Stereoselective Synthesis of γ-Fluorinated α-Amino Acids Using 2-Hydroxy-3-pinanone as an Auxiliary

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(+)-(*S*)-2-Amino-4-fluorobutanoic acid (**5a**) (> 96% *ee*), its α-methylated derivative (+)-(*S*)-**5b** (85% *ee*), and (–)-(*S*)-2-amino-4-fluoro-4-pentenoic acid (**10**) (81% *ee*) were synthesized by diastereoselective alkylation in the presence of LDA at low temperatures. Alkylation of (+)-(*R*,*R*,*R*)-2-hydroxy-3-pinanone based imines of glycine *tert*-butyl ester **1a** or alanine isopropyl ester **1b** with 1-bromo-2-fluoroethane (**2**) or 3-bromo-2-fluoropropene (**7**), respectively, followed by stepwise deprotection was used. The selectivity of the alkylation increased by lithium/magnesium exchange or for **1b** also by addition of DMPU. Differences in the reactivity of enolate alkylations of enantiomerically pure or racemic Schiff base **1a** with **2** or **7**, respectively, can be explained by the formation of structurally different aggregates of the enolates in solution, caused by diastereomeric interactions between enantiomers in the transition state of alkylation.

Introduction

During the past decades, biologically active fluorinated compounds gained considerable attention.[1] These compounds are particularly important as enzyme inhibitors, substrate analogues, anti-metabolites, transition-state analogues, and suicide substrates. Thus, the enantiocontrolled synthesis of fluoroorganic compounds developed quite extensively.[2] There are various reason for this interest: Among these, the similar size of a hydrogen atom, or to some extent of a hydroxy group, and the fluorine atom is most important.[3] Due to its extreme electronegativity, the latter substituent can act as a hydrogen-bond acceptor,[3,4] and moreover can strongly influence the acidity of neighboring groups and the polarity of substrates.[5] In addition, the solubility of compounds is affected. Furthermore, applying the fluorine atom as a probe, the determination of the conformation and the stereochemistry of receptor interaction become more effective with the opportunity to use ^{19}F NMR spectroscopy.

Particular attention has been paid to fluorinated amino acids and derived peptides, because of the enormous variety of their biological activities.[6] Among these compounds only a limited number of γ-fluoro α-amino acids have been synthesized so far.[7] Most of them were prepared by substitution of a γ-hydroxy group or a γ-halogen atom by a fluorine atom in the corresponding amino acids, or by amination of γ-fluorinated α-halocarboxylic acids.[8,9] We became interested in the application of easily accessible fluorinated building blocks such as 1-bromo-2-fluoroalkanes[10] or 3-bromo-2-fluoropropene (**7**)[11] to the α-alkylation of amino acid derivatives to obtain γ-fluoro α-amino acids.[12,13] Using a Schiff base of (+)-(*R*)-camphor and glycine esters for diastereoselective synthesis of γ-fluoro α-amino acids, moderate to good diastereomeric excesses have been achieved.[14,15]

Results and Discussion

This paper reports the results of our efforts on diastereoselective alkylation of Schiff bases **1a** and **1b** derived from (+)-(*R*,*R*,*R*)-2-hydroxy-3-pinanone and glycine *tert*-butyl ester or alanine isopropyl ester, respectively, with 1-bromo-2-fluoroethane (**2**) or 3-bromo-2-fluoropropene (**7**) to yield γ-fluorinated α-amino acids or the corresponding α-methylated analogues.

The aforementioned enantiopure auxiliary was first used by Yamada et al.[16] for asymmetric amino acid syntheses by alkylations of glycine *tert*-butyl ester. Subsequently, many other groups used this attractive auxiliary because it can easily be obtained in both enantiomeric forms from the inexpensive (+)- or (−)-α-pinenes, either by direct oxidation with potassium permanganate[17] or in two steps by *cis*-hydroxylation with osmium(VIII) oxide and subsequent Swern-type oxidation.[18] The Schiff bases of glycine or alanine esters are available in good yields by heating in benzene under reflux, in the presence of boron trifluoride−diethyl ether using a Dean−Stark trap.[19,20a] When benzene is replaced by the noncarcinogenic toluene, the pressure should be reduced to 250 mbar in order to run the reaction at lower temperature and to avoid partial decomposition of the product. The aforementioned auxiliary has been applied earlier for syntheses of other amino acids,[21−23] α,α-disubstituted α-amino acids,[20,21] α-aminophosphonic acids,[24] and optically active amines.[25]

