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TETRAHEDRON: *ASYMMETRY*

Lipase mediated preparation of differently protected homochiral 2-aryl-2-fluoro-1,3-propanediols

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Abstract

Lipase mediated asymmetric monohydrolysis of 2-aryl-2-fluoromalonic acid diesters or monoacetylation of 2-aryl-2-fluoro-1,3-propanediols affords chiral fluorinated polyfunctionalized C_3 synthons in excellent enantiomeric excess and acceptable chemical yields.

2-Substituted-1,3-propanediols are simple but very versatile units that can be used as starting materials in the synthesis of many biological targets.[1,2] Moreover, if the two hydroxyl groups are protected differentially, these compounds are chiral and thanks to their enantiodivergency[3] both enantiomers of a given target can be achieved starting from the same homochiral precursor.

Enzymes, and particularly lipases, have been shown to be very efficient catalysts for obtaining these compounds in optically active form.[2] Using this methodology, some of these chiral building blocks have been prepared and then used as precursors in many synthetic applications.[2,4]

Fluorine containing compounds are extremely rare in nature, however many 'man made' organofluoro derivatives are known.[5] It has been shown that the introduction of fluorine into a compound can significantly affect its behaviour and that, in the case of optically active derivatives, strong differences of activity between the two enantiomers can occur.[6] Biological tools have also been used in the preparation of fluorine compounds, but asymmetrization of prochiral or *meso* fluorinated compounds with hydrolytic enzyme catalysis are reported to occur successfully only in a limited number of cases.[5b,7]

In connection with our standing interest in the synthesis of small, highly functionalized chiral building blocks through biological strategies,[4] we report here some preliminary results on the chemoenzymatic synthesis of some differentially protected 2-aryl-2-fluoro-1,3-propanediols. The reasons that prompted us to undertake this research are: (a) the aim of achieving some new versatile homochiral units to be used as precursors to fluorinated analogues of aromatic targets; and (b) interest in studying the effect of fluorine on the arrangement of the substrate in the active site of the enzyme. Recently, on the basis of

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some results collected by us and others on the PPL catalysed hydrolysis of non-fluorinated derivatives, we proposed a model for the active site of this enzyme.[3]

The asymmetrized diols **4** and thence **5** have been prepared from corresponding malonic diesters through two convergent pathways: (a) enzymatic asymmetrization of malonic diesters, followed by stepwise reduction and protection of the two oxygenated branches; and (b) reduction of malonic diesters to 1,3-propanediols and enzymatic acylation.

The compounds **1**[8] were synthesised from commercially available (for **1a**) or from known (for **1b** and **1c**)[4a] arylmalonates through fluorination under basic conditions,[9] and then submitted to lipase catalysed hydrolysis, using enzymes of both microbial (lipase Amano AY, from *Candida*, AYL) or animal (lipase from porcine pancreas supported on Celite,[10] S-PPL) origin. The most significant results are reported in Table 1. Enantiomeric excess was always measured by converting monoacids **2** into diastereoisomeric amides, using either (*R*)- or (*S*)-α-methylbenzylamine, and analysing both ^{1}H and ^{19}F NMR spectra.[11]

Table 1
Lipase catalysed asymmetrization of arylfluoromalonic acid diesters (**1a–c**)[a]

Entry	Subs	Lipase (mg / mmol subs)	Time / h	Conversion[b] / %	Yield[c] of 2 / %	e. e.[d] / %	$[\alpha]_D$[c]
1	**1a**	S-PPL (230)	21	64	60 (63)	≥96	-11.1
2	**1a**	AYL (450)	18	46	90 (92)	52[f]	n. d.
3	**1b**	S-PPL (320)	45	13	5 (24)[g]	n. d.	n. d.
4	**1c**	S-PPL (270)	4.5	50	77 (86)	96	-8.7

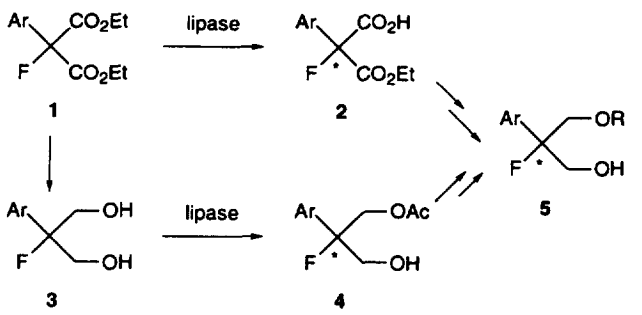
[a] All experiments were run at room temperature, at pH 7 in a 0.01 M phosphate buffer and followed by titration with 0.1 N or 1 N NaOH, using a pH-stat apparatus. [b] Conversion was defined as the percent equivalents of consumed NaOH with respect to the amount required for quantitative conversion of diesters into diacids. [c] Isolated yield; in brackets is reported yield based on unrecovered starting material. Malonic diacids were never recovered. [d] Enantiomeric excesses were measured by analysis of both ^{1}H and ^{19}F NMR spectra of monoamides from either (*R*)- or (*S*)-α-methylbenzylamine. [e] $CHCl_3$, $c \approx 1$. [f] The opposite enantiomer with respect to run 1 was obtained. [g] The main isolated product was ethyl 2-fluoro-2-(2-naphthyl)acetate.

