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Lipase-catalysed Enantioselective Synthesis of Naphthyl Trifluoromethyl Carbinols and Their Corresponding Non-Fluorinated Counterparts

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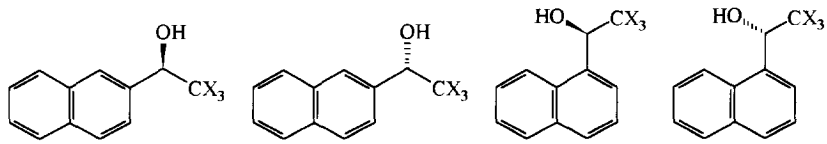
Abstract: Enantioselective synthesis of both enantiomers of β- and α-naphthyl trifluoromethyl carbinols (*R*)-**1a**, (*S*)-**1a**, (*R*)-**2a**, (*S*)-**2a** has been achieved through acylation of the corresponding racemic alcohols (*RS*)-**1a** and (*RS*)-**2a** with vinyl acetate in the presence of lipase PS. The effect of fluorine atoms on the extent and enantioselectivity of the process has been tested by carrying out the same biocatalytic transformation on their non-fluorinated counterparts (*RS*)-**1b** and (*RS*)-**2b**. The order of reactivity follows the trend (*RS*)-**1b** > (*RS*)-**2b** ≈ (*RS*)-**1a** > (*RS*)-**2a**. Effect of the hydrophobicity of the solvent in the resolution of (*RS*)-**1a** is also presented.

Enantiomerically pure secondary alcohols have become very valuable chiral auxiliaries in organic synthesis, In this context, a lot of effort has been devoted to the microbial enantioselective synthesis of secondary alcohols by kinetic resolution of the racemic compounds, especially through lipase-mediated hydrolysis of the corresponding esters, most commonly acetates, or by trans-esterification of the alcohols with the appropriate acylating agents[1,2]. On the other hand, much attention has also been paid in the last few years to the utilization of bioactive fluorinated compounds, due to the unique physical and biological properties imparted by fluorine[3]. Among the fluorinated derivatives, trifluoromethyl carbinols are important intermediates in the synthesis of polifunctional bioactive molecules[4] and have been used as synthons in the construction of ferroelectric crystals[5]. They are also precursors of trifluoromethyl ketones, an important class of compounds which have been found to be potent inhibitors of serine esterases[6], including antennal esterases of insects[7]. A very recent work by Linderman *et al.*[8] disclosed for the first time that 3-octylthio-1,1,1-trifluoropropan-2-ol and 3-octylthio-1,1,1-trifluorobutan-2-ol, the reduction products of the known esterase inhibitor 3-octylthio-1,1,1-trifluoropropan-2-one[6c], were also very potent inhibitors of JH esterase. In the context of our ongoing program of inhibition of antennal esterases in the Egyptian armyworm *Spodoptera littoralis*[7b,9], these results prompted us to develop an efficient enantioselective synthesis of both enantiomers of β- and α-naphthyl trifluoromethyl carbinols (*R*)-**1a**, (*S*)-**1a**, (*R*)-**2a**, (*S*)-**2a**, to test the potential substrate chiral recognition by the antennal esterase of the insect (Figure 1).

Very few reports on the enzymatic preparation of trifluoromethyl carbinols (*R*)-**1a**, (*S*)-**1a**, (*R*)-**2a** and

(*S*)-**2a** have been found in the literature. Only Bucciarelli *et al.*[10] prepared optically active (*R*)-**1a** and (*R*)-**2a** through fermenting yeast reduction, while Baba *et al.*[11] described the asymmetric reduction of the parent ketones with the aid of an achiral NADH model compound in a chiral enzymatic medium. The e.e. of the compounds were in this latter case relatively modest. Therefore, the synthesis of the four enantiomers through lipase-catalysed acylation of the racemic alcohols was undertaken.

