 Hz). IR (neat): ν 2975, 2950, 1740, 1720 cm^{-1}.

(2*R*,3*R*)-Diethyl 3-(Trifluoromethyl)-2-methylglutarate (17c). To a stirred solution of EtOH (0.11 mL, 1.8 mmol) and pyridine (74 mL, 0.9 mmol) in 5 mL of freshly distilled CH_2Cl_2 was added a solution of the above acid chloride (0.235 g, 0.9 mmol) in 3 mL of freshly distilled CH_2Cl_2 at 0 °C under a N_2 atmosphere. After the mixture was stirred overnight at room temperature, the reaction was quenched with aqueous 3 N HCl and diluted with CH_2Cl_2, followed by the separation of the resulting organic layer. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Short path silica gel column chromatography (*n*-hexane:AcOEt = 5:1) and distillation under reduced pressure afforded the desired glutarate (0.148 g, 0.55 mmol, 61% yield). Bp: 95–100 °C/0.09 mmHg (bath temperature). R_f = 0.40 (*n*-hexane:AcOEt = 10:1). $[\alpha]^{26.0}_D$: −8.57 (*c* 1.16, MeOH). ^1H NMR: δ 1.22 (3 H, dq, J = 7.19, 0.88 Hz), 1.27 and 1.28 (3 H each, t, J = 7.15 and 7.15 Hz, respectively), 2.57 (2 H, d, J = 6.35 Hz), 2.90 (1 H, dq, J = 7.14, 4.47 Hz), 3.37 (1 H, dtq, J = 9.46, 6.41, 4.47 Hz), 4.17 (4 H, q, J = 7.12 Hz). ^{13}C NMR: δ 12.52 (q, J = 1.3 Hz), 14.12, 14.14, 30.15 (q, J = 2.5 Hz), 37.72 (q, J = 2.0 Hz), 41.39 (q, J = 26.5 Hz), 61.39, 61.42, 127.63 (q, J = 281.2 Hz), 171.16, 174.11. ^{19}F NMR ($CDCl_3$): δ 8.2 (d, J = 9.0 Hz). IR (neat): ν 3000, 2900, 2850, 1740 cm^{-1}.

(3*R*,4*R*)-Ethyl *N*,*N*-Dimethyl-3-(trifluoromethyl)-4-methylglutamate (17d). To a stirred solution of the above acid chloride (0.195 g, 0.75 mmol) in 5 mL of THF was added dimethylamine (50% in water) (0.194 g, 1.65 mmol) at 0 °C. After the mixture was stirred for 30 min at 0 °C, the reaction was quenched with aqueous 3 N HCl, and the mixture was diluted with ether, followed by the separation of the resulting organic layer. The aqueous layer was extracted twice with ether, and the combined ethereal layers were washed with brine, dried ($MgSO_4$), and evaporated. Purification by silica gel column chromatography (*n*-hexane:AcOEt = 2:1) afforded the desired amide (0.171 g, 0.64 mmol, 85% yield). R_f = 0.36 (*n*-hexane:AcOEt = 1:1). $[\alpha]^{26.5}_D$: −3.96 (*c* 1.03, MeOH). ^1H NMR: δ 1.16 (3 H, dq, J = 6.74, 0.80 Hz), 1.27 (3 H, t, J = 7.15 Hz), 2.51 (1 H, dd, J = 16.89, 6.92 Hz), 2.82 (1 H, dd, J = 16.90, 4.49 Hz), 2.95 and 3.10 (3 H each, s), 3.23 (2 H, m), 4.16 (2 H, q, J = 7.15 Hz). ^{13}C NMR: δ 14.16 (q, J = 1.1 Hz), 14.15, 29.74 (q, J = 2.4 Hz), 33.02 (q, J = 2.9 Hz), 36.02, 37.31, 41.05 (q, J = 25.8 Hz), 61.25, 127.90 (q, J = 281.6 Hz), 171.53, 174.09. ^{19}F NMR: δ 7.9 (d, J = 8.7 Hz). IR (neat): ν 3000, 2950, 1740, 1655 cm^{-1}.

(3*S,1′*S**,2′*S**)- and (3*S**,1′*S**,2′*R**)-3-(2′-Hydroxycyclohexyl)-3-(trifluoromethyl)propanol (18a and 18b).** To a stirred solution of lithium aluminum hydride (0.36 g, 9.4 mmol) in 10 mL of freshly distilled THF was added a solution of 2.78 g (10.4 mmol) of **5** in 10 mL of freshly distilled THF at 0 °C under a nitrogen atmosphere. After the mixture was stirred overnight at room temperature, the reaction was quenched by cautious addition of 4.5 N aqueous KOH. The supernatant was separated by decantation, and the resulting precipitates were washed twice with THF. The combined supernatants

