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TRIFLUOROMETHYL GROUP INDUCED HIGHLY STEREOSELECTIVE SYNTHESIS OF α-HYDROXY CARBONYL COMPOUNDS

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Abstract: The reaction of enolate prepared from ethyl 3-methyl-4,4,4-trifluorobutyrate with MoO_5-Py-HMPA complex provides ethyl (2S*,3S*)-2-hydroxy-3-methyl-4,4,4-trifluorobutyrate predominantly. In contrast, $NaBH_4$ reduction of the corresponding 2-oxobutyrate affords (2R*,3S*)-hydroxyester preferentially.

Fluorinated organic compounds have attracted much interest because of the characteristic chemical behavior of fluorine atom. Whereas fluorinated enolates have been reported, e.g. enolate of α-trifluoromethyl ester,[1] ethyl fluoroacetate,[2] there is no study on β-trifluoromethyl ester enolate. Here we wish to report that α-hydroxy-β-trifluoromethyl ester is synthesized highly stereoselectively with the aid of the electronic effect of trifluoromethyl group.

To the lithium enolate of ethyl 3-methyl-4,4,4-trifluorobutyrate (**1**) (5.8 g, 31.9 mmol) in THF(200 ml) at -78°C was added molybdenum peroxide reagent (MoO_5-pyridine-HMPA, (Vedejs' reagent[3])) (21.3 g, 49 mmol) over a period of 10 min and the whole was stirred for 3 hr at -20°C. Extractive workup (sat. sodium sulfite solution, ether) followed by purification by silica gel column chromatography gave ethyl 2-hydroxy-3-methyl-4,4,4-trifluorobutyrate (**2a**[4] and **2b**) in a 97:3 ratio (4.7 g, 75% yield). Lithium hexamethyldisilazide was as effective as lithium diisopropylamide as a base. The similar stereoselectivity was also observed in the reaction with another reagent (2-sulfonyloxa-

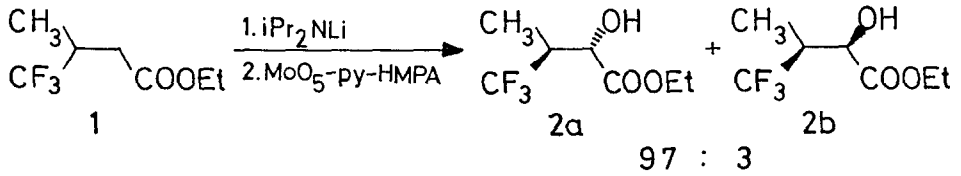
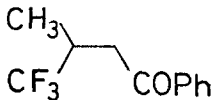
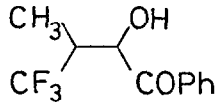
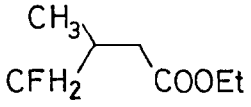
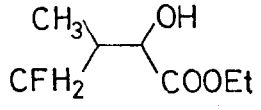
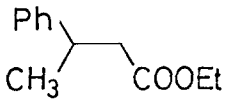
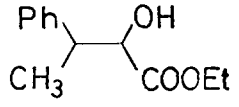
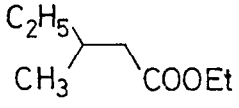
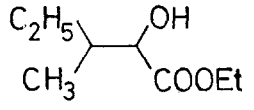
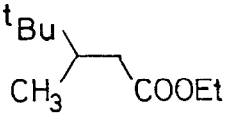
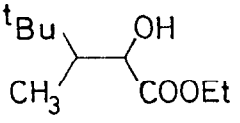


Table 1. Synthesis of α-Hydroxy Carbonyl Compounds

Entry	Substrate	Yield(%)[a]	Product	Isomer ratio[b]
1		58		>99 : <1
2		60		63 : 37
3		77		85 : 15[c]
4		65		60 : 40[d]
5		45		>95 : <5

[a] Isolated yields.
[b] Determined by the examination of the NMR spectra.
[c] The major isomer was (2S*,3R*)-2-hydroxy-3-phenylbutyric acid ethyl ester (**3**). Stereochemical assignment of the compound **3** was confirmed by reduction with $LiAlH_4$ followed by acetylation to the corresponding diacetate which was compared with the authentic sample (T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima, and H. Nozaki, Tetrahedron Lett., 23, 3597 (1982)).
[d] The major isomer was (2S*,3R*)-2-hydroxy-3-methylpentanoic acid ethyl ester (**4**). B. B. Snider and J. W. van Straten, J. Org. Chem., 44, 3567 (1979).

ziridine-$KN(SiMe_3)_2$[5], the ratio of **2a** to **2b**, 95:5). Other examples of hydroxylation are summarized in Table 1.

