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Chemoenzymatic synthesis of 2-substituted 2-fluoro-1,3-dioxygenated chiral building blocks

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Abstract

A series of 2-substituted-2-fluoro-1,3-dioxygenated chiral building blocks are synthesized via a chemoenzymatic route using either (i) lipase catalyzed monohydrolysis of suitably functionalized malonic diesters, or (ii) lipase catalyzed monoacetylation of suitably functionalized 1,3-propanediols.

1. Introduction

Chiral highly functionalized small molecules are very attractive building blocks thanks to their usually high versatility, which allows them to be used in the synthesis of very different complex molecules. Among them, asymmetrized 2-substituted 1,3-propanediols[1,2] are particularly interesting because they combine high versatility and enantiodivergency,[3] i.e. both enantiomers can be prepared starting from the same homochiral precursor.

Asymmetrization of 2-substituted 1,3-propanediols or their equivalents can be conveniently obtained via an enzymatic route,[2] in particular when using lipases. Lipases have found broad application in organic chemistry as chiral catalysts, since they can usually be easily obtained, stored and manipulated, are cheap and usually have a low substrate selectivity, i.e. they accept 'unnatural' substrates, with very profound modifications in structure and functionality. They have proved to be really powerful instruments in allowing the chiral arsenal of chemists to be enriched.

Asymmetrization of prochiral diols via a hydrolytic enzyme catalyzed reaction can usually be conducted either via monoacylation of the diol itself or via monohydrolysis of the corresponding diacetate.

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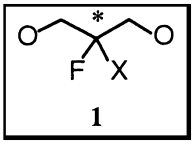
In recent years we have been engaged in successfully applying this method to different 2-substituted 1,3-propanediols: for example, asymmetrized 2-aryl-1,3-propanediols have been used as precursors of 2-arylpropionic acids (antiinflammatory drugs)[4a] and of 11-deoxyanthracyclinones (aglycone portion of some antibiotics),[4b] while 2-heterocyclic-1,3-propanediols are precursors of quinuclidine drugs,[4c] but surely the most impressive result has been the asymmetrization of 2-alkenyl-1,3-propanediols, which are precursors of asymmetrized tris(hydroxymethyl)methane (THYM*),[3] which in turn has been used in the synthesis of very different targets: top and bottom fragments of talaromicin A;[4d] a key intermediate for carbapenem synthesis;[4e] open-chain phosphonomethoxy analogues of nucleotides;[4f] an intermediate for the synthesis of lasalocide A;[4g] and an intermediate for the synthesis of hypocholesterolemic agent 1233A.[4h]

Fluorine containing organic compounds are almost xenobiotic: that is, they are scarcely present in nature, however introduction of a fluorine atom at a specific site in organic molecules is of considerable interest because fluorine can deeply modify biological activity and allow fluorinated substrates to be used in biomedical chemistry as drugs or in the study of bioorganic processes.[5] For this reason many fluorine-containing new compounds have been synthesized, with particular attention to chirality, since strong differences in activity between the two enantiomers have been observed.[6] Nevertheless, only sparse reports have been found on enantioselective fluorination of optically inactive materials or asymmetrization of compounds having a fluorine atom at the stereogenic center.[5b] Recently, chemoenzymatic routes to monofluorinated analogues of anti-inflammatory agents via lipase mediated resolutions of racemic materials have been reported,[7a,b] as well as the resolution of 4-fluoroglutamic acids using acylases.[7c] To the best of our knowledge, asymmetrization of fluorinated prochiral or *meso*-compounds through enzyme-catalyzed reactions is reported as occurring only in a very limited number of cases.[8]

2. Results and discussion



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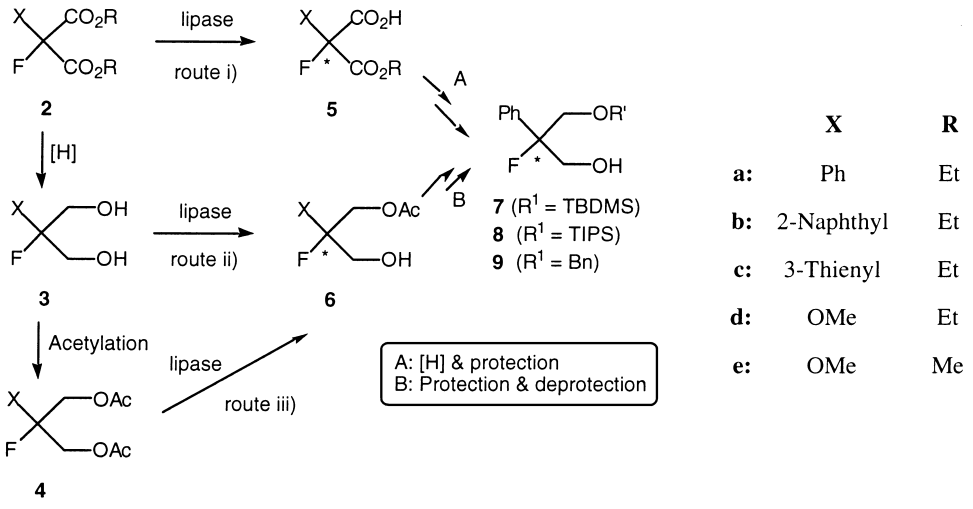
In connection with our ongoing interest in the synthesis of small, highly-functionalized chiral building blocks via biochemical strategies, we report here our results on the asymmetric synthesis of 2-substituted 2-fluoro-1,3-dioxygenated C_3 fragments **1**.[9] Synthesis of these very versatile building blocks can be realized by following at least three different convergent pathways (Scheme 1): (i) enzymatic asymmetrization of 2-substituted 2-fluoromalonic diesters **2**; (ii) enzymatic asymmetrization of 2-substituted 2-fluoro-1,3-propanediols **3** via monoacylation; or (iii) enzymatic asymmetrization of 2-substituted 2-fluoro-1,3-diacetoxypropanes **4** via monohydrolysis. A suitable stepwise reduction strategy, along with protection/deprotection of hydroxy groups, should lead in each case to the same type of chiral building block. Of course, routes (ii) and (iii) should give the two opposite enantiomeric forms of monoacetate **6**, but thanks to the *enantiodivergency* of these molecules this should be neither an advantage nor a drawback.

*2.1. Synthesis of prochiral fluorinated malonic diesters **2**, 1,3-propanediols **3**, and 1,3-diacetoxypropanes **4***

Compounds **2** were synthesized from commercially available (for **2a** and **2e**) or from known (for **2b**,**c**[4a] and for **2d**[10]) 2-substituted malonates, through fluorination under basic conditions.[11] In our



Scheme 1.

hands, diethyl 2-methoxymalonate, the starting material for **2d**, was better prepared from dimethyl 2-methoxymalonate via transesterification under classical acidic conditions than via ethoxycarbonylation of ethyl methoxyacetate[10] (large quantities of ethyl 2,4-dimethoxy-3-oxobutanoate were always formed).

Having 2-fluoromalonates **2** in hand, the most straightforward route to diols **3** appeared to be the reduction of the malonates themselves. This reaction proved to be more troublesome than expected. As a matter of fact, conditions that were suitable for non-fluorinated analogues (i.e. lithiumaluminumhydride in tetrahydrofuran),[4a] when applied to **2a** led only to traces of diol **3a**. Low yields[10] or difficulties when using too active hydride sources[12] had already been observed in similar reactions.

Using **2a** as a probe, a variety of reductive conditions were assayed: diisobutylaluminum hydride[13] in toluene at −78°C (traces of **3a**, extensive decomposition); Red-Al[14] in toluene at 0°C (extensive decomposition); and sodium borohydride[15] in dimethylsulfoxide at high temperature (60°C or 150°C).[16] Acceptable yields[17] were at last obtained using in situ generated calcium borohydride.[15,18] When the same conditions were applied to **2b**, diol **3b** was obtained in moderate yield, while neither **2c** nor **2d** gave the corresponding diols. By treatment with sodium borohydride in dimethylsulfoxide, **2c**, as could be expected from results obtained using **2a**, gave 2-fluoro-2-(3-thienyl)-1-ethanol. Since chiral building blocks of type **1** with X=3-thienyl or methoxy could be obtained from route (i) (Scheme 1) (vide infra), no further attempt to synthesize diols **3c**,**d** was made.

An attempt to synthesize diacetate **4a** under conditions (acetic anhydride, Et_3N) that were suitable for its non-fluorinated counterpart,[4a] afforded the desired product only in low yield, probably due to instability of diol **3a** under basic conditions.[17] Diacetate **4a** was better synthesized via enzyme catalyzed acetylation, using lipase from *Candida antarctica* (CAL) (vide infra). The same enzyme catalyzed acetylation was also applied to the synthesis of **4b**.

*2.2. Enzyme catalyzed asymmetrization of 2-substituted 2-fluoromalonic acid diesters **2a–d***

Several reports on enzyme catalyzed asymmetrization of 2-substituted malonic acid diesters have appeared,[2,8] and usually satisfactory chemical yield and enantiomeric excess are obtained, provided that no acidic α-proton (prone to racemization) is present[8,19] in the malonate to be hydrolyzed or that anhydrous conditions are used for the enzymatic transesterification.[20] Recently, some papers reporting enzymatic asymmetrization under aqueous conditions of 2-monosubstituted malonates showing no[21] or

slow[22] racemization have appeared. Esterases,[19,21] aminoacylases,[22] and lipases[8,20] of both microbial and mammalian origin have been used at times. The efficiency of a lipase in catalyzing hydrolysis or transesterification of malonates seems strongly dependent on the substitution pattern and reaction conditions; for example, diethyl 2-fluoro-2-methylmalonate is a substrate for PPL (lipase from porcine pancreas) in the hydrolytic reaction,[8a] while dimethyl 2-methylmalonate is not in the transesterification process.[20] A study on the active site of PLE has been conducted using 2-aryl-2-methylmalonic acid diester[19d] as probes.

We assayed a series of lipases of both microbial (Amano AY, AYL, from *Candida*; CAL, from *Candida antarctica*) and mammalian (PPL, from porcine pancreas, from which S-PPL, supported on Celite,[23] was prepared) origin. The aim was (i) to obtain new small functionalized fluorinated building blocks and (ii) to gain more information on PPL (on the basis of some results collected by us and others on the PPL catalyzed hydrolysis of non-fluorinated derivatives, we have proposed a model for the active site of this enzyme[3]), studying the effects of introducing fluorine instead of hydrogen.