Diesters **1a** and **1c** were easily asymmetrized in very high enantiomeric excess (e.e.) using supported PPL (entries 1 and 4), while some trouble was encountered in the hydrolysis of **1b**. As a matter of fact, monoesters **2** turned out to be rather prone to decarboxylate to corresponding substituted fluoroacetates; in particular, **2c** is quite stable, while **2a** decarboxylated on silica gel or in very acidic aqueous solution (pH≤1) and **2b** decarboxylated even at pH 3, so that it was always isolated in a very poor yield and mixed with the decarboxylation product, ethyl 2-fluoro-2-(2-naphthyl)acetate.

Since the chiral synthon **4b** and hence **5b** could not be obtained *via* this route (see entry 3), we turned to the alternative asymmetrization of 2-aryl-2-fluoro-1,3-propanediols, which can also afford the same type of chiral building block (Scheme 1).

The new 2-aryl-2-fluoro-1,3-propanediols **3a** and **3b**[12] were synthesised *via* hydride reduction of the corresponding diethyl 2-aryl-2-fluoromalonates, while unsatisfactory results were obtained when the same protocol was applied to the synthesis of **3c**. Since the chiral building block **5c** could be conveniently obtained from the enzyme catalysed hydrolysis of diester **1c**, no further effort was made to synthesise **3c**.

The enzymatic asymmetrization of diols **3** was run in diisopropyl ether as solvent, using vinyl acetate as an 'irreversible' acetylating agent.[10] Lipase from *Pseudomonas* (PSL), from *Candida cyclindracea* (CCL) and Novozym, from *Candida antarctica* (CAL) were tested, in addition to S-PPL, already used for malonic acid diesters. Most significant results are reported in Table 2. Enantiomeric excess was always measured by converting monoalcohols **4** into diastereoisomeric Mosher's esters, using either (*R*)- or (*S*)-MTPA-chlorides, and analysing ^{1}H NMR spectra.[11]



Ar = Ph (**a**), 2-Naphthyl (**b**), 3-Thienyl (**c**)

Scheme 1.

Table 2
Lipase catalysed asymmetrization of 2-aryl-2-fluoro-1,3-propanediols (**3a–b**)[a]

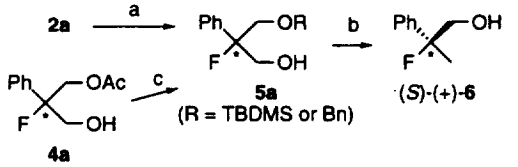
Entry	Subs	Lipase (mg / mmol subs)	Temp. / °C	Time / h	Conv.[b] / %	Diacetate : monoacetate : diol ratio[c]	Yield[d] of 4 / %	e. e.[e] / %	$[\alpha]_D$[f]
1	**3a**	S-PPL (170)	10	90	46	1 : 90 : 9	85 (92)	≥96	+17.7
2	**3a**	CAL (80)	-10	20	58	n. d.	52	51[g]	+9.5
3	**3a**	CAL (180)	10	15	100	100 : 0 : 0	-[h]	-	-
4	**3a**	CCL (175)	10	24	28	n. d.	44	14[g]	+2.5
5	**3a**	PSL (175)	0	130	54	9 : 91 : traces	82	94[g]	+17.4
6	**3b**	S-PPL (240)	10	97	35	traces : 69 : 31	64 (88)	≥96	+19.8
7	**3b**	CAL (450)	r. t.	24	75	n. d.	19[i]	47[l]	+9.7

[a] All experiments were run using vinyl acetate as acetylating agent and diisopropyl ether as solvent, in the presence of a small amount of powdered 3 Å molecular sieves. [b] For a definition of conversion (determined from ^{1}H NMR spectra), see ref. 3. [c] Diacetate : monoacetate : diol ratio was determined weighing isolated compounds. [d] Isolated yield; in brackets is reported yield based on unrecovered starting material. [e] Enantiomeric excesses were measured by analysis of both ^{1}H and ^{19}F NMR spectra of Mosher's esters of **4**. [f] $CHCl_3$, $c \approx 1$. [g] Calculated from optical rotatory power, assuming a value of +18.4 for enantiomerically pure monoacetate (from entry 1). [h] Diacetate was isolated in 86% yield. [i] Diacetate was isolated in 63% yield. [l] Calculated from optical rotatory power, assuming a value of +20.6 for enantiomerically pure monoacetate (from entry 6).