The selectivity of hydroxylation in the case of nonfluorinated compounds (entry 3, 4, 5) may be rationalized by consideration of the steric effect of the substituent (R_L, R_S, Fig. 1).[6, 7] Attack by MoO_5-pyridine-HMPA takes

place anti to the R_L group to produce hydroxy ester **3** or **4** (entry 3,4) as a major isomer. On the other hand, the high selectivity observed in hydroxylation of β-trifluoromethyl ester or ketone can not be fully understood by the above discussion. Since the ratio of sum of covalent radii (C-F/C-H) is calculated to be only 1.36, the steric bulk of CF_3 group is similar to that of CH_3 one.[8] The electronic factor of trifluoromethyl group might play an important role in this system. One possibility is that the lithium atom is chelated to trifluoromethyl group as shown in Fig. 2. Indeed, the lithium enolate was trapped with chlorotrimethylsilane giving one isomer exclusively.[9] Then, the bulky electrophile, MoO_5-pyridine-HMPA, attacks on the less hindered side.

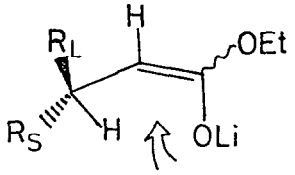


Fig.1

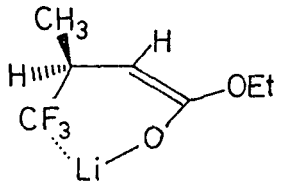
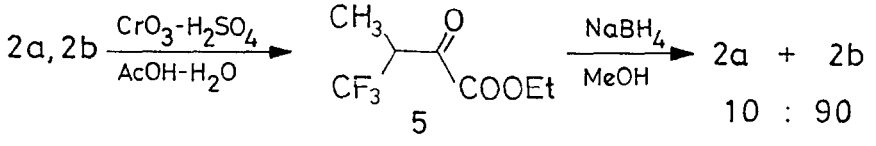


Fig.2

Remarkably, trifluoromethyl group effected selective hydride reduction of keto ester. Diastereomer mixture of α-hydroxyester (**2a**, **2b**) was converted into α-keto ester (**5**), which was treated with $NaBH_4$ in methanol at 0°C to give **2a** and **2b**[10] in a 10:90 ratio. Thus, each diastereomeric isomer was synthesized under good control of stereoselectivity.



Further application and extention of the unprecedented high selectivities caused by the CF_3 group substituted β on the carbonyl compounds are presently being explored.

References and Notes

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4. **2a:** ^{1}H-NMR ($CDCl_3$) δ 1.10 (d, J = 7.08 Hz, 3H), 1.33 (t, J = 7.08 Hz, 3H), 2.6-2.8 (m, 1H), 3.00 (d, J = 5.12 Hz, 1H, -OH), 4.31 (q, J = 7.08 Hz, 2H), 4.55 (dd, J = 5.12, 1.95 Hz, 1H). ^{19}F-NMR ($CDCl_3$, ext. CF_3COOH) 5.33 (d, J = 9.28 Hz).
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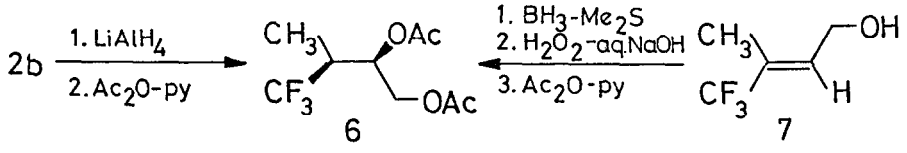
9. The examination of the silyl ketene acetal by ^{19}F-NMR showed that one isomer was formed (>95%). ^{19}F-NMR ($CDCl_3$, ext. CF_3COOH) : 2.28 (d, J = 8.89 Hz). The stereochemistry is currently investigated.
10. **2b:** ^{1}H-NMR ($CDCl_3$) δ 1.32 (t, J = 7.08 Hz, 3H), 1.32 (d, J = 7.33 Hz, 3H), 2.7-2.9 (m, 1H), 2.97 (d, J = 5.6 Hz, 1H), 4.20 (dd, J = 5.61, 3.66 Hz, 1H), 4.30 (q, J = 7.08 Hz, 2H). ^{19}F-NMR ($CDCl_3$, ext. CF_3COOH) 8.03 (d, J = 8.97 Hz). Stereochemistry was determined as shown in scheme. Hydroxy ester (**2b**) was reduced with $LiAlH_4$ followed by acetylation to give diacetate (**6**). The authentic one was obtained by hydroboration of allylic alcohol (**7**) (C. D. Poulter, D. M. Satterwhite, and H. C. Rilling, J. Am. Chem. Soc., 98, 3376 (1976)) followed by oxidative workup and acetylation.



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