The most significant results are listed in Table 1. Particular attention should be devoted to workup of crude reaction mixtures from enzymatic hydrolysis, since at pH 7 only non-acidic materials (namely unreacted diester and by-products) could be extracted from an aqueous layer using an organic solvent (ethyl acetate). It is necessary to lower pH at values ≤ 3 in order to extract monoesters **5a**–**e** from the aqueous layer, but too low a pH caused the monoesters themselves to decarboxylate, giving 2-substituted 2-fluoroacetic acid esters. In particular, **5a** (X=Ph) completely decarboxylates to probably optically inactive[19a] ethyl 2-fluoro-2-phenylacetate at pH 1, but it is reasonably stable at pH 3 (workup of reaction mixture should be very rapid), while **5c**–**e** (X=3-thienyl, MeO) are fairly stable at pH 3 and **5b** (X=2-naphthyl) is quite unstable even at pH 3 [only a poor quantity of **5b** is obtained from a crude reaction mixture of enzymatic hydrolysis, along with a sensible amount of ethyl 2-fluoro-2-(2-naphthyl)acetate]. An attempt to purify **5a** using flash chromatography resulted in complete decarboxylation, so that monoesters **5** were always isolated, characterized, and further reacted as crude products. Formation of a decarboxylated by-product has been previously observed in PLE catalyzed monohydrolysis of a 2,2-disubstituted malonate:[19f] in our case, maybe decarboxylation is due to the presence, on the same carbon atom between the two carboxylic groups, of two additional 'acidifying' substituents, such as the highly electronegative fluorine and an aromatic group. 2-Fluoro-2-substituted malonic acids were never detected in the reaction mixture: they are either too unstable or too water-soluble to be isolated under the employed workup conditions.

A perusal of Table 1 indicates that, in the case of 2-aryl-2-fluoromalonates **2a** and **2c**, satisfactory results, both in terms of chemical yield and enantiomeric excess, can be achieved using S-PPL (entries 1 and 6), which seems to be somewhat superior (at least in terms of reaction rate) to unsupported enzyme (cf. entries 1 and 3). The microbial lipase Amano AY is also effective, producing the opposite enantiomer, but in lower enantiomeric excess (entry 4). Diester **2b** was a substrate for PPL (entry 5), notwithstanding its low reaction rate, but unfortunately monoester **5b**, as already stated, is very unstable even at pH 3 and was always isolated in very low yield (enantiomeric excess was not measured). Since a chiral buinding block **1**, having X=2-naphthyl, can be conveniently obtained from route (ii) of Scheme 1, no particular effort was made in order to isolate **5b** in acceptable yield. As for 2-fluoro-2-methoxymalonic acid diesters **2d**,**e**, initial runs were performed on dimethyl ester **2e**, more directly obtained from commercial material (see above), but results proved to be quite disappointing, both with S-PPL and lipases of microbial origin (AYL, CAL) (entries 10–12). A 'blank' run (identical reaction conditions to enzymatic hydrolysis, but in the absence of any added lipase) showed that chemical hydrolysis plays a major role in the process, thus lowering the enantiomeric excess of the monoester. A similar problem of hydrolysis under very mild conditions of a methyl ester having an electronegative fluorine atom in the α position had already been

Table 1
Lipase catalyzed asymmetrization of 2-substituted 2-fluoromalonic acid diesters (**2a–e**)[a]

Entry	Substrate (X)	Lipase (mg / mmol subs)	Time / h	Conv.[b] / %	Yield[c] of 5 / %	e. e.[d] / %	Optical rotation sign[e]
1	**2a** (Ph)	S-PPL (230)	21	64	60 (63)	≥96	(-)
2	**2a** (Ph)	S-PPL (260)	24	70	50 (n.d.)	≥96	n. d.
3	**2a** (Ph)	PPL	24	23	35 (72)	90	n. d.
4	**2a** (Ph)	AYL (450)	18	46	90 (92)	52[f]	n. d.
5	**2b** (2-Naphthyl)	S-PPL (320)	45	13	5 (24)[g]	n. d.	n. d.
6	**2c** (3-Thienyl)	S-PPL (270)	4.5	50	77 (86)	96	(-)
7	**2d** (MeO)	S-PPL (280)	3	43	42 (n. d.)	40	n. d.
8	**2d** (MeO)	AYL (260)	0.5	50	73 (n. d.)	≥96[h]	(-)
9	**2d** (MeO)	CAL (250)	5	50	51 (n. d.)	70	n. d.
10	**2e** (MeO)	S-PPL (110)	2.5	49	41 (n. d.)	8	n. d.
11	**2e** (MeO)	AYL (260)	5.5	47	81 (84)	22[i]	n. d.
12	**2e** (MeO)	CAL (250)	1.75	49	42 (n. d.)	82	n. d.

[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 (see Experimental). [b] Conversion was defined as in Ref. 9. [c] Isolated yield; in brackets is reported yield based on unrecovered starting material. Malonic diacids were never recovered. [d] Enantiomeric excess was measured by analysis of both ^{1}H and ^{19}F NMR spectra of monoamides from either (*R*)- or (*S*)-α-methylbenzylamine. [e] $CHCl_3$. [f] The opposite enantiomer with respect to run 1 was obtained. [g] The main isolated product was ethyl 2-fluoro-2-(2-naphthyl)acetate. [h] The opposite enantiomer with respect to run 7 was obtained. [i] The opposite enantiomer with respect to run 10 was obtained.

observed.[7c] Fortunately, use of the diethyl ester minimized chemical hydrolysis, and good results were obtained when AYL was used as a catalyst (entry 8). It should be noted that AYL showed, with any substrate tested in Table 1, the opposite enantiomeric preference with respect to S-PPL (cf. entries 1 and 4, 7 and 8, 10 and 11).

Enantiomeric excess of **5a**, **5c**, and **5d** could not be determined simply by running ^{1}H NMR spectra of these monoacids in the presence of a chiral amine, such as (*S*)- or (*R*)-α-methylbenzylamine.[19a,f,24] We had to react monoacids themselves with the chiral amine, in order to obtain diastereoisomeric amides.[8b] The ratio of diastereoisomeric amides could be determined either via gas-chromatographic techniques (for **5a** and **5c**) or via ^{1}H or ^{19}F NMR analysis (for **5a**, **5c–e**).

The absolute configuration was determined for levorotatory **5a**, via chemical correlation (vide infra) to the already known levorotatory (*R*)-2-fluoro-2-phenyl-1-propanol[7b] and assessed to be (*S*). The same absolute configuration was also tentatively assigned to monoester **5c**, with the assumption that an arrangement of substrate in the active site of an enzyme does not alter when changing aromatic substituents.

The monoethyl ester of 2-fluoro-2-methylmalonic acid had already been obtained with (*S*)-configuration from MYL (from *Candida cyclindracea*) catalyzed monohydrolysis of diester.[8b]

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

Entry	Subs (X)	Lipase (mg / mmol subs)	T / °C	Time / h	Conv.[b] / %	4 : 6 : 3 ratio[c]	Yield[d] of 6 / %	e. e.[e] / %	$[\alpha]_D$[f]
1	**3a** (Ph)	S-PPL (170)	10	90	46	1 : 90 : 9	85 (92)	≥96	+17.7
2	**3a** (Ph)	CAL (80)	-10	20	58	n. d.	52	51[g]	+9.5
3	**3a** (Ph)	CAL (180)	10	15	100	100 : 0 : 0	- [h]	-	-
4	**3a** (Ph)	CCL (175)	10	24	28	n. d.	44	14[g]	+2.5
5	**3a** (Ph)	PSL (175)	0	130	54	9 : 91 : traces	82	94[g]	+17.4
6	**3b** (2-Naphthyl)	S-PPL (240)	10	97	35	traces : 69 : 31	64 (88)	≥96	+19.8
7	**3b** (2-Naphthyl)	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. 23. [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 excess was 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 specific rotation 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 specific rotation, assuming a value of +20.6 for enantiomerically pure monoacetate (from entry 6).

*2.3. Enzyme catalyzed asymmetrization of 2-aryl-2-fluoro-1,3-propanediols **3a–b***

Compounds 2-aryl-2-fluoro-1,3-propanediols **3a–b** were subjected to irreversible enzyme catalyzed monoacetylation, under already reported experimental conditions.[23] More significant results are reported in Table 2.

As already found for a series of 2-monosubstituted 1,3-propanediols, S-PPL gave very satisfactory results both for **3a** (entry 1) and for **3b** (entry 6). Reaction of **3b** was slower, as already observed in the hydrolysis of the corresponding non-fluorinated diacetates;[4a] nevertheless, it gave monoacetate **6b** in very good enantiomeric excess. Lipase from *Pseudomonas* (PSL) gave monoacetate **6a** in good chemical yield, comparable to S-PPL, but a somewhat inferior enantiomeric excess (entry 5), while lipases from *Candida* (CCL, CAL) gave **6a** in very poor enantiomeric excess (entries 2–4). In particular, CAL gave very fast reactions that did not stop at the monoacetate but went further to the diacetate: indeed, CAL catalyzed acetylation was used to prepare diacetates **4a**,**b** (entries 3 and 7) in good chemical yield, since classical acetylation conditions failed (see above). The same enantiomeric preference was steadily found for every tested enzyme.

The absolute configuration was determined for dextrorotatory **6a** to be (*S*), via chemical correlation to levorotatory **5a**, whose absolute configuration had in turn been ascertained by chemical correlation (see above) and found to be (*S*). These results are in accord with an earlier model proposed by us[3] for the catalytic site of PPL: it is apparent that hydrogen-replacing fluorine in the prochiral center takes the place of hydrogen in the proposed model. Also, the absolute configuration of **6b** is tentatively assigned as (*S*), on the basis of enzyme selectivity.