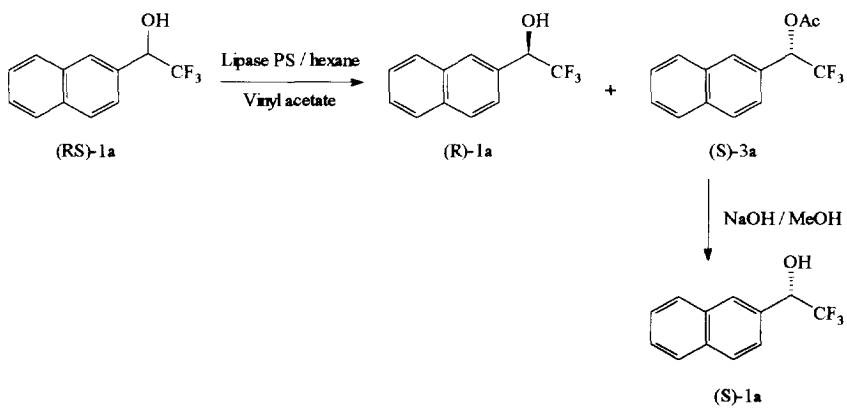


X=F: (R)-1a X=F: (S)-1a X=F: (R)-2a X=F: (S)-2a

X=H: (R)-1b X=H: (S)-1b X=H: (R)-2b X=H: (S)-2b

Figure 1

For the enantioselective resolution of alcohol (*RS*)-**1a** various lipases commercially available were tested, *i.e.* lipase AY, AP6 and *Pseudomonas cepacia* (PS) from Amano, and *Candida cylindracea* (CCL) and porcine pancreatic lipase (PPL) from Sigma. Among them, only lipase PS successfully produced alcohols (*R*)-**1a** and (*S*)-**1a**, the latter obtained after hydrolysis of the originally formed chiral acetate (*S*)-**3a**, in good yield and excellent enantioselectivity. By contrast, α-naphthyl trifluoromethyl carbinol (*RS*)-**2a** was much more reluctant to biocatalytic resolution, since after testing the array of lipases cited above along with lipase PGE (Amano), *Pseudomonas fluorescens* (PFL, Fluka) and *Rhizopus arrhizus* (Fluka), only lipase PS showed a certain degree of enantiodifferentiation, affording alcohols (*R*)-**2a** and (*S*)-**2a** in modest e.e. All reactions were conducted in the presence of vinyl acetate as the acylating agent and with a substrate:lipase:vinyl acetate ratio of 1:2:10.



(RS)-1a (R)-1a (S)-3a (S)-1a

Figure 2

In order to test the effect of fluorine atoms on the extent and enantioselectivity of the reaction, we also

carried out the same biocatalytic transformation on β and α-naphthyl ethanols (*RS*)-**1b** and (*RS*)-**2b**[12]. The results are depicted in Table 1. Here again reactivity of the β isomer (*RS*)-**1b** towards lipase PS acylation was not only notably higher than that of the α isomer (*RS*)-**2b**, but also than the corresponding fluorinated isomer (*RS*)-**1a**. The most reactive carbinol (*RS*)-**1b** only needed 8 h to be resolved into the corresponding enantiomers in a excellent enantiomeric ratio (E>300). The order of reactivity of β and α-naphthyl carbinols towards lipase PS-catalysed acylation follows, therefore, the trend (*RS*)-**1b** > (*RS*)-**2b** ≈ (*RS*)-**1a** > (*RS*)-**2a**. From these results it is apparent that the fluorinated derivatives are less reactive than the non-fluorinated parent compounds and that the β isomers react faster than the corresponding α isomers. Moreover, in contrast to the β compounds, the more constrained α isomers in both types of derivatives do not comfortably fit into the active site of the enzyme, in agreement with the results obtained from theoretical calculation of the contributions of steric and electronic effects on similar compounds[13].

Table 1. Enantioselective acylation of β- and α-naphthyl carbinols (R,S)-**1a**, (*RS*)-**2a**, (*RS*)-**1b** and (*RS*)-**2b**[a].

