Efficient synthesis of a new, highly versatile chiral derivatizing agent, α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA)

Yoshio Takeuchi,*[a] Miyuki Konishi,[a] Hitoshi Hori,[a] Tamiko Takahashi,[a] Tadashi Kometani[b] and Kenneth L. Kirk[c]

[a] *Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan*
[b] *Toyama National College of Technology, Hongo 13, Toyama 939, Japan*
[c] *Laboratory of Bioorganic Chemistry NIDDK, National Institutes of Health, Bethesda, MD, 20892, USA*

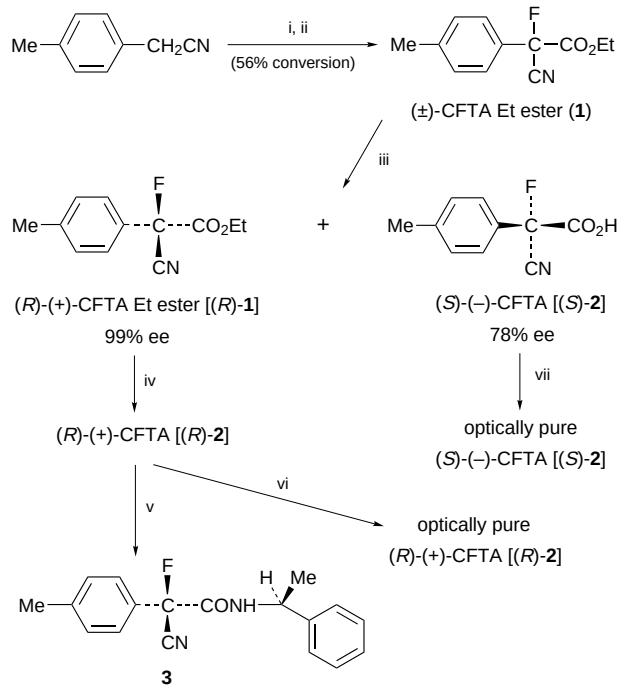
The new and versatile chiral derivatizing agent, α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA), has been efficiently synthesized in optically pure form by *Candida rugosa* lipase-mediated kinetic resolution of racemic CFTA ethyl ester, the latter being readily prepared by fluorination of ethyl α-cyano-*p*-tolylacetate with $FClO_3$.

Rapid progress has been made in the development of techniques for determination of ees of chiral molecules. However, despite many advances, there are few agents that can be applied to a broad spectrum of molecules encountered in modern synthetic and analytical chemistry.[1] We recently developed one such agent, α-cyano-α-fluorophenylacetic acid (CFPA), which far surpassed the capabilities of existing chiral derivatizing agents (CDAs) with respect both to reactivity[2] and resolution efficiency.[3] However, the involved synthesis of this agent has precluded its general use. We now report a related CDA, α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA), that retains the merits of CFPA but, through effective use of enzymatic resolution, is readily available in its optically pure state.

Treatment of *p*-xylyl cyanide with $CO(OEt)_2$ produced ethyl α-cyano-*p*-tolylacetate which, in turn, was treated with $FClO_3$† to give CFTA ethyl ester **1** in excellent overall yield. Among twenty commercial hydrolytic enzymes that were screened for the enantioselective hydrolysis of **1**, *Candida rugosa* lipase (CRL)‡ gave the best results with respect to reactivity, although the enantioselectivity (*E* value[5] of *ca.* 3) was clearly insufficient for our purposes. Fortunately, after much investigation, we found that pre-treatment of CRL with Pr^{i}OH improved the enantioselectivity more than ten-fold, consistent with the previous results obtained by Kazlauskas for the resolution of 2-aryl- and 2-aryloxy-propionic esters.[6] Thus, hydrolysis of racemic ester **1**, catalysed by pre-treated commercial CRL [50% (v/v) Pr^{i}OH in 2-(*N*-morpholino)ethanesulfonate buffer solution (pH 6.0), according to the procedure of Kazlauskas], gave, at 56% conversion, (*R*)-**1** with an ee of 99% and (*S*)-CFTA [(*S*)-**2**] with an ee of 78%, corresponding to an *E* value of 40 (Scheme 1). This dramatic increase in enantioselectivity can be attributed to a change in stereostructure of CRL caused by Pr^{i}OH treatment, as demonstrated earlier by Kazlauskas (see below).[6]

The *R* configuration of the remaining ester **1** was determined by X-ray crystallographic analysis§ of the (*S*)-α-phenethylamide **3** prepared from **1**. Therefore, the more readily hydrolysed ester has the *S*-configuration and (*S*)-**2** is enriched in the product. Kazlauskas proposed an empirical rule¶ to predict the stereochemical outcome of ester hydrolysis catalysed by Pr^{i}OH-treated CRL, as shown in Fig. 1.[7] The active site of the CRL apparently accepts F as a replacement for H, with CN corresponding to the medium-sized substituent.