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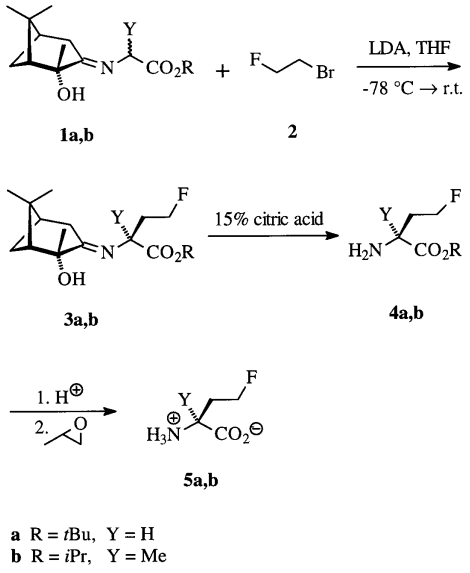
Alkylation of the Schiff base **1a**, derived from (+)-(*R*,*R*,*R*)-2-hydroxy-3-pinanone, with 1-bromo-2-fluoroethane (**2**) after deprotonation with LDA succeeded with a diastereoselectivity of 90% (Scheme 1, Table 1). Chromatography of the crude product afforded the alkylated imine **3a** with > 98% *ds* and 37% chemical yield. The ratio of diastereomers can easily be determined by ^{19}F NMR spectroscopy (δ = −221.0 for the minor diastereomer, δ = −222.7 for the major diastereomer).



1a,b **2** **3a,b** **4a,b** **5a,b**

a R = *t*Bu, Y = H
b R = *i*Pr, Y = Me

Scheme 1

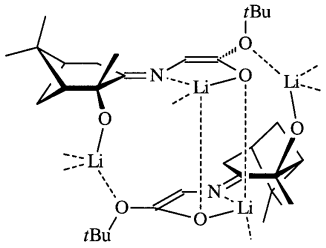
Table 1. Alkylations of ester imines **1** in the presence of 3 equiv. of DMPU, hydrolyses of the alkylation products **3** to the esters **4** and the carboxylic acids **5**

	R	Y		Yield	*ds*[a]		Yield	*ee*		Yield	*ee*[c]
1a	*t*Bu	H	**3a**	37	> 98	**4a**	48	> 96	**5a**	79	> 96
1b	*i*Pr	CH_3	**3b**	n. i.[d]	88	**4b**	13[e]	76	**5b**	24	85

[a] Determined by ^{19}F NMR spectroscopy. − [b] Determined by ^{19}F NMR spectroscopy in the presence of Eu(hfc)$_3$. − [c] Determined by ^{19}F NMR spectroscopy after derivatization with (+)-(*S*)-2-chloropropionic acid (see ref.[26]). − [d] Not isolated. − [e] Overall yield, two steps.

Deprotection of **3a** was achieved in two steps. The *tert*-butyl ester **4a** was prepared in 48% yield by hydrolysis of the imine bond with 15% citric acid. Finally, (*S*)-(+)-2-amino-4-fluorobutanoic acid (**5a**) was obtained by hydrolysis of the ester function with refluxing 6 N hydrochloric acid and subsequent treatment of the crude hydrochloride with propene oxide in ethanol. The optical purity of the acid was determined by ^{19}F NMR spectroscopy of the amide derived from **5a** and (+)-(*S*)-2-chloropropionic acid.[26] The absolute configuration of the amino acid was determined to be (*S*) by comparison of the optical rotation with that of the (+)-(*R*) enantiomer.[14]