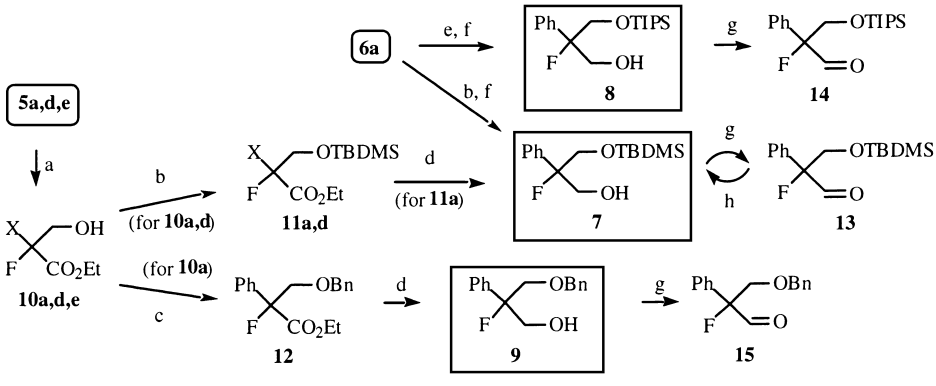
The enantiomeric excess of the monoacetates was determined either by gas-chromatographic analysis using a chiral stationary phase (for **6a**) or by converting the monoacetates into diastereoisomeric esters,

using either (*R*) or (*S*) Mosher's acid chloride (for **6a** and **6b**). The two enantiomers of **6a** were also distinguishable in the ^{1}H NMR spectra in the presence of the chiral shift reagent Eu(hfc)$_3$ {europium tris[(3-heptafluoropropylhydroxymethylene)-(+)-camphorate]}, but rapid racemization (catalyzed by the same shift reagent) made this analytical method impracticable.

A preliminary attempt to hydrolyze diacetate **4a** under standard working conditions, using PPL as catalyst, gave very disappointing results (good chemical yield, but very low enantiomeric excess). Since route (iii) gives no improvement with respect to route (ii), but on the contrary is a step longer and requires a more difficult and time-consuming workup, no further efforts were made.

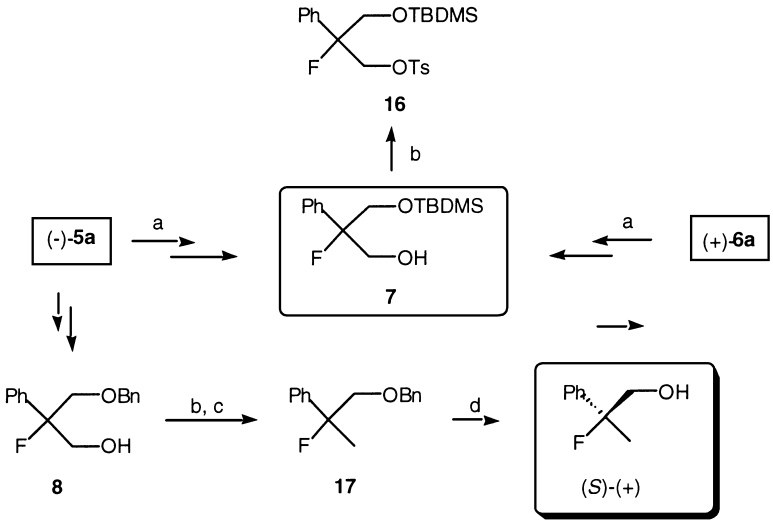
*2.4. Determination of absolute configuration of monoester **5a** and monoacetate **6a** and synthetic manipulation of these C_3 polyfunctionalized chiral building blocks*

In order to test synthetic applications of chiral building blocks obtained from enzymatic reactions, selective independent manipulation of the two oxygenated branches of both **5a**,**d**,**e** and **6a** were performed, as shown in Scheme 2. At the same time, some of these transformations allowed us to determine absolute configuration of both (−)-**5a** and (+)-**6a**, via chemical correlation to 2-fluoro-2-phenyl-1-propanol,[7b] as summarized in detail in Scheme 3.



Scheme 2. Reagents and conditions: (a) $(COCl)_2$, DMF, then $NaBH_4$; 60% for **10a**, 33% for **10d**, 27% for **10e**. (b) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2; 92% for **11a**, 22% for **11d**. (c) BnBr, NaH, DMF, 58%. (d) $NaBH_4$, DMSO, 110°C; 20% for **7**, 61% for **9**. (e) TIPS-OTf, 2,6-lutidine, CH_2Cl_2. (f) NaOH, THF, MeOH, H_2O; 90% for **7**, 47% for **8** (two steps from **6a**). (g) $(COCl)_2$, DMSO, *i*-Pr_2EtN, −78°C, quantitative yield for **13** and **15**; −20°C, 76% for **14**. (h) $NaBH_4$, EtOH, quantitative yield

Initial selective reduction of malonate **5a** was attempted using both basic ($NaBH_4$ reduction of activated carboxylic acid moiety)[8b,19f,g] and acidic (BH_3)[19f,g,20] conditions: using the latter conditions, both the reduction of either the *acidic* moiety[20] or the *ester* one[19f,g] in malonic monoesters has been reported. In our hands, borane reduction of **5a** gave extensive decomposition, while $NaBH_4$ reduction of the activated carboxylic acid moiety gave the desired hydroxy ester **10a** in acceptable yield. When the same reduction conditions were applied to **5d** and **5e**, hydroxy esters **10d**,**e** were obtained in somewhat lower yield: as a matter of fact, they appeared to be even more base-sensitive than **10a**. Protection of the hydroxyl function of **10a**,**d** as silyl or benzyl ether run under usual conditions allowed, in turn, **11a**,**d** or **12** to be obtained. Further reduction of the remaining ester function afforded monoprotected diol **7** (from **11a**) or **9** (from **12**). The same monoprotected diols can, in principle, be obtained via protection of the hydroxyl of **6a**, followed by acetyl removal. As a matter of fact, compound **7**, along with the analogous silylated compound **8**, was obtained from **6a** in very good yield, while direct synthesis of **9** from **6a** was not useful, since, as for the non-fluorinated analogue, this reaction results in a completely racemic product, probably via acetyl group exchange under strongly basic conditions.[3] Monoprotected diols **7**–**9**



Scheme 3. Reagents and conditions: (a) See Scheme 2. (b) TsCl, Et_3N, DMAP, CH_2Cl_2, 81% for **16**. (c) $NaBH_4$ DMSO, 150°C, 75% (two steps from **8**). (d) H_2, 10% Pd/C, $CaCO_3$, MeOH, 50%

were in turn transformed into the corresponding aldehydes **13**–**15** (**14** required positively more vigorous conditions that both **13** and **15**). Aldehyde **13** was also reverted to **7**, in order to confirm the preservation of stereochemical integrity during these manipulations.

Convergent synthesis of monoprotected diol **7**, both from **5a** and **6a**, was important, since it allowed stereochemical correlation between the malonic acid monoester and the monoprotected diol. As a matter of fact, **7** showed a specific rotation close to zero when derived from both (−)-**5a** and (+)-**6a**, but synthesis and NMR spectrometric analysis of the corresponding Mosher's ester showed that in both cases **7** had the same enantiomeric excess as the starting material and that the same enantiomer was obtained from both (−)-**5a** and (+)-**6a**, thus indicating that they should have the same configuration (Scheme 3).

Activation of the alcoholic group of **7** as a tosylate ester afforded diprotected diol **16**, which proved to be very resistant to the reductive removal of the sulfonate function, even when subjected to prolonged heating with $NaBH_4$ in DMSO.[4a] On the contrary, monoprotected diol **8**, obtained from (−)-**5a**, could be easily transformed into the corresponding activated tosylate ester, which was in turn reduced to the protected alcohol **17**. Catalytic hydrogenation gave dextrorotatory 2-fluoro-2-phenyl-1-propanol,[7b] thus establishing the (*S*)-configuration of (−)-**5a** and, as a consequence, of (+)-**6a**.

In an attempt to shorten the transformation from **5a** to **17**, the hydroxy group of **10a** was activated as a tosylate ester, which was then subjected to reduction using $NaBH_4$ in DMSO at high temperature, but unfortunately this reaction stopped at the stage of monotosylated diol (2-fluoro-2-phenyl-3-tosyloxy-1-propanol), resistant to any further reduction. It is possible that the neighboring ionized alcohol function prevents the tosylate from undergoing nucleophilic attack by hydride.

3. Conclusions

In conclusion, we have shown a possible enzymatic route to 2-fluorinated-1,3-dioxygenated chiral building blocks **1**. In detail, synthetic equivalents of **1a** and **1b** could be obtained both from (i) enzyme catalyzed monohydrolysis of malonic acid diesters and (ii) enzyme catalyzed monoacetylation of corresponding 1,3-propanediols, while **1c** and **1d** could be conveniently obtained from route (i).

Effective independent manipulation of the two oxygenated branches, which also means the possibility to obtain both enantiomeric forms of a given diol such as **7**–**9** through suitable sequential introductions of protecting groups, has also been shown. For example, the enantiomer of **16**, obtained from (−)-**5a** or (+)-**6a** as shown in Schemes 2 and 3, was obtained from (+)-**6a** by protection of the hydroxy group of monoacetate as a tosylate ester, hydrolysis of acetate ester, and final protection of the second hydroxy group as silyl ether.

Further manipulation of aldehydes **13**–**15**, as well as of monoesters **5** and **6**, for example in the synthesis of fluorinated analogs of antiinflammatory arylpropionic acids,[4a,7a,b] will be reported in due course.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions on a Varian Gemini 200 spectrometer at 200 MHz (^{1}H) and 50 MHz (^{13}C) using tetramethylsilane (TMS) as the internal standard; ^{19}F NMR spectra were recorded as $CDCl_3$ solutions on a Varian FT-80 (80 MHz) spectrometer using CF_3COOH as the internal standard; chemical shifts (δ) are in ppm, coupling constants (J) are in hertz; a '*' means that the value was obtained through double resonance experiments. Designation of ^{13}C signals was also made with the aid of DEPT and HETCOR experiments. Optical rotatory powers ($[\alpha]_D$) were measured with a JASCO DIP 181 polarimeter as $CHCl_3$ (containing 0.75% EtOH) solutions. Melting points were taken using a Büchi 535 apparatus. GC–MS was carried out on an HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 175°C. Unless otherwise stated, analyses were performed with a constant helium flow (0.9 ml/min), starting at 60°C for 2 min and then raising the temperature by 20°C/min up to 280°C (10 min). Gas-chromatographic (GC) analyses were performed on a Carlo Erba HRGC 5300 instrument, using a chiral capillary column Dmet.Terbut.SBeta (Mega) (stationary phase: persilylated β-cyclodextrin; 25 m long, 0.25 mm wide) and helium as a carrier gas (unless otherwise stated: $T_{injector}$=200°C, $T_{detector}$=220°C).

'Usual workup' means that the given reaction mixture was extracted three times (Et_2O or AcOEt or CH_2Cl_2), the organic layer was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure.

Tetrahydrofuran (THF) was always freshly distilled from K/Ph_2CO; CH_2Cl_2, Et_2O, *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), and hexamethylphosphorous triamide (HMPA) were purchased as dry solvents from Aldrich and stored over 4 Å molecular sieves. Petroleum ether (PE) refers to the fraction boiling in the range 40–60°C.