As already found for the asymmetrization of non-fluorinated 1,3-diols,[4] both **3a** and **3b** gave satisfactory chemical and optical results using PPL, despite the presence of a highly hydrophilic fluorine atom instead of a hydrogen atom. Different batches of S-PPL gave different reaction rates, but consistantly very high enantiomeric excesses (the minor enantiomer could scarcely be detected by NMR techniques). CAL gave very fast acetylation, but poor enantiomeric excess. The reactions of **3b** are sensibly slower, as it appeared to be for the non-fluorinated analogues in the hydrolysis reaction,[4a] but nevertheless they afford the desired chiral building block.

In order to test the synthetic utility of new chiral building blocks **2** and **4**[13] and to define their absolute configuration, we performed selective manipulation of the two oxygenated branches (Scheme 2).

Reduction of the acidic moiety of **2a** (from S-PPL catalysed monohydrolysis of **1a**), followed by hydroxyl function protection and reduction of the ester moiety, led to monoprotected diol **5a** (R=TBDMS or Bn). Further manipulation of **5a** (R=Bn) gave dextrorotatory 2-fluoro-2-phenyl-1-propanol **6**, which is known to possess the (*S*) configuration,[14] thus allowing us to establish the (*S*) configuration for



a) i: $(COCl)_2$, DMF, then $NaBH_4$, 60%; ii: TBDMS-Tf, 2,6-lutidine, CH_2Cl_2 (for R = TBDMS; 92%) or BnBr, NaH, DMF (for R = Bn; 58%); iii: $NaBH_4$, DMSO, 110°C; 20% for R = TBDMS, 61% for R = Bn. (b) (for R = Bn) i: TsCl, Et_3N, DMAP, CH_2Cl_2, 95%; ii: $NaBH_4$ DMSO, 150°C, 79%; iii: H_2, 10% Pd/C, $CaCO_3$, MeOH, 50%. c) i: TBDMS-Tf, 2,6-lutidine, CH_2Cl_2 ii: NaOH, THF, MeOH, H_2O, 90% (two steps).

Scheme 2.

monoester **2a**. The chemical correlation between monoester **2a** and monoacetate **4a** (from S-PPL catalysed monoacetylation of diol **3a**), through monoprotected diol **5a** (R=TBDMS), allowed the (*S*) configuration for monoacetate **4a** to be established. This means that, in our case, the model previously proposed by us for the acetylation/deacetylation reaction catalysed by PPL[3] is still followed when fluorine replaces hydrogen.

Further manipulations of chiral monoesters **2** and monoacetates **4**, as well as full experimental details on their achievement[15] will be reported in due course.

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8. Only **1a** was a known compound (Banks, R. E.; Besheesh, M. K.; Tsiliopoulos, E. *J. Fluorine Chem.* **1996**, *78*, 39–42). ^1H NMR[11]: 1.32 (t, *J* 7.1, 6H, 2×C*H*$_3$), 4.35 (q, *J* 7.1, 4H, 2×C*H*$_2$), 7.48–7.57 (m, 2H) and 7.68 (app dd, *J* 1.8 and 8.8, 1H) and 7.83–7.91 (m, 3H) and 8.08 (app d, *J* 1.8, 1H) (Ar*H*) for **1b**; 1.32 (t, *J* 7.1, 6H, 2×C*H*$_3$), 4.34 (q, *J* 7.1, 4H, 2×C*H*$_2$), 7.25–7.38 (m, 2H) and 7.58–7.60 (m, 1H) (Ar*H*) for **1c**. ^{19}F NMR[11] ($CDCl_3$, CF_3CO_2H): 84.40 (s) for **1b**, 78.53 (s) for **1c**.
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11. Spectra were recorded in $CDCl_3$, using TMS (for ^1H) or CF_3COOH (for ^{19}F) as the internal standard.
12. ^1H NMR ($CDCl_3$, TMS, after exchanging with D_2O) for **3a**: 3.96 and 4.04 (AB part of an ABX system, *J* 12.8 and 17.8 and 22.5, 4H, 2×C*H*$_2$OH), 7.35–7.41 (m, 5H, *Ph*). ^{19}F NMR:[11] 93.66–94.76 (m) for **3a**, 96.70–97.76 (m) for **3b**.
13. ^{19}F NMR:[11] 84.09 (s) for **2a**, 84.21 (s) for **2b**, 78.31 (s) for **2c**, 94.57–95.64 (m) for **4a**, 93.80–94.94 (m) for **4b**.
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