Lipase	Substrate	Time (h)	Conv.[b] (%)	Yield[c] alcohol	ee[d] (config.)	Yield[c,e] alcohol	ee[d] (config)	E[f]
PS	(*RS*)-**1a**	27	52	38	94 (R)	27	88 (S)	55
PS	(*RS*)-**1a**	125	54	51	>99 (R)	37	85 (S)	64
PS	(*RS*)-**2a**	25	8	73	6 (R)	5	66 (S)	5
PS	(*RS*)-**2a**	288	28	54	17 (R)	25	44 (S)	3
PFL	(*RS*)-**2a**	288	8	80	4 (R)	11	45 (S)	3
PS	(*RS*)-**1b**	8	51	43	99 (S)	37	97 (R)	>300
PS	(*RS*)-**2b**	8	17	64	20 (S)	19	>99 (R)	>200
PS	(*RS*)-**2b**	25	41	40	69 (S)	32	>99 (R)	>200

[a]In hexane at 37°C using vinyl acetate as acylating agent. Substrate:lipase:vinyl acetate ratio was 1:2:10.
[b]Percentage of conversion was calculated by comparison of the relative intensities of the CH absorptions of the alcohol (δ 5.18, q J=6.8 Hz) and the acetate (δ 6.29, q J=7.0 Hz) in the corresponding ^{1}H NMR spectra or from the ee values according to Sih et al. (Chen, Ch.-Sh.; Wu, Sh.-H.; Girdaukas, G.; Sih, Ch.J. *J. Am. Chem. Soc.* **1987**, *109*, 2812).
[c]Yields refer to pure isolated products after column chromatography purification.
[d]The enantiomeric purity of the alcohols was based on the ^{19}F NMR analysis of the corresponding Mosher's ester[14].
[e]Overall yield of alcohol derived from hydrolysis of the initially formed chiral acetate.
[f]Enantiomeric ratio (E) values were determined from the ee of the residual substrate and the extent of conversion (Chen, Ch.-Sh.; Fujimoto, Y.; Girdaukas, G.; Sih, Ch.J. *J. Am. Chem. Soc.* **1982**, *104*, 7294).

We also studied the effect of organic solvents on the enantioselectivity of the resolution reaction of

alcohol (*RS*)-**1a**[15]. Several solvents were tested with the log P values ranging from -0.23 (acetone) to 6.6 (dodecane). Although good to excellent E values were generally obtained, best results were achieved with the utilization of non-polar solvents (hexane, dodecane), the most reacting enantiomer having in all cases the *S* configuration. However, excellent e.e. was also obtained in more polar solvents, like THF or acetone, although they required considerably longer reaction times (240 h) to achieve ca. 50% conversion (Table 2).

Table 2. Organic solvents effect on the lipase PS-mediated acylation of alcohol (*RS*)-**1a**.

Solvent	log P[a]	ε[b]	Time (h)	Conv. (%)	ee (*R*)-**1**	ee (*S*)-**1**	E
Tetrahydrofuran	0.49	7.6	25	7	8	>99	215
"	"	"	240	51	>99	95	206
Acetone	-0.23	20.7	25	8	9	99	217
"	"	"	240	52	>99	91	111
t-Butyl methyl ether	2		25	13	14	90	22
Diethyl ether	0.85	4.3	25	17	20	96	60
Toluene	2.5	2.4	25	25	32	96	67
Benzene	2.0	2.3	25	25	32	98	135
Dodecane	6.6	2.0	25	41	66	94	64
Hexane	3.5	1.9	25	42	69	94	67

[a]Log P values were taken from the literature (Laane, C.; Boeren, S.; Vos, K.; Veeger, C. *Biotech. Bioeng.* **1987**, *30*, 81).
[b]Dielectric constants were taken from *Handbook of Chemistry and Physics.*, 70th ed., CRC Press Inc.: Boca Ratón, Florida, 1989-90.