F-TEDA-BF_4 stands for 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate),[11] Tf for trifluoromethanesulfonyl (triflyl), Ts for *p*-toluenesulfonyl (tosyl), TBDMS for *t*-butyldimethylsilyl, TIPS for triisopropylsilyl, Bn for benzyl, MTPA for α-methoxy-α-(trifluoromethyl)phenylacetyl.

All reactions requiring dry conditions were run under an inert atmosphere (N_2).

TLC analyses were carried out on silica gel plates, which were observed under UV (254 nm) light and developed by dipping into a solution of 21 g of $(NH_4)_4MoO_4\cdot 4H_2O$ and 1 g of $Ce(SO_4)_2\cdot 4H_2O$ in 31 ml H_2SO_4 and 469 ml H_2O or a 2% aqueous solution of potassium permanganate and warming. R_fs were measured after an elution of 7–9 cm. Column chromatographies were run following the method of 'flash chromatography', using 230–400 mesh silica gel (Merck).

All compounds gave satisfactory spectroscopic and chromatographic data: an extensive selection of this data is reported. Diesters **2a**[11,25] and **2e**,[26] as well as racemic monoprotected diol **7**,[27] were already known compounds.

PPL (lipase from porcine pancreas), from which S-PPL[23] was prepared, and CCL (lipase from *Candida cylindracea*) were purchased from Sigma; lipases AYL (from *Candida*) and PSL (from *Pseudomonas*) were kindly donated by Amano; CAL (lipase from *Candida antarctica*) was a kind gift from Novo Nordisk.

4.2. Dialkyl 2-substituted 2-fluoromalonates *2a–e*

To an oil-free suspension of NaH (1.2 mmol) in dry THF (2 ml) a THF (7 ml) solution of 2-substituted malonate (1.0 mmol) and 2 ml of dry DMF were added at room temperature. After stirring for 20 min at the same temperature, F-TEDA-BF_4 (1.3 mmol) was added as a solid and stirring continued overnight. The reaction mixture was cooled to 0°C and 5% H_2SO_4 was added. The product was extracted using Et_2O, and the organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and evaporated to dryness. In the case of 2-fluoro-2-methoxymalonates **2d**,**e**, the reaction mixture was quenched using water instead of 5% H_2SO_4 and washing with $NaHCO_3$ obviously omitted. Chromatographic purification (PE:AcOEt, 9:1, for **2a**–**c**, 8:2 for **2d**,**e**) afforded 2-substituted 2-fluoromalonates **2a**–**e** as yellow oils.

4.2.1. Diethyl 2-fluoro-2-phenylmalonate *2a*[11,25]

This product was obtained in 94% yield.

4.2.2. Diethyl 2-fluoro-2-(2-naphthyl)malonate *2b*

Yield: 90%; R_f=0.35 (PE:AcOEt, 9:1); ^{1}H NMR and ^{19}F NMR: see literature;[9] ^{13}C NMR: 13.95 (*Me*), 63.07 (*C*H_2), 94.27 (d, *J* 199.8, *C*F), 123.06 (d, *J* 7.3), 125.17 (d, *J* 10.4), 126.55, 127.05, 127.61, 128.10, 128.59, 130.52 (d, *J* 21.8), 133.03 (d, *J* 44.4) (*ArC*), 165.64 (d, *J* 25.6, *C*=O); GC–MS: R_t=10.5 min, *m/z* (%) 304 (M^+, 45), 231 (100), 203 (37), 159 (17), 155 (20), 127 (9).

4.2.3. Diethyl 2-fluoro-2-(3-thienyl)malonate *2c*

Yield: 78%; R_f=0.40 (PE:AcOEt, 9:1); ^{1}H NMR and ^{19}F NMR: see literature;[9] ^{13}C NMR: 13.86 (*Me*), 62.98 (*C*H_2), 92.52 (d, *J* 197.6, *C*F), 124.19 (d, *J* 8.8), 125.99 (d, *J* 4.9), 126.04, 133.64 (d, *J* 24.0) (*ArC*), 165.12 (d, *J* 25.8, *C*=O); GC–MS: R_t=7.9 min, *m/z* (%) 260 (M^+, 20), 187 (100), 159 (35), 131 (55), 115 (39).

4.2.4. Diethyl 2-fluoro-2-methoxymalonate *2d*

Yield: 72%; R_f=0.47 (PE:AcOEt, 8:2); ^{1}H NMR: 1.34 (t, *J* 7.1, 6H, 2×*Me*CH_2), 3.59 (d, *J* 1.4, 3H, *Me*O), 4.36 (q, *J* 7.1, 4H, 2×C*H*$_2$); ^{13}C NMR: 13.91 (*Me*CH_2), 53.25 (d, *J* 3.1, *Me*O), 63.08 (*C*H_2), 104.52 (d, *J* 239.7, *C*F); ^{19}F NMR: 48.67 (bs); GC–MS: R_t=5.2 min, *m/z* (%) 178 (M^+−30, 6), 135 (100), 121 (15), 107 (10), 93 (10).

4.2.5. Dimethyl 2-fluoro-2-methoxymalonate *2e*[26]

This product was obtained in 86% yield.

4.3. General procedure for the synthesis of 2-aryl-2-fluoro-1,3-propanediols **3a**,**b**

To a suspension of anhydrous $CaCl_2$ (6.0 mmol) in dry EtOH:THF 1:1 (2 ml), cooled to 0°C, $NaBH_4$ (10.0 mmol) was added as a solid. After stirring for 20 min, a solution of diethyl 2-aryl-2-fluoromalonate (1.0 mmol) in THF (10 ml) was added and stirring continued for 2 h. The reaction mixture was quenched (1 N HCl) and worked up as usual (Et_2O). Flash chromatography (CH_2Cl_2:Et_2O, 1:1) afforded pure diols as white solids.

4.3.1. 2-Fluoro-2-phenyl-1,3-propanediol **3a**

Yield: 47%; m.p. 67–68.5°C; R_f=0.47 (Et_2O); ^{1}H NMR: 2.65 (bt, *J* 5.0, 2H, 2×O*H*; disappeared after exchanging with D_2O), 3.87–4.16 [m, 4H, 2×CH_2OH; after exchanging with D_2O: 3.96 and 4.04 (AB as part of an ABX system, J_{AB} 12.8, J_{AX} 17.8, J_{BX} 22.5], 7.35–7.41 (m, 5H, *Ph*); ^{13}C NMR: 66.40 (d, *J* 25.3, *C*H_2), 98.76 (d, *J* 175.6, *C*F), 124.77 (d, *J* 9.4), 128.47 (d, *J* 12.8), 128.61, 137.74 (d, *J* 20.9) (*Ph*); ^{19}F NMR: 93.66–94.76 (m); GC–MS: R_t=6.8 min, *m/z* (%) 170 (M^+, 0.3), 122 (100), 91 (68).

4.3.2. 2-Fluoro-2-(2-naphthyl)-1,3-propanediol **3b**

Yield: 30%; m.p. 69–70.5°C; R_f=0.40 (PE:Et_2O, 2:8); ^{1}H NMR: 2.11 (bs, 2H, 2×O*H*; disappeared after exchanging with D_2O), 4.03–4.34 [m, 4H, 2×CH_2OH; after exchanging with D_2O: 4.10 and 4.18 (AB as part of an ABX system, J_{AB} 13.1, J_{AX} 18.2, J_{BX} 21.5], 7.46–7.56 (m, 3H) and 7.83–7.92 (m, 4H) (*ArH*); ^{13}C NMR: 66.49 (d, *J* 25.4, *C*H_2), 99.14 (d, *J* 175.4, *C*F), 122.29 (d, *J* 8.9) and 124.37 (d, *J* 10.5) and 126.58 and 127.65 and 128.23 and 128.55 and 128.59 and 132.99 (d, *J* 1.8) and 146.95 (*ArC*); ^{19}F NMR: 96.70–97.76 (m); GC–MS: R_t=9.8 min, *m/z* (%) 220 (M^+, 8), 182 (9), 172 (14), 149 (100), 141 (51), 115 (11).

4.4. General procedure for the synthesis of 2-aryl-2-fluoro-1,3-diacetoxypropanes **4a**,**b**

4.4.1. Chemical acetylation

To a solution of diol **3a** (1.0 mmol) in dry CH_2Cl_2 (6 ml), cooled to 0°C, triethylamine (5.0 mmol), Ac_2O (2.5 mmol), and DMAP (0.1 mmol) were sequentially added. After stirring for 1.5 h at the same temperature, the reaction was quenched (saturated aqueous NH_4Cl) and worked up (Et_2O). Flash chromatography (PE:AcOEt, 9:1 → 8:2) afforded diacetate **4a** (10%) as an oil: R_f=0.34 (PE:AcOEt, 8:2); ^{1}H NMR: 2.04 (s, 6H, 2×*Me*), 4.47 and 4.53 (AB as part of an ABX system, J_{AB} 12.4, J_{AX} 20.6, J_{BX} 20.3, 4H, 2×CH_2), 7.39 (bs, 5H, *Ph*); ^{13}C NMR: 20.66 (*Me*), 60.67 (d, *J* 25.7, *C*H_2), 95.44 (d, *J* 181.1, *C*F), 124.84 (d, *J* 9.3) and 128.57 and 128.62 (d, *J* 4.9) and 136.68 (d, *J* 21.6) (*Ph*), 170.33 (*C*=O); ^{19}F NMR: 85.65–86.75 (m); GC–MS (temperature was raised at a rate of 10°C/min): R_t=12.1 min, *m/z* (%) 254 (M^+, 1), 181 (11), 122 (100).

4.4.2. Enzymatic acetylation

To a solution of diols **3a** or **3b** (1.0 mmol) in diisopropyl ether (17 ml) and vinyl acetate (23 ml), in the presence of a small amount of 3 Å molecular sieves, CAL was added. The reaction was stopped by filtering off the enzyme on a Celite pad and washing with Et_2O. Evaporation of solvent and chromatographic purification (PE:AcOEt, 9:1 → 7:3 for **4b**) afforded diacetates **4a** or **4b** (see Table 2 for temperatures, enzyme quantities, times and yields).