were dried ($MgSO_4$) and evaporated. The mixture was purified by silica gel column chromatography (AcOEt:*n*-hexane = 1:1) and recrystallization (ether:*n*-hexane = 1:3) to give pure diol in 85% yield (66% de). (3*S**,1′*S**,2′*S**)-Isomer (major). R_f = 0.49 (AcOEt). Mp: 76.0–77.0 °C. ^{1}H NMR: δ 1.00–1.44 (4 H, m), 1.64–1.86 (6 H, m), 1.96–2.08 (1 H, m), 2.78–3.02 (1 H, m), 3.26 (2 H, br), 3.32–3.47 (1 H, m), 3.62–3.89 (2 H, m). ^{13}C NMR: δ 24.97, 25.36, 25.06 (q, J = 1.5 Hz), 25.24 (q, J = 2.0 Hz), 35.31, 38.12 (q, J = 24.2 Hz), 44.23 (q, J = 1.8 Hz), 61.43, 70.00, 129.14 (q, J = 280.8 Hz). ^{19}F NMR: δ 11.6 (d, J = 11.7 Hz). IR (KBr): ν 3400 (br), 2950, 2850 cm^{-1}. HRMS calcd for $C_{10}H_{18}F_3O_2$ *m/e* (M + H) 227.1259, found 227.1289. Anal. Calcd for $C_{10}H_{17}F_3O_2$: C, 53.09; H, 7.57; N, 0.00. Found: C, 52.89; H, 7.66; N, 0.03. (3*S**,1′*S**,2′*R**)-Isomer (minor). R_f = 0.55 (AcOEt). Mp: 68.0–69.0 °C. ^{1}H NMR: δ 1.00–1.44 and 1.64–1.86 (10 H, m), 1.96–2.08 (1 H, m), 2.78–3.02 (1 H, m), 3.26–3.27 (2 H, m), 3.32–3.47 (1 H, m), 3.62–3.89 (2 H, m). ^{13}C NMR: δ 19.62, 22.02, 26.03, 26.35 (q, J = 2.4 Hz), 34.08, 39.83 (q, J = 2.0 Hz), 43.58 (q, J = 24.0 Hz), 61.71, 71.88, 129.09 (q, J = 279.9 Hz). ^{19}F NMR: δ 8.6 (d, J = 11.0 Hz). IR (KBr): ν 3350 (br), 2950, 2900 cm^{-1}. HRMS calcd for $C_{10}H_{18}F_3O_2$ *m/e* (M + H) 227.1259, found 227.1252.

(3*S,2′*S**)-3-Pentan-5′-olide-2′-yl-3-(trifluoromethyl)-propionic Acid (19).** To a suspension of 10% Pd/C (150 mg) in ethanol (20 mL) was added the benzyl ester 2.5 g (7.5 mmol) at room temperature under an atmosphere of hydrogen. The whole mixture was stirred overnight at that temperature and then filtered, and the solvent was removed to afford the white solid, which was purified by recrystallization (ether:*n*-hexane = 1:1) to give pure carboxylic acid in 91% yield. Mp: 152.0–153.0 °C. ^{1}H NMR: δ 1.75–2.15 (4 H, m), 2.43 (1 H, dd, J = 15.73, 7.72 Hz), 2.58 (1 H, dd, J = 15.75, 6.55 Hz), 2.85–3.00 (1 H, m), 3.60–3.82 (1 H, m), 4.20–4.40 (2 H, m), 8.25 (1 H, br). ^{13}C NMR: δ 20.84, 22.48, 29.91 (q, J = 2.5 Hz), 39.29 (q, J = 1.9 Hz), 39.83 (q, J = 26.6 Hz), 69.00, 127.33 (q, J = 280.2 Hz), 170.99, 172.46. ^{19}F NMR: δ 9.8 (d, J = 9.7 Hz). IR (KBr): ν 3000, 1740, 1720, 1700 cm^{-1}. HRMS calcd for $C_9H_{12}F_3O_4$ *m/e* (M + H) 241.0688, found 241.0703.

(3*R*,4*S*,5*S*)-4-(Ethoxycarbonyl)-5-methyl-3-(trifluoromethyl)pentan-5-olide (21). A stirred solution of **12** (0.30 g, 1.0 mmol) dissolved in 10 mL of benzene was treated with a catalytic amount of *p*-TosOH. After the mixture was stirred for 3 h at 100 °C, to the reaction mixture were added aqueous $NaHCO_3$ and ether, and the resulting organic layer was separated. The usual workup procedure gave the resulting crude material, which was purified by silica gel column chromatography (*n*-hexane:AcOEt = 1:3) to afford lactone in 96% yield. R_f = 0.41 (AcOEt:*n*-hexane = 1:3). Mp: 60.5 °C. $[\alpha]^{21.0}_D$: −85.90 (*c* 0.68, $CHCl_3$). ^{1}H NMR: δ 1.37 (3 H, t, J = 7.16 Hz), 1.47 (3 H, d, J = 6.58 Hz), 2.65 (1 H, dd, J = 16.0, 7.25 Hz), 2.89 (1 H, dd, J = 16.0, 10.7 Hz), 3.00 (1 H, dd, J = 8.61, 3.80 Hz), 3.30 (1 H, dddq, J = 10.9, 7.18, 3.74, 9.00 Hz), 4.26 (2 H, dq, J = 0.81, 7.16 Hz), 4.66 (1 H, dq, J = 3.72, 6.58 Hz). ^{13}C NMR: δ 14.14, 17.94, 27.16 (q, J = 2.8 Hz), 37.62 (q, J = 28.7 Hz), 43.38 (q, J = 2.1 Hz), 62.17, 72.95, 126.39 (q, J = 278.5 Hz), 168.73, 169.52. ^{19}F NMR: δ 4.6 (dd, J = 1.0, 9.0 Hz). IR (KBr): ν 3030, 2980, 1770, 1740 cm^{-1}. HRMS calcd for $C_{10}H_{14}F_3O_4$ *m/e* (M + H) 255.0844, found 255.0855.

Acknowledgment. This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture, Japan. N.S. is grateful to the JSPS Fellowship for Japanese Junior Scientists. We also thank Drs. I. Ueda, M. Haratake, K. Mizuki, and Y. Tsuda of Yoshitomi Pharmaceutical Industries, Ltd. for the X-ray structure determination.

Supporting Information Available: Proton NMR spectra for compounds **5**–**21** (45 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO950505L