Somewhat surprising is the E value attained with the bulky *tert*-butyl methyl ether, in contrast to previous observations in which enzymatic resolution of amines[16a] and nitroalcohols[16b] with the highest enantioselectivities were accomplished with bulky solvents. On the other hand, no correlation was obtained after plotting E values *vs* hydrophobicity (log P) or dielectric constant of the medium, although the acylation rate increased with the hydrophobicity of the solvent, as previously noted[15a].

In summary, both enantiomers of β- and α-naphthyl trifluoromethyl carbinols have been obtained for the first time through lipase PS catalysed resolution of the corresponding racemic alcohols, the β enantiomers being obtained in excellent yield and e.e., and therefore amenable for biological testing.

Experimental

Elemental analyses were determined on Carlo Erba models 1106 and 1500. IR spectra were recorded on a Bomem MB-120 with Fourier transform instrument. [^{1}H] and [^{13}C]NMR spectra were obtained in $CDCl_3$ solutions on a Varian Unity 300 spectrometer, operating at 300 MHz for [^{1}H] and 75 MHz for [^{13}C]. The values are expressed in δ scale relative to internal Me_4Si. [^{19}F]NMR spectra were recorded on a Varian Unity 300 instrument at 282 MHz and the values are reported in δ scale relative to external trifluoroacetic acid. Low resolution mass spectra were run on a HP 5995 mass spectrometer using a SPB-5 30m x 0,32μm ID fused silica capillary column. GLC analyses were performed on Carlo Erba models 2350 and 4130, equipped with a FID detector, using a 3% OV-101 2m x 3mm ID glass column on Chromosorb W and nitrogen as carrier gas, or a SE-54 50m x 0,32 μm ID fused silica capillary column and hydrogen as carrier gas. Commercial analytical-grade reagents were obtained from commercial suppliers (Aldrich Chemie, Fluka Chemie) and were used directly without further purification. Optical rotations were measured on a Perkin Elmer 141 polarimeter.

Anhydrous tetrahydrofuran (THF) was prepared by previously drying with KOH followed by distillation from Na/benzophenone under N_2, methylene chloride by distillation from P_2O_5, and triethylamine by distillation from KOH. Ethyl trifluoroacetate was freshly distilled from $NaHCO_3$.

(RS)-β-Naphthyl trifluoromethyl carbinol ((RS)-1a). β-Naphthyl trifluoromethyl ketone was obtained as previously described by us[9]. Thus, starting from 2.68 g (12.9 mmole) of 2-bromonaphthalene, 8.9 ml of 1.6M *n*-BuLi in 10 ml of anh. THF and 2.2 g (15.5 mmole) of ethyl trifluoroacetate, the ketone was obtained as a crude in 86% yield. The crude was dissolved in 35 ml of abs. ethanol and allowed to react with 126 mg (3.3 mmole) of sodium borohydride. The mixture was stirred for 2 h, the solvent removed under vacuum and the residue treated with water and extracted with ether. The organic phase was washed with brine and dried ($MgSO_4$). Evaporation of the solvent left a crude, which was chromatographed on silica gel eluting with hexane:ether 93:7 to yield 1.34 g (46% from 2-bromonaphthalene) of the expected **RS-1a**. IR ν: 3350, 1265, 1166, 1122, 819 cm^{-1}. ^{1}H NMR δ: 8.0-7.8 (m, 4H, arom. H), 7.7-7.4 (m, 3H, arom. H), 5.18 (q J=6.8 Hz, 1H, C*H*OH), 2.77 (s, 1H, OH). ^{13}C NMR δ: 133.7, 132.8, 131.3, 128.5, 128.2, 127.7, 127.3, 126.9, 126.6, 124.3 (arom. C), 124.3 (q *J*=282 Hz, C(OH)*C*F$_3$), 73.0 (q J=36 Hz, *C*(OH)CF$_3$). ^{19}F NMR δ: -2.44 (d J=6.2 Hz). MS m/z (%): 226 (M$^+$, 39), 224 (22), 157 (54), 155 (49), 129 (100), 128 (78), 127 (94). Elemental Analysis: Calculated for $C_{12}H_9OF_3$: C, 63.72; H, 3.98; Found: C, 63.98; H, 4.10.