4b: oil; R_f=0.53 (PE:AcOEt, 7:3); ^{1}H NMR: 2.04 (s, 6H, 2×*Me*), 4.58 and 4.62 (AB as part of an ABX system, J_{AB} 12.4, J_{AX} 20.4, J_{BX} 20.7, 4H, 2×CH_2), 7.44–7.58 (m, 3H), 7.85–7.92 (m, 4H) (*ArH*); ^{13}C NMR: 20.67 (*Me*), 65.75 (d, *J* 25.2, *C*H_2), 95.71 (d, *J* 181.4, *C*F), 122.24 (d, *J* 8.8), 124.52 (d, *J* 10.2),

126.61, 126.73, 127.66, 128.32, 128.44, 132.92, 133.10, 134.02 (d, *J* 29.0) (*ArC*), 170.36 (*C*=O); ^{19}F NMR: 91.21–92.27 (m); GC–MS: R_t=10.5 min, *m/z* (%) 304 (M^+, 52), 231 (39), 189 (14), 172 (100), 141 (36), 115 (4).

4.5. General procedure for the enzymatic synthesis of 2-substituted 2-fluoromalonic acid monoesters ***5a–e***

To a suspension of 2-substituted 2-fluoromalonic acid diester (1.0 mmol) in a 0.01 M pH 7 phosphate buffer (40 ml), lipase was added at room temperature and under vigorous stirring. Addition of 0.1 M NaOH via a pH-stat apparatus allowed the pH to be kept constant and to monitor the hydrolysis. The reaction was stopped by filtering off the enzyme through a Celite pad and washing with AcOEt. The organic phase was separated from the aqueous layer and the latter was extracted twice with AcOEt (this organic phase contained unreacted diester and decarboxylated by-products), then acidified (diluted HCl) to pH 3, and extracted (three times) with AcOEt. Anhydrification and evaporation of this organic phase yielded almost pure 2-substituted 2-fluoromalonic acids monoesters **5a–e** as yellow oils. Temperatures, enzymes (type and quantities), times, optical rotatory powers, chemical yields, and enantiomeric excesses are reported in detail in Table 1. When reactions were scaled up, 1 N instead of 0.01 N NaOH was used to titrate the hydrolysis. Analytical data for ethyl 2-fluoro-2-(naphthyl)acetate, the main product isolated from hydrolysis of **2b** (see entry 5 of Table 1), are also reported.

4.5.1. Monoethyl 2-fluoro-2-phenylmalonate ***5a***

R_f=0.33 (AcOEt:EtOH, 7:3); ^{1}H NMR: 1.30 (t, *J* 7.1, 3H, *Me*), 4.33 (q, *J* 7.1, 2H, C*H*$_2$), 7.39–7.42 (m, 3H), 7.58–7.63 (m, 2H) (*Ph*), 9.21 (s, 1H, O*H*; disappeared after exchanging with D_2O); ^{13}C NMR: 13.79 (*Me*), 63.48 (*C*H_2), 93.68 (d, *J* 199.7, *C*F), 125.55 (d, *J* 9.0), 128.41, 129.67, 132.55 (d, *J* 21.9) (*Ph*), 165.53 (d, *J* 25.4, *C*O_2Et), 159.53 (d, *J* 26.4, *C*O_2H); ^{19}F NMR: 84.09 (s).

4.5.2. Monoethyl 2-fluoro-2-(2-naphthyl)malonate ***5b***

R_f=0.28 (AcOEt:EtOH, 7:3); ^{1}H NMR: 1.33 (t, *J* 7.1, 3H, *Me*), 4.35 (q, *J* 7.1, 2H, C*H*$_2$), 7.51–8.09 (m, 7H, *ArH*); ^{13}C NMR: 13.96 (*Me*), 63.10 (*C*H_2); ^{19}F NMR: 84.21 (s).

4.5.3. Monoethyl 2-fluoro-2-(3-thienyl)malonate ***5c***

R_f=0.28 (AcOEt:EtOH, 7:3); ^{1}H NMR: 1.33 (t, *J* 7.1, 3H, *Me*), 4.36 (q, *J* 7.1, 2H, C*H*$_2$), 7.28 (app dd, *J* 1.4 and 5.2, 1H), 7.34–7.39 (m, 1H), 7.60–7.62 (m, 1H) (*ArH*), 10.71 (s, 1H, O*H*; disappeared after exchanging with D_2O); ^{13}C NMR: 13.87 (*Me*), 63.63 (*C*H_2), 92.22 (d, *J* 198.8, *C*F), 124.58 (d, *J* 8.5), 128.84 (d, *J* 5.2), 126.47, 132.90 (d, *J* 24.8) (*ArC*), 165.03 (d, *J* 25.6, *C*O_2Et), 169.64 (d, *J* 26.9, *C*O_2H); ^{19}F NMR: 78.31 (s).

4.5.4. Monoethyl 2-fluoro-2-methoxymalonate ***5d***

R_f=0.20 (AcOEt:EtOH, 7:3); ^{1}H NMR: 1.36 (t, *J* 7.1, 3H, *Me*CH_2), 3.61 (d, *J* 1.4, 3H, *Me*O), 4.38 (q, *J* 7.1, 2H, C*H*$_2$), 8.44 (bs, 1H, O*H*; disappeared after exchanging with D_2O); ^{13}C NMR: 13.80 (*Me*CH_2), 53.67 (d, *J* 3.4, *Me*O), 63.61 (*C*H_2), 104.28 (d, *J* 240.2, *C*F), 162.95 (d, *J* 34.6, *C*O_2Et), 166.12 (d, *J* 34.6, *C*O_2H).

4.5.5. Monomethyl 2-fluoro-2-methoxymalonate ***5e***

R_f=0.20 (AcOEt:EtOH, 7:3); ^{1}H NMR: 3.61 (d, *J* 1.4, 3H, *Me*OCF), 3.92 (s, 3H, *Me*OCO), 6.39 (bs, 1H, O*H*; disappeared after exchanging with D_2O); ^{13}C NMR: 53.71–53.84 (m, *Me*OCF and *Me*OCO), 104.36 (d, *J* 244.2, *C*F), 163.46 (d, *J* 34.4, *C*O_2Me), 165.77 (d, *J* 35.1, *C*O_2H); ^{19}F NMR: 48.65 (bs).

4.5.6. Ethyl 2-fluoro-2-(2-naphthyl)acetate

Oil; R_f=0.59 (PE:AcOEt, 8:2); ^{1}H NMR: 1.26 (t, *J* 7.1, 3H, *Me*), 4.17–4.38 (m, 2H, CH_2), 5.94 (d, *J* 47.6, 1H, *H*CF), 7.51–7.55 (m, 3H), 7.84–7.95 (m, 4H) (*ArH*); ^{13}C NMR: 14.25 (*Me*), 62.11 (*C*H_2), 89.76 (d, *J* 184.9, *C*F), 123.69 (d, *J* 5.2), 126.17, 126.82, 127.13, 127.98, 128.42, 128.95, 131.79 (d, *J* 19.8), 133.69 (d, *J* 39.0) (*ArC*), 168.83 (d, *J* 22.5, *C*=O); ^{19}F NMR: 96.61 (d).

4.6. General procedure for the enzymatic synthesis of 3-acetoxy-2-aryl-2-fluoro-1-propanols ***6a–b***

To a solution of diol **3a** or **3b** (1.0 mmol) in diisopropyl ether (17 ml) and vinyl acetate (23 ml), in the presence of a small amount of 3 Å molecular sieves, lipase was added. The reaction was stopped by filtering off the enzyme on a Celite pad and washing with Et_2O. Evaporation of the solvent and chromatographic purification (PE:AcOEt, 7:3) afforded monoacetates **6a** or **6b** as oils. Temperatures, enzymes (type and quantities), times, optical rotatory powers, chemical yields and enantiomeric excesses are reported in detail in Table 2.

4.6.1. 3-Acetoxy-2-fluoro-2-phenyl-1-propanol ***6a***

R_f=0.33 (PE:AcOEt, 7:3); ^{1}H NMR: 2.05 (s, 3H, *Me*), 3.97 [dd, *J* 5.9 and 19.1, 2H, CH_2OH; after exchanging with D_2O: 3.97 (d, *J* 19.2)], 4.52 and 4.57 (AB as part of an ABX system, J_{AB} 11.9, J_{AX} 18.6, J_{BX} 21.7, 2H, CH_2OAc), 7.39–7.43 (m, 5H, *Ph*); ^{13}C NMR: 20.70 (*Me*), 65.60 (d, *J* 25.4), 65.68 (d, *J* 26.0) (*C*H_2OH and *C*H_2OAc), 97.28 (d, *J* 177.5, *C*F), 124.89 (d, *J* 9.6), 128.57, 137.19 (d, *J* 21.0) (*Ph*), 170.76 (*C*=O); ^{19}F NMR: 94.57–95.64 (m); GC–MS: R_t=8.3 min, *m/z* (%) 212 (M^+, 0.02), 182 (2), 122 (100), 91 (22); GC (P=150 kg/cm^2, T_{oven}=145°C): R_t=14.1 min for the (*S*)-enantiomer and 14.7 min for the (*R*)-enantiomer.

4.6.2. 3-Acetoxy-2-fluoro-2-(2-naphthyl)-1-propanol ***6b***

R_f=0.32 (PE:AcOEt, 7:3); ^{1}H NMR: 2.04 (s, 3H, *Me*), 2.13 (bt, *J* 5.6, 1H, O*H*; disappeared after exchanging with D_2O), 4.05 [dd, *J* 5.2 and 19.0, 2H, CH_2OH; after exchanging with D_2O: 4.05 (d, *J* 19.0)], 4.62, 4.67 (AB as part of an ABX system, J_{AB} 12.5, J_{AX} 21.3, J_{BX} 20.7, 2H, CH_2OAc), 7.46–7.56 (m, 3H), 7.83–7.91 (m, 4H) (*ArH*); ^{13}C NMR: 20.70 (*Me*), 65.40–65.90 (m, *C*H_2OH and *C*H_2OAc), 97.56 (d, *J* 177.7, *C*F), 122.34 (d, *J* 8.5), 124.50 (d, *J* 10.1), 126.55, 126.62, 127.64, 128.27, 128.45 (d, *J* 1.8), 132.95, 133.04, 134.55 (d, *J* 21.0) (*ArC*), 170.83 (*C*=O); ^{19}F NMR: 93.80–94.94 (m); GC–MS: R_t=10.2 min, *m/z* (%) 262 (M^+, 22), 231 (7), 189 (9), 172 (100), 141 (51), 128 (11), 115 (8).