(*R*)-CFTA [(*R*)-**2**] was obtained by LiOH hydrolysis of the remaining ester (*R*)-**1**. The (*S*)-α-phenethylamine salt of (*R*)-**2** and the (*R*)-α-phenethylamine salts of the (*S*)-**2**-enriched hydrolysis product were each recrystallized from $CHCl_3$–hexane to afford optically pure enantiomers, the (*R*)-α-phenethylamine salt of (*S*)-CFTA {mp 135–137 °C, $[\alpha]_D^{25}$ −3.3 (*c* 0.99, MeOH)} and the (*S*)-α-phenethylamine salt of (*R*)-CFTA {mp 135–137 °C, $[\alpha]_D^{25}$ +3.3 (*c* 0.99, MeOH)}. These enantiomeric salts were treated with acid to afford (*R*)-CFTA {$[\alpha]_D^{25}$ +36.8 (*c* 1.21, $CHCl_3$)} and (*S*)-CFTA {$[\alpha]_D^{25}$ −36.3 (*c* 1.05, $CHCl_3$)} as colourless oils in isolated overall yields of 38 and 19%, respectively, from racemic CFTA ethyl ester.‖



Scheme 1 *Reagents and conditions*: i, NaH, $CO(OEt)_2$, THF, reflux, 2 h, 98%; ii, NaH, THF, room temp., 1 h, then $FClO_3$, room temp., 40 min, 90%; iii, Pr^{i}OH-treated CRL, isooctane, 1 M phosphate buffer (pH 7.0), 25 °C, 41% for (*R*)-**1** (99% ee), 46% for (*S*)-**2** (78% ee); iv, 1 M LiOH, THF–H_2O (1 : 1), room temp., 5 min, 100%; v, (*S*)-α-phenethylamine, DCC, CH_2Cl_2, room temp., 6 h, 95%; vi, (*S*)-α-phenethylamine, recrystallization, then 1 M HCl, 78%; vii, (*R*)-α-phenethylamine, recrystallization, then 1 M HCl, 41%

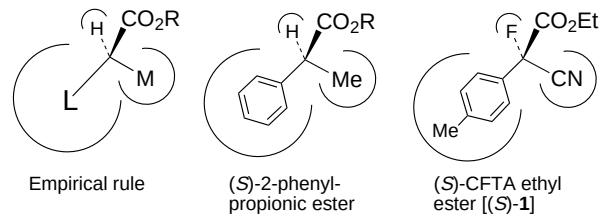
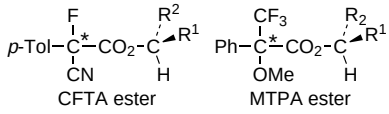


Fig. 1 Enantiopreference of Pr^{i}OH-treated CRL-mediated kinetic hydrolysis

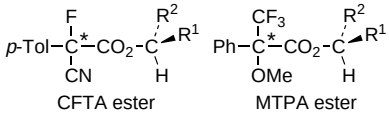
Table 1 ^{19}F NMR Chemical shift differences ($\Delta\delta_F$ values in ppm) for diastereomeric CFTA and MTPA esters



		$\Delta\delta_F = \delta_{SR} - \delta_{RR}$	
R^1	R^2	CFTA ester	MTPA ester
Me	Et	+0.09	0.00[a]
Me	Pr^i	+0.51	−0.18[a]
Me	C_6H_{11}	+0.32	−0.05[a]
Me	Ph	+0.88	−0.20[a]
Bornyl		+0.71	+0.10[b]
Menthyl		+0.58	−0.12[a]

[a] Ref. 8. [b] Ref. 9.

Table 2 ^{1}H NMR Chemical shift differences ($\Delta\delta_H$ values in ppm) for diastereomeric CFTA and MTPA esters



		$\Delta\delta_H = \delta_{SR} - \delta_{RR}$			
		CFTA ester		MTPA ester	
R^1	R^2	Me of R^1	Me of R^2	Me of R^1	Me of R^2
Me	Et	+0.14	−0.22	+0.13[a]	−0.10[a]
Me	Pr^i	+0.16	−0.19	+0.08[a]	−0.08[a]
Me	C_6H_{11}	+0.14	−0.03	+0.08[a]	—
Me	Ph	+0.10	—	+0.06[a]	—
Bornyl		—	−0.22[c]	—	−0.08[b,c]
Menthyl		+0.03[d]	−0.26[e]	+0.03[b,d]	−0.12[b,e]
			−0.19[e]		−0.10[b,e]

[a] Ref. 10. [b] Ref. 9. [c] C1-Me. [d] C5-Me. [e] Me of Pr^i.