(R)-(-)-β-Naphthyl trifluoromethyl carbinol ((R)-1a). In an erlenmeyer-flask was placed a solution of 39 mg (0.2 mmole) of the racemic alcohol (*RS*)-**1a** in 3 ml of hexane. To the solution was added 190 mg (2.2 mmole) of vinyl acetate followed by 80 mg of lipase PS. The erlenmeyer-flask was capped and shaken in a thermostatized bath at 37°C and 80 U/min. The progress of the reaction was monitored by TLC and GC. When the conversion was 54% (125 h), the mixture was filtered off and the enzyme washed with ether. After removal of the solvent, the crude was purified by column chromatography on silica gel, eluting with hexane:ether 90:10, to furnish alcohol **(R)-1a** (20 mg, 51%) and acetate **(S)-3a** (22 mg, 48%). **(R)-1a**: $[\alpha]_D^{24}$= -33.0 (c=0.3, $CHCl_3$). IR ν: 3338, 1263, 1168, 1122, 817 cm^{-1}. ^{1}H NMR δ: 8.0-7.8 (m, 4H, arom. H), 7.7-7.4 (m, 3H, arom.

H), 5.18 (q J=6.8 Hz, 1H, C*H*OH), 2.20 (s, 1H, OH). **(S)-3a**: IR ν: 2923, 1751, 1228, 1134, 1066, 827 cm^{-1}. ^1H NMR δ: 8.0-7.8 (m, 4H, arom. H), 7.6-7.4 (m, 3H, arom. H), 6.29 (q J=7.0 Hz, 1H, CHOAc), 2.21 (s, 3H, CH_3). ^{13}C NMR δ 168.7 (CO), 133.8, 132.8, 128.6, 128.5, 128.3, 128.3, 127.7, 127.1, 126.7, 124.6 (arom. C), 123.2 (q *J*=281 Hz, C(OH)*C*F_3), 72.1 (q J=33 Hz, *C*(OH)CF_3), 20.7 (CH_3). ^{19}F NMR δ: 0.13 (d J=7.8 Hz).

(S)-(+)-β-Naphthyl trifluoromethyl carbinol ((S)-1a). To a solution of the acetate **(S)-3a** (22 mg) in 2 ml of methanol was added 160 µl of 10% NaOH soln. and the mixture stirred for 2 h. The crude was repeatedly extracted with ether. Usual work-up yielded 17 mg (77%) of alcohol **(S)-1a**. $[\alpha]_D^{24}$=+32.4 (c=1.0, $CHCl_3$). IR ν: 3450, 1255, 1205, 1124, 817 cm^{-1}. ^1H NMR δ: 8.0-7.8 (m, 4H, arom. H), 7.7-7.4 (m, 3H, arom. H), 5.19 (q J=6.8 Hz, 1H, C*H*OH), 2.67 (s, 1H, OH).

(RS)-α-Naphthyl trifluoromethyl carbinol ((RS)-2a). Starting from the corresponding ketone[17] and following the same procedure as described for **(RS)-1a**, racemic alcohol **(RS)-2a** was obtained in 93% yield. IR ν: 3388, 1263, 1166, 1124, 800 cm^{-1}. ^1H NMR δ: 8.03 (d J=8.4 Hz, 1H, arom. H), 8.0-7.8 (m, 3H, arom. H), 7.6-7.4 (m, 3H, arom. H), 5.87 (q J=6.4 Hz, 1H, C*H*OH), 2.83 (s, 1H, OH). ^{13}C NMR δ: 133.6, 131.0, 130.2, 129.9, 129.0, 126.8, 125.9, 125.8, 125.2, 122.8 (arom. C), 124.6 (q *J*=279 Hz, CH(OH)*C*F_3), 68.9 (q J=32 Hz, *C*H(OH)CF_3). ^{19}F NMR δ: -1.28 (d J=6.5 Hz). MS m/z (%): 226 (M^+, 61), 157 (89), 129 (100), 128 (59), 127 (39). Elemental Analysis: Calculated for $C_{12}H_9OF_3$: C, 63.72; H, 3.98; F, 25.20. Found: C, 63.77; H, 4.13; F, 25.20.