4.7. Synthesis of hydroxy esters ***10a,d,e***

These hydroxy esters were prepared from the corresponding half-esters according to a reported procedure,[7b] except that the reaction temperature of the reduction step was kept for 3 h at −78°C. Pure products were obtained after chromatographic purification (PE:AcOEt, 9:1→ 7:3).

4.7.1. Ethyl 2-fluoro-3-hydroxy-2-phenylpropanoate ***10a***

Yield: 60%, white solid, mp 38.0–39.5°C; R_f=0.47 (PE:AcOEt, 7:3); ^{1}H NMR: 1.30 (t, *J* 7.1, 3H, *Me*), 4.02 and 4.33 (AB as part of an ABX system, J_{AB} 12.6, J_{AX} 15.7, J_{BX} 29.4, 2H, CH_2OH), 4.30 (q, *J* 7.1, 2H, MeCH_2), 7.38–7.55 (m, 5H, *Ph*); ^{13}C NMR: 14.00 (*Me*), 62.33 (Me*C*H_2), 67.52 (d, *J* 22.5, *C*H_2OH), 97.62 (d, *J* 188.7, *C*F), 124.71 (d, *J* 9.0), 128.62, 129.04, 134.69 (d, *J* 21.8) (*Ph*), 168.93 (d, *J* 26.6, *C*=O); ^{19}F NMR: 94.76–95.39 (m); GC–MS: R_t=7.2 min, *m/z* (%) 182 (M^+−30, 100), 154 (53), 119 (41), 91 (79).

4.7.2. Ethyl 2-fluoro-3-hydroxy-2-methoxypropanoate ***10d***

Yield: 27%, oil; R_f=0.35 (PE:AcOEt, 7:3); ^{1}H NMR: 1.36 (t, *J* 7.1, 3H, *Me*CH_2), 1.6 (bs, 1H, O*H*; disappeared after exchanging with D_2O), 3.49 (d, *J* 1.1, 3H, *Me*O), 3.82–3.90 (m, 2H, CH_2OH), 4.34 (q, *J* 7.1, 2H, CH_2Me).

4.7.3. Methyl 2-fluoro-3-hydroxy-2-methoxypropanoate ***10e***

Yield: 33%, oil; R_f=0.32 (PE:AcOEt, 7:3); ^{1}H NMR: 2.22 (bt, 1H, O*H*; disappeared after exchanging with D_2O), 3.49 (d, *J* 0.9, 3H *Me*OCF), 3.83–3.92 (m, 2H, CH_2), 3.89 (s, 3H, *Me*OCO); ^{13}C NMR: 29.41 (d, *J* 40.9, *C*H_2), 52.98 (*Me*OCO), 64.65 (d, *J* 28.0, *Me*OCF), 110.56 (d, *J* 23.1, *C*F), 166.53 (d, *J* 39.8, *C*=O).

*4.8. Ethyl 3-(*t*-butyldimethylsilyloxy)-2-fluoro-2-phenylpropanoate* ***11a***

To a solution of **10a** (1.0 mmol) in dry CH_2Cl_2 (20 ml), cooled to 0°C, 2,6-lutidine (3.0 mmol) and TBDMS-OTf (2.0 mmol) were sequentially added. Stirring was continued at room temperature overnight, then the reaction mixture was cooled again to 0°C, quenched (saturated aqueous NH_4Cl), and worked up as usual (AcOEt). Chromatographic purification (PE:Et_2O, 95:5 → 9:1) afforded **11a** (82%, 92% based on unrecovered substrate) as an oil. R_f=0.79 (PE:AcOEt, 8:2); ^{1}H NMR: 0.07 and 0.08 (2s, 3H each, Me_2Si), 0.89 (s, 9H, Me_3C), 1.31 (t, *J* 7.1, 3H, *Me*CH_2), 3.94 and 4.35 (AB as part of an ABX system, J_{AB} 11.5, J_{AX} 15.9, J_{BX} 32.1, 2H, CH_2OSi), 4.24 and 4.31 (AB as part of an ABX system, J_{AB} 7.1, J_{AX} 2.2, J_{BX} 2.4, 2H, CH_2Me), 7.33–7.44 (m, 3H), 7.54–7.59 (m, 2H) (*Ph*); ^{13}C NMR: −5.50 and −5.42 (Me_2Si), 14.11 (*Me*CH_2), 18.24 (*C*Si), 25.70 (Me_3C), 61.82 (*C*H_2Me), 68.51 (d, *J* 21.7, *C*H_2OSi), 97.52 (d, *J* 193.8, *C*F), 125.00 (d, *J* 9.1), 128.37, 128.75, 135.43 (d, *J* 21.8) (*Ph*), 168.96 (d, *J* 25.5, *C*=O); ^{19}F NMR: 100.06–102.43 (m); GC–MS: R_t=9.1 min, *m/z* (%) 311 (M^+−15, 0.4), 269 (35), 197 (14), 177 (47), 151 (64), 123 (30), 103 (41), 91 (60), 77 (100).

*4.9. Ethyl 3-(*t*-butyldimethylsilyloxy)-2-fluoro-2-methoxypropanoate* ***11d***

The same procedure described above for the synthesis of **11a** was applied, but with a reaction temperature of −15°C and timed for 1 h; **11d** was obtained as an oil (32%) after chromatographic purification (PE:AcOEt, 95:5). R_f=0.76 (PE:AcOEt, 8:2); ^{1}H NMR: 0.04 and 0.05 (2s, 3H each, Me_2Si), 0.86 (s, 9H, Me_3C), 1.33 (t, *J* 7.1, 3H, *Me*CH_3), 3.42 (d, *J* 0.7, 3H *Me*O), 3.80, 3.94 (AB as part of an ABX system, J_{AB} 10.9, J_{AX} 10.5, J_{BX} 23.3, 2H, CH_2OSi), 4.30 (q, *J* 7.1, 2H, CH_2Me); ^{13}C NMR: −5.60 and −5.51 (Me_2Si), 14.17 (*Me*CH_2), 18.77 (Me$_3$*C*), 25.64 (Me_3C), 52.54 (*Me*O), 61.98 (*C*H_2Me), 65.61 (d, *J* 27.1, *C*H_2OSi), 111.08 (d, *J* 233.8, *C*F), 166.10 (d, *J* 40.3, *C*=O); ^{19}F NMR: 56.19–56.77 (m); GC–MS: R_t=6.6 min, *m/z* (%) 265 (M^+−15, 0.2), 223 (40), 151 (14), 131 (70), 116 (44), 89 (33), 77 (78), 73 (100).

4.10. Ethyl 3-(benzyloxy)-2-fluoro-2-phenylpropanoate **12**

To a solution of **10a** (1.0 mmol) in dry DMF (1.5 ml), cooled to 0°C, benzyl bromide (2.0 mmol) and NaH (50% dispersion in mineral oil) (2.0 mmol) were sequentially added. After stirring at room temperature for 2 h, the reaction mixture was again cooled to 0°C, quenched (saturated aqueous NH_4Cl), and worked up as usual (AcOEt). Chromatographic purification (PE:AcOEt, 95:5) afforded **12** (58%) as an oil. R_f=0.54 (PE:AcOEt, 8:2); ^{1}H NMR: 1.29 (t, *J* 7.1, 3H, *Me*CH_3), 3.78–4.34 (m, 4H, CH_2OBn and CH_2Me), 4.55–4.74 (m, 2H, CH_2Ph), 7.28–7.56 (m, 10H, 2×*Ph*); ^{13}C NMR: 14.05 (*Me*CH_2), 62.13, 67.55, 74.18 (d *J* 20.7) (*C*H_2O*C*H_2Ph and *C*H_2Me), 97.13 (d, *J* 193.0, *C*F), 124.94 (d, *J* 9.1), 127.70, 128.04, 128.39, 128.52, 128.90, 135.28 (d, *J* 21.9), 137.71 (2×*Ph*), 168.83 (d, *J* 27.1, *C*=O); ^{19}F NMR: 91.68–92.84 (m).

4.11. 3-(t-Butyldimethylsilyloxy)-2-fluoro-2-phenyl-1-propanol **7**

4.11.1. From compound **11a**

To a solution of **11a** (1.0 mmol) in dry DMSO (10 ml) $NaBH_4$ (8.0 mmol) was added as a solid and the reaction mixture was heated for 3 h to 110°C. After cooling to room temperature, saturated aqueous NH_4Cl was added and the reaction mixture was worked up as usual (Et_2O). Chromatographic purification (PE:EtOAc, 9:1) afforded **7** (20%) as an oil. R_f=0.60 (PE:AcOEt, 8:2); ^{1}H NMR: see literature;[27] ^{13}C NMR: −5.64 and −5.58 (*Me*$_2$Si), 18.23 (*C*Si), 25.76 (*Me*$_3$C), 66.20 (d, *J* 24.5), 67.44 (d, *J* 28.1) (*C*H_2OSi and *C*H_2OH), 98.06 (d, *J* 177.3, *C*F), 124.94 (d, *J* 9.8), 128.11, 128.32 (d, *J* 1.8), 138.56 (d, *J* 21.0) (*Ph*); ^{19}F NMR: 96.09 (app quintuplet, *J* 20.8).

4.11.2. From compound **6a**

4.11.2.1. Silylation. A dry CH_2Cl_2 solution of **6a** was sequentially treated with 2,6-lutidine and TBDMS-OTf as described above in the synthesis of **11a**. The usual workup afforded crude 1-acetoxy-3-(*t*-butyldimethylsilyloxy)-2-fluoro-2-phenylpropane (oil), which was used as such in the subsequent reaction. R_f=0.84 (PE:AcOEt, 8:2).

4.11.2.2. Saponification. A solution of crude acetate (1.0 mmol) in THF:MeOH, 10:1 (11 ml) was treated with 1 N NaOH (1.5 ml) at room temperature for 30 min. Saturated aqueous NH_4Cl was added and the reaction mixture worked up as usual (AcOEt). Chromatographic purification afforded pure **7**. When synthesized from (+)-**6a**, having an e.e.≥96% (see entry 1 of Table 2), (*R*)-**7** showed $[\alpha]_D$=−1.0 (*c* 1.1); ^{1}H NMR analysis of Mosher's esters showed an e.e.≥96%.

4.11.3. From aldehyde **14**

To a solution of aldehyde **14** in 95% EtOH (1.0 mmol in 6 ml), cooled to 0°C, $NaBH_4$ (1.1 mmol) was added as a solid. After stirring for 5 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and most of the solvent was evaporated under reduced pressure; the residue was kept using AcOEt and the reaction worked up as usual (AcOEt) to give **7** in quantitative yield.