The chemical shift differences between the two diastereomers ($\Delta\delta$ values)** in both the ^{19}F and ^{1}H NMR spectra for several CFTA and MTPA esters are shown in Tables 1 and 2, respectively.†† The greater efficiency of CFTA compared to MTPA in ee determinations is apparent from the much greater $\Delta\delta$ values consistently obtained for the CFTA derivatives.[8–10] Furthermore, in addition to the greater magnitude of the $\Delta\delta$ values, the consistency of the sign of these shifts suggests that the CFTA procedure is more reliable[11] than the Mosher method in assigning absolute configurations of secondary alcohols based on ^{19}F NMR[8,9] and ^{1}H NMR[9,10] spectroscopy. We are currently investigating in greater detail the relationship between stereostructure and chemical shift value, especially in the ^{19}F NMR spectra.

We thank Ms H. Kakuda for the X-ray crystallographic analysis of **3**. This work was supported by a Grant-in-Aid from the Ministry of Education, Science, Sports and Culture, Japan and a grant from the Ciba-Geigy Foundation (Japan).

Notes and References

* E-mail: takeuchi@ms.toyama-mpu.ac.jp

† $FClO_3$ gas diluted with N_2 is safely and conveniently generated in ordinary glassware by reaction of $KClO_4$ with FSO_3H (ref. 4).

‡ Lipase OF (CRL) was purchased from Meito Sangyo Co., Ltd.

§ *Crystal data* for **3**: $C_{18}H_{17}FN_2O$, M = 296.34, monoclinic, a = 9.647(2), b = 17.686(3), c = 9.915(2) Å, β = 109.64(1)°, U = 1593.3(5) Å^3, T = 203 K, space group $P2_1$ (no. 4), Z = 4, μ(Cu-Kα) = 0.698 mm^{-1}, 2626 reflections measured, 2469 reflections unique, 1322 reflections observed [$I > 3\sigma(I)$]. Two aryl groups (phenyl and *p*-tolyl) were disordered over two positions with occupancies 0.5 for all disorder components. For this reason, the R value was relatively high. The final cycle of full-matrix least-squares refinement (for 218 parameters) was converged with R_w = 0.111, R = 0.116. CCDC 182/709.

¶ The rule was derived from the results of enantioselective hydrolysis of 16 esters, where L is a large substituent such as Ar or OAr, and M is a medium-sized substituent such as Me or OH (refs. 6 and 7).

‖ The enantiomeric purity of both (*R*)- and (*S*)-CFTA was determined to be > 99.5% by comparison of the ^{1}H and ^{19}F NMR spectra of their cholesteryl esters with those of the cholesteryl ester of recemic CFTA.

** The $\Delta\delta$ value is defined as the difference in the ^{19}F (F or CF_3 signal for CFTA or MTPA ester, respectively) or ^{1}H (Me signal of R^1 and R^2) NMR chemical shifts for the (*S*)-agent/(*R*)-alcohol diastereomer (δ_{SR}) and the (*R*)-agent/(*R*)-alcohol diastereomer (δ_{RR}) for each CFTA or MTPA ester (ref. 9).

†† The preparation of CFTA chloride and condensation of CFTA chloride with chiral alcohols were carried out according to procedures described for derivatization of CFPA (ref. 3).

1 S. Hamman, *J. Fluorine Chem.*, 1993, **60**, 225; Y. Takeuchi and T. Takahashi, in *Enantiocontrolled Synthesis of Fluoro-organic Compounds. Stereochemical Challenges and Biomedical Targets*, ed. V. Soloshonok, Wiley, Chichester, 1998 and references cited therein.
2 Y. Takeuchi, N. Itoh and T. Koizumi, *J. Chem. Soc., Chem. Commun.*, 1992, 1514; *Chem. Ind.*, 1992, 874.
3 Y. Takeuchi, N. Itoh, H. Note, T. Koizumi and K. Yamaguchi, *J. Am. Chem. Soc.*, 1991, **113**, 6318; Y. Takeuchi, N. Itoh, T. Satoh, T. Koizumi and K. Yamaguchi, *J. Org. Chem.*, 1993, **58**, 1812.
4 Y. Takeuchi, K. Nagata and T. Koizumi, *J. Org. Chem.*, 1989, **54**, 5453.
5 C. Chen, Y. Fujimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, 1982, **104**, 7294.
6 I. J. Colton, S. N. Ahmed and R. J. Kazlauskas, *J. Org. Chem.*, 1995, **60**, 212.
7 S. N. Ahmed, R. J. Kazlauskas, A. H. Morinville, P. Grochulski, J. D. Schrag and M. Cygler, *Biocatalysis*, 1994, **9**, 209.
8 G. R. Sullivan, J. A. Dale and H. S. Mosher, *J. Org. Chem.*, 1973, **38**, 2143.
9 I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
10 J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.
11 T. Kusumi, *J. Synth. Org. Chem.*, 1993, **51**, 462 and references cited therein.

Received in Cambridge, UK, 28th October 1997; 7/07755F