(R)-(-)-α-Naphthyl trifluoromethyl carbinol ((R)-2a). In an analogous manner as described above, starting from 24 mg of racemic alcohol **(RS)-2a** in 3 mol of hexane, 51 mg of lipase PS and 95 mg of vinyl acetate, were obtained 13 mg (54%) of alcohol **(R)-2a** and 7 mg of the acetate **(S)-4a** after 288 h reaction. **(R)-2a**: $[\alpha]_D^{22}$= -2.9 (c=0.52, $CHCl_3$). IR ν: 3413, 1263, 1166, 1126, 800 cm^{-1}. ^1H NMR δ: 8.05 (d J=8.8 Hz, 1H, arom. H), 8.0-7.8 (m, 3H, arom. H), 7.6-7.4 (m, 3H, arom. H), 5.89 (q J=6.6 Hz, 1H, CHOH), 2.70 (s, 1H, OH). **(S)-4a**: IR ν: 3055, 1760, 1271, 1220, 1172, 1134, 800 cm^{-1}. ^1H NMR δ: 8.14 (d J=8.4 Hz, 1H, arom. H), 7.90 (t J=8.4 Hz, 2H, arom. H), 7.74 (d J=7.2 Hz, 1H, arom. H), 7.7-7.4 (m, 3H, arom. H), 7.01 (q J=6.6 Hz, 1H, CHOAc), 2.21 (s, 3H, CH_3). ^{13}C NMR δ 168.7 (CO), 133.6, 131.1, 130.5, 129.0, 127.3, 127.1, 126.7, 126.1, 125.0, 122.8 (arom. C), 123.6 (q *J*=281 Hz, C(OH)*C*F_3), 68.2 (q J=33 Hz, *C*(OH)CF_3), 20.7 (CH_3). ^{19}F NMR δ: 0.60 (d J=6.2 Hz).

(S)-(+)-α-Naphthyl trifluoromethyl carbinol ((S)-2a). Starting from acetate **(S)-4a**, the corresponding alcohol **(S)-2a** was obtained in 25% overall yield from the racemic **(RS)-2a**. $[\alpha]_D^{22}$=+7.1 (c=0.21, $CHCl_3$). IR ν: 3413, 1263, 1166, 1126, 800 cm^{-1}. ^1H NMR δ: 8.05 (d J=8.6 Hz, 1H, arom. H), 8.0-7.8 (m, 3H, arom. H), 7.6-7.4 (m, 3H, arom. H), 5.89 (q J=6.2 Hz, 1H, C*H*OH), 2.70 (s, 1H, OH).

Determination of the enantiomeric excess of alcohols (R)-1a, (S)-1a, (R)-2a, (S)-2a. (*R*)-(+)-α-Methoxy-(trifluoromethyl)phenylacetic acid (MTPA) was converted into the acid chloride as previously described[14]. As a typical example determination of the e.e. of **(R)-1a** is given. To a solution of 8.3 mg of MTPA chloride in 300 µl of anh. CH_2Cl_2 was added 2.6 mg of **(R)-1a**, 15 µl of Et_3N and one crystal of DMAP. After 2 h of stirring, no starting material was detected on TLC. Direct ^{19}F NMR spectrum of the crude ester allowed

calculation of the e.e. by integration of the CF_3 signals: **(R)-1a**: ^{19}F NMR δ: 3.83 (s, CF_3C), 0.06 (d J=7.0 Hz, CF_3CH), e.e.>99%; **(S)-1a**: 4.03 (s, CF_3C), 0.27 (d J=7.0 Hz, CF_3CH), e.e.>99%; **(R)-2a**: 3.85 (s, CF_3C), 0.87 (d J=6.2 Hz, CF_3CH), e.e.=17%; **(S)-2a**: 4.03 (s, CF_3C), 0.58 (d J=6.2 Hz, CF_3CH), e.e.=44%.

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