4.12. 3-Benzyloxy-2-fluoro-2-phenyl-1-propanol **9**

Applying to **12** the same procedure described above for the synthesis of **7** from **11a**, monoprotected diol **9** was obtained (61%) as an oil after chromatographic purification (PE:AcOEt, 9:1). R_f=0.28 (PE:AcOEt, 8:2); ^{1}H NMR: 2.18 (bt, *J* 6.7, 1H, O*H*), 3.89 (d, *J* 20.1, 2H), 3.87–4.21 (m, 2H) (CH_2OBn,

C*H*$_2$OH), 4.62, 4.58 (AB system, J_{AB} 12.1, 2H, C*H*$_2$Ph), 7.27–7.43 (m, 10H, 2×*Ph*); ^{13}C NMR: 66.48 (d, *J* 25.0), 73.25 (d, *J* 26.2), 73.84 (*C*H$_2$O*C*H$_2$Ph, *C*H$_2$OH), 98.16 (d, *J* 176.7, *C*F), 124.93 (d, *J* 9.5), 127.72, 127.86, 128.22, 128.44, 128.48, 137.58, 138.41 (d, *J* 21.4) (2×*Ph*); ^{19}F NMR: 94.28 (app quintuplet, *J* 20.6); GC–MS: R_t=10.0 min, *m/z* (%) 260 (M^+, 1), 210 (1), 199 (2), 139 (7), 122 (35), 119 (23), 91 (100). When synthesized starting from (−)-**5a**, having an e.e.≥96% (see entry 1 of Table 1), (*R*)-**9** showed [α]$_D$=−20.2 (*c* 0.3); GC (P=250 kg/cm^2, T_{oven}=160°C): R_t=40.0 min for the (*S*)-enantiomer and 41.7 min for the (*R*)-enantiomer] showing an e.e.≥96%.

*4.13. 2-Fluoro-3-(triisopropylsilyloxy)-2-phenyl-1-propanol **8***

4.13.1. Silylation

A dry CH_2Cl_2 solution of **6a** (1.0 mmol in 13 ml), cooled to 0°C, was sequentially treated with 2,6-lutidine (3.0 mmol) and TIPS-OTf (2.0 mmol). Stirring was continued at room temperature overnight, then the reaction mixture was cooled again to 0°C, quenched (saturated aqueous NH_4Cl), and worked up as usual (Et_2O).

4.13.2. Saponification

Crude acetate was dissolved in THF:MeOH, 1:1 (1.0 mmol in 25 ml) and treated with 1 N NaOH (1 ml) at room temperature for 2 h. Saturated aqueous NH_4Cl was added; the usual workup and chromatographic purification (PE:AcOEt, 85:15) afforded pure **8** as an oil (47%, two steps from **6a**). R_f=0.43 (PE:AcOEt, 9:1); ^{1}H NMR: 1.01–1.25 (m, 21H, 3×C*HMe*$_2$), 2.36 (bt, *J* 6.6, 1H, O*H*), 3.93–4.31 (m, 4H, C*H*$_2$OH and C*H*$_2$OSi), 7.32–7.46 (m, 5H, *Ph*); ^{13}C NMR: 11.90 and 12.33 (*Me*$_2$CH), 17.76 (d, *J* 6.5, Me$_2$*C*H), 66.24 (d, *J* 24.5), 67.91 (d, *J* 28.8) (*C*H$_2$OH and *C*H$_2$OSi), 98.18 (d, *J* 176.3, *C*F), 125.01 (d, *J* 9.7), 128.15 (d, *J* 11.4), 128.27, 138.75 (d, *J* 20.1) (*Ph*). When synthesized starting from (+)-**6a**, having an e.e.≥96% (see entry 1 of Table 2), (*R*)-**8** showed [α]$_D$=−0.4 (*c* 1.0).

4.14. General procedure for the synthesis of O*-protected 3-hydroxyaldehydes **13**–**15** from corresponding monoprotected diols **7**–**9***

To 1.1 ml (2.6 mmol) of a 2.4 M solution of $(COCl)_2$ in dry CH_2Cl_2, cooled to −78°C, 3.5 ml (3.5 mmol) of a 1 M solution of DMSO in CH_2Cl_2 were added; the reaction mixture was stirred for 15 min at the same temperature, then 1.0 mmol of **7** or **9** was added as a CH_2Cl_2 (10 ml) solution and, after an additional 15 min, 8.0 mmol of *i*-Pr$_2$NEt was added. After stirring overnight at −78°C, a 5% (w/w) aqueous solution of $NH_4H_2PO_4$ and 1 N HCl were added to neutral pH. The usual workup (CH_2Cl_2) afforded the desired aldehyde as an oil.

The same procedure was also applied to monoprotected diol **8**, but the reaction was stirred, after the addition of the amine, for 3 days at −20°C before quenching; aldehyde **14** was isolated as an oil which crystallized on freezing.

*4.14.1. 3-(*t*-Butyldimethylsilyloxy)-2-fluoro-2-phenylpropanal **13***

Quantitative yield; R_f ~0.60 (PE:AcOEt, 8:2) (elongated spot); ^{1}H NMR: 0.05 and 0.06 (2s, 3H each, *Me*$_2$Si), 0.86 (s, 9H, *Me*$_3$C), 3.96 and 4.31 (AB as part of an ABXM system, J_{AB} 11.8, J_{AX} 16.6, J_{BX} 31.0, J_{AM} 1.4, 2H, C*H*$_2$), 7.28–7.49 (m, 5H, *Ph*), 9.81 (dd, *J* 1.4 and 5.6, 1H, *H*–C=O); ^{13}C NMR: −5.57 and −5.52 (*Me*$_2$Si), 18.27 (Me$_3$*C*), 25.70 (*Me*$_3$C), 67.87 (d, *J* 21.4, *C*H$_2$), 100.93 (d, *J* 185.3, *C*F), 124.91 (d, *J* 9.7), 128.68, 128.89, 133.24 (d, *J* 21.4) (*Ph*), 198.60 (d, *J* 43.7, *C*=O); ^{19}F NMR: 89.48–90.18 (m).

*4.14.2. 2-Fluoro-3-(triisopropylsilyloxy)-2-phenylpropanal **14***

Yield: 76%; white crystals, mp 29.5–30°C; R_f ~0.58 (PE:AcOEt, 9:1) (elongated spot); ^{1}H NMR: 1.04–1.27 (m, 21H, 3×C*H*Me_2), 3.99–4.51 (m, 2H, CH_2), 7.16–7.49 (m, 5H, *Ph*), 9.84 (dd, *J* 1.4 and 5.6, 1H, *H*–C=O); ^{13}C NMR: 11.89 (*C*Si), 17.80 (*Me*), 68.56 (d, *J* 21.5, *C*H_2OSi), 100.97 (d, *J* 185.6, *C*–F), 124.92 (d, *J* 14.2), 128.64 (d, *J* 1.7), 128.85, 133.36 (d, *J* 21.7) (Ar*C*), 198.78 (d, *J* 42.4, *C*=O); ^{19}F NMR: 97.57–98.26 (m); GC–MS (temperature was raised at a rate of 10°C/min): R_t=15.4 min, *m/z* (%) 281 (M^+−43, 2), 233 (23), 211 (10), 105 (33), 103 (32), 77 (100).

*4.14.3. 3-(Benzyloxy)-2-fluoro-2-phenylpropanal **15***

Yield: 92%; R_f ~0.46 (PE:AcOEt, 9:1) (elongated spot); ^{1}H NMR: 3.78–4.26 (m, 2H, CH_2CF), 4.60 (s, 2H, CH_2Ph), 7.25–7.43 (m, 10H, 2×*Ph*), 9.80 (dd, *J* 1.4 and 5.3, 1H, *H*C=O); ^{13}C NMR: 73.34 (d, *J* 20.6, *C*H_2CF), 73.95 (*C*H_2Ph), 100.61 (d, *J* 185.12, *C*F), 124.90 (d, *J* 9.3), 127.74, 127.91, 128.47, 128.81, 129.06, 132.99 (d, *J* 22.1), 137.27 (2×*Ph*), 197.65 (d, *J* 42.1, *C*=O).

*4.15. 1-(*t*-Butyldimethylsilyloxy)-2-fluoro-2-phenyl-3-(*p*-toluenesulfonyloxy)propane **16***

To a solution of **7** (1.0 mmol) in dry CH_2Cl_2 (35 ml), cooled to 0°C, Et_3N (6.0 mmol), *p*-toluenesulfonyl chloride (4.4 mmol), and DMAP (2.0 mmol) were sequentially added. After stirring at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and worked up as usual (CH_2Cl_2). Chromatographic purification (PE:AcOEt, 95:5) gave pure **16** (81%) as an oil. R_f=0.42 (PE:AcOEt, 9:1); ^{1}H NMR: −0.04 and −0.02 (2s, 3H each, *Me*$_2$Si), 0.82 (s, 9H, *Me*$_3$C), 2.44 (s, 3H, *Me*Ar), 3.81 and 3.91 (AB as part of an ABX system, J_{AB} 11.1, J_{AX} 19.1, J_{BX} 13.8, 2H, CH_2OSi), 4.37 and 4.48 (AB as part of an ABX system, J_{AB} 10.8, J_{AX} 21.3, J_{BX} 19.1, 2H, CH_2OTs), 7.28–7.32 (m, 7H), 7.68–7.73 (m, 2H) (*ArH*); ^{13}C NMR: −5.64 (*Me*$_2$Si), 18.19 (Me$_3$*C*), 21.68 (*Me*Ar), 25.73 (*Me*$_3$C), 66.06 (d, *J* 29.5), 70.43 (d, *J* 25.6) (*C*H_2OSi, *C*H_2OTs), 96.00 (d, *J* 181.4, *C*F), 125.05 (d, *J* 9.7), 128.07, 128.32 (d, *J* 1.8), 128.44, 129.81, 132.61, 137.10 (d, *J* 21.1), 144.86 (*ArC*); ^{19}F NMR: 93.02–94.00 (m).

*4.16. 1-Benzyloxy-2-fluoro-2-phenylpropane **17***

4.16.1. Tosylation

Monoprotected alcohol **8** was tosylated as described above for the synthesis of **16**. Chromatographic purification (PE:AcOEt, 95:5) afforded pure 1-benzyloxy-2-fluoro-2-phenyl-3-(*p*-toluenesulfonyloxy)propane (95%) as an oil. R_f=0.52 (PE:AcOEt, 8:2); ^{1}H NMR: 2.42 (s, 3H, *Me*Ar), 3.77 and 3.82 (AB as part of an ABX system, J_{AB} 10.8, J_{AX} 18.9, J_{BX} 16.4, 2H, CH_2OBn), 4.37 and 4.47 (AB as part of an ABX system, J_{AB} 10.9, J_{AX} 20.0, J_{BX} 20.0, 2H, CH_2OTs), 4.53 (s, 2H, CH_2Ph), 7.23–7.33 (m, 12H), 7.69 (app d, *J* 8.3, 2H) (*ArH*); ^{13}C NMR: 22.10 (*Me*Ar), 71.27 (d, *J* 26.4), 72.57 (d, *J* 27.2) (*C*H_2OBn and *C*H_2OTs), 74.27 (*C*H_2Ph), 96.20 (d, *J* 180.7, *C*F), 125.48 (d, *J* 9.4), 128.08, 128.29, 128.44, 128.90, 129.03, 130.27, 137.38 (d, *J* 21.4), 137.92, 145.34 (*ArC*); ^{19}F NMR: 90.95–91.94 (m); GC–MS: R_t=9.9 min, *m/z* (%) 279 (M^+−135, 0.06), 223 (4), 205 (3), 149 (100).

4.16.2. Reduction

1-Benzyloxy-2-fluoro-2-phenyl-3-(*p*-toluenesulfonyloxy)propane was dissolved in dry DMSO (1.0 mmol in 8 ml) and $NaBH_4$ (5.0 mmol) was added as a solid. After heating at 150°C for 5 h, the reaction mixture was cooled to room temperature, quenched (saturated aqueous NH_4Cl), and worked up as usual (PE:AcOEt, 1:1). Chromatographic purification (PE:AcOEt, 95:5) afforded pure 1-benzyloxy-2-fluoro-2-phenylpropane **17** (68%, 79% based on unrecovered substrate) as an oil. R_f=0.30 (PE:AcOEt, 95:5);

^{1}H NMR: 1.73 (d, *J* 22.9, 3H, *Me*), 3.64 and 3.71 (AB as part of an ABX system, J_{AB} 11.1, J_{AX} 24.5, J_{BX} 17.7, 2H, CH_2OBn), 4.56 and 4.63 (AB system, J_{AB} 12.2, 2H, CH_2Ph), 7.25–7.38 (m, 10H, 2×*Ph*); ^{13}C NMR: 24.08 (d, *J* 24.6, *Me*), 74.07 and 76.78 (d, *J* 25.3) (*C*H$_2$O*C*H$_2$Ph), 97.59 (d, *J* 173.5, *C*F), 125.04 (d, *J* 9.2), 128.07, 128.68, 128.83, 138.55, 142.32 (d, *J* 21.3) (*ArC*).

4.17. (S)-(+)-2-Fluoro-2-phenyl-1-propanol

A solution of 1.0 mmol of **17** (obtained starting from levorotatory **5a**) in 96% MeOH (30 ml) was hydrogenated at room temperature and ambient pressure in the presence of a small amount of $CaCO_3$ and 10% Pd/C. After 7 h, the solid residue was filtered off and the solvent evaporated to give dextrorotatory 2-fluoro-2-phenyl-1-propanol[7b] (50%).

*4.18. Synthesis and reduction of ethyl 2-fluoro-2-phenyl-3-(*p*-toluenesulfonyloxy)propanoate*

4.18.1. Tosylation

Hydroxy ester **10a** was tosylated as described above for the synthesis of **16**. Chromatographic purification (PE:AcOEt, 9:1 → 8:2) afforded ethyl 2-fluoro-2-phenyl-3-(*p*-toluenesulfonyloxy)propanoate (71%) as an oil: R_f=0.44 (PE:AcOEt, 8:2); ^{1}H NMR: 1.27 (t, *J* 7.1, 3H, *Me*CH$_2$), 2.45 (s, 3H, *Me*Ar), 4.25 (q, *J* 7.1, 2H, CH_2Me), 4.36 and 4.72 (AB as part of an ABX system, J_{AB} 11.1, J_{AX} 15.8, J_{BX} 27.9, 2H, CH_2OTs), 7.31–7.47 (m, 7H), 7.75 (app d, *J* 8.3, 2H) (*ArH*); ^{13}C NMR: 13.93 (*Me*CH$_2$), 21.67 (*Me*Ar), 62.75, 71.61 (d, *J* 21.7) (*C*H$_2$OTs, *C*H$_2$Me), 94.44 (d, *J* 196.1, *C*F), 124.65 (d, *J* 8.9), 128.00, 128.79 (d, *J* 1.8), 129.55, 129.86, 132.49, 133.26 (d, *J* 21.5), 145.11 (*ArC*), 167.09 (d, *J* 26.3, *C*=O).

4.18.2. Reduction

Applying to ethyl 2-fluoro-2-phenyl-3-(*p*-toluenesulfonyloxy)propanoate the same reduction conditions described above for the synthesis of **7** from **11a**, 2-fluoro-2-phenyl-3-(*p*-toluenesulfonyloxy)-1-propanol (78%) was obtained as a white solid after chromatographic purification (PE:AcOEt, 8:2 → 1:1). R_f=0.17 (PE:AcOEt, 8:2); ^{1}H NMR: 2.01 (bt, *J* 7.0, 1H, O*H*; disappeared after exchanging with D_2O), 2.45 (s, 3H, *Me*), 3.97 [app dd, *J* 6.0 and 18.8, 2H, CH_2OH; after exchanging with D_2O: 3.95 (d, *J* 18.7)], 4.27–4.55 (m, 2H, CH_2OTs), 7.27–7.34 (m, 7H), 7.72 (app d, *J* 8.3, 2H) (*ArH*); ^{13}C NMR: 21.68 (*Me*), 65.14 (d, *J* 26.0), 70.48 (d, *J* 27.0) (*C*H$_2$OTs, *C*H$_2$OH), 96.52 (d, *J* 179.3, *C*F), 124.90 (d, *J* 9.4), 127.97, 128.63, 128.72, 129.00, 132.55, 136.30 (d, *J* 20.9), 145.13 (*ArC*).

*4.19. Diastereoisomeric amides from monoesters **5a**,**c**–**d***

The two diastereoisomeric amides were synthesized, according to the procedure reported in the literature,[8b] using either (*R*)- or (*S*)-α-methylbenzylamine. Some selected analytical data for each diastereoisomer are reported here. Retention times (R_t) refers to GC (P=150 kg/cm^2, $T_{injector}$=250°C, $T_{detector}$=300°C, T_{oven}=210°C) on chiral column (see Section 4.1).

*4.19.1. Amides from **5a** [(S)-enantiomer, from entry 1 of Table 1]*

PE:AcOEt, 97:3 → 9:1 (for chromatographic purification), 8:2 (for TLC); diastereoisomer A [from (*S*)-amine]: R_f=0.41; ^{1}H NMR: 1.25 (d, *J* 7.0, *Me*CH; s, irradiating at 5.14 ppm); ^{19}F NMR: 80.70 (s); R_t=17.7 min; diastereoisomer B [from (*R*)-amine]: R_f=0.46; ^{1}H NMR: 1.30 (d, *J* 7.0, *Me*CH; s, irradiating at 5.14 ppm); ^{19}F NMR: 70.08 (s); R_t=16.8 min.

*4.19.2. Amides from **5c***

PE:AcOEt, 95:5 → 8:2 (for chromatographic purification), 7:3 (for TLC); diastereoisomer A: R_f=0.32; ^{1}H NMR: 1.25 (t, *J* 7.1, *Me*CH_2; s, irradiating at 4.30 ppm), 4.39* (s, CH_2Me, irradiating at 1.28 ppm), 7.59–7.62 (m, *ArH*); R_t=18.0 min; diastereoisomer B: R_f=0.37; ^{1}H NMR: 1.32 (t, *J* 7.1, *Me*CH_2; s, irradiating at 4.30 ppm), 4.44* (s, CH_2Me, irradiating at 1.28 ppm), 7.50–7.53 (m, *ArH*); R_t=17.6 min.

*4.19.3. Amides from **5d***

PE:AcOEt, 9:1 → 8:2 (for chromatographic purification), 7:3 (for TLC); diastereoisomer A: R_f=0.33; ^{1}H NMR: 3.43 (d, *J* 1.3, *Me*O); diastereoisomer B: R_f=0.39; ^{1}H NMR: 3.48 (d, *J* 1.5, *Me*O).

*4.19.4. Amides from **5e***

PE:AcOEt, 9:1 → 8:2 (for chromatographic purification), 7:3 (for TLC); diastereoisomer A: R_f=0.29; ^{1}H NMR: 3.52 (d, *J* 1.4, *Me*OCF), 3.86 (s, *Me*OCO); diastereoisomer B: R_f=0.24; ^{1}H NMR: 3.55 (d, *J* 1.4, *Me*OCF), 3.88 (s, *Me*OCO).

*4.20. Diastereoisomeric Mosher's esters from monoacetates **6a**,**b** and from monoprotected diol **7***

The two diastereoisomeric Mosher's esters were always synthesized,[28] using either (*R*)- or (*S*)-MTPA-Cl. Some selected analytical data for each diastereoisomer are reported here.

*4.20.1. Esters from **6a** [(*S*)-enantiomer, from entry 1 of Table 2]*

Chromatographic purification: PE:AcOEt, 9:1; diastereoisomer A [from (*R*)-chloride]: ^{1}H NMR: 2.04 (s, *Me*CO), 3.38 (app bd, *J* 1.0, *Me*O); diastereoisomer B [from (*S*)-chloride]: ^{1}H NMR: 2.06 (s, *Me*CO), 3.40 (app bd, *J* 1.1, *Me*O).

*4.20.2. Esters from **6b***

Chromatographic purification: PE:AcOEt, 9:1; diastereoisomer A: ^{1}H NMR: 2.04 (s, *Me*CO), 3.37 (app bd, *J* 1.2, *Me*O); diastereoisomer B: ^{1}H NMR: 2.06 (s, *Me*CO), 3.39 (app bd, *J* 1.1, *Me*O).

*4.20.3. Esters from **7***

Chromatographic purification: PE:AcOEt, 95:5; diastereoisomer A: ^{1}H NMR: 3.40 (app bd, *J* 0.9, *Me*O); diastereoisomer B: ^{1}H NMR: 3.37 (app bd, *J* 1.0, *Me*O).

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