Earlier, Soladié-Cavallo et al. reported (*S*) selectivity for other alkylation reactions using (+)-(*R*,*R*,*R*)-2-hydroxy-3-pinanone as the auxiliary, and explained this unexpected result by formation of a dimeric enolate structure **6**[27] (Figure 1). Enolates forming dimers and even higher aggregates are already well described in literature.[28]



6

Figure 1. Enantiopure dimer **6** of the enolate of **1a**, see ref.[27]

The counter ion of the enolate of **1a** has a strong influence on the selectivity of the reaction. In order to improve the selectivity of the alkylation step, transmetallations with magnesium, zinc, and potassium salts were done (Table 2). The best diastereoselectivity was achieved with magnesium as counter ion, although the chemical yield decreased. Magnesium has a strong coordinating ability to reinforce the formation of dimers, and thus to increase the diastereoselectivity.[21a,27]

As mentioned above, Schiff bases of alanine esters and 2-hydroxy-3-pinanone have already been used successfully for the preparation of α-methylated α-amino acids.[20] However, the alkylation of **1b** with 1-bromo-2-fluoroethane (**2**) to form **3b** succeeded only with rather low yield (37%, GC) and poor diastereoselectivity (68:32). In addition to the formation of **3b**, side reactions occurred. Also, in this case, transmetallation with magnesium bromide (2.0 equiv.) enhanced the diastereoselectivity up to 88%, while the chemical yield dropped again (Table 3). The fact that 0.5 equivalent of magnesium salt was sufficient, and larger amount did not increase the selectivity significantly, again indicates that the enolate is not monomeric. On the other hand, addi-

Table 2. Transmetallation experiments for alkylation of **1a**

Entry	Counter ion	Base (2 equiv.)	Metal salt	**3a** (%, GC)	*ds*[a]
1	Li^+	LDA	−	74	90
2	Mg^{2+}	LDA	$MgCl_2$ (0.5 equiv.)	69	77
3	Mg^{2+}	LDA	$MgCl_2$ (1.0 equiv.)	64	> 98
4	Mg^{2+}	LDA	$MgCl_2$ (2.0 equiv.)	52	> 98
5	Mg^{2+}	LDA	$MgBr_2$ (2.0 equiv.)	54	> 98
6	Zn^{2+}	LDA	$ZnCl_2$ (0.5 equiv.)	16	85
7	K^+	KO*t*Bu	−	17	58[b]

[a] Determined by ^{19}F NMR spectroscopy. − [b] (+)-(*R*)-**3a** is the main product.

Table 3. Transmetallation experiments for alkylation of **1b**

Entry	DMPU	$MgBr_2OEt_2$	**3b** (%, GC)	*ds*[a]
1	–	–	37	68
2	–	0.5 equiv.	26	86
3	–	1.0 equiv.	26	84
4	–	2.0 equiv.	25	88
5	3 equiv.	–	58	89
6	3 equiv.	0.5 equiv.	28	84
7	3 equiv.	1.0 equiv.	28	87

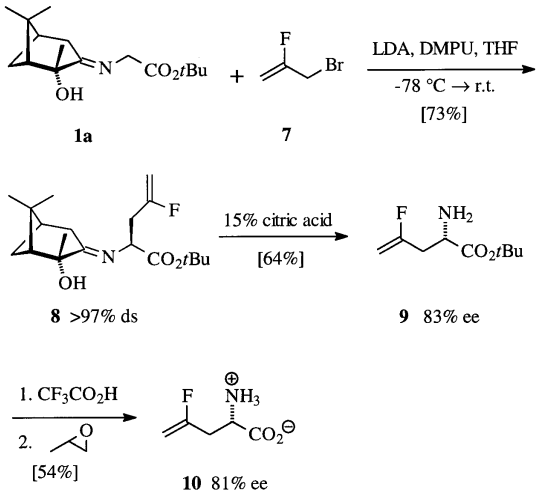
[a] Determined by ^{19}F NMR spectroscopy.

tion of *N*,*N*′-dimethylpropylene urea (DMPU)[29] to the reaction mixture improved both the yield of **3b** (58%, GC) and the diastereoselectivity (89%). In contrast, DMPU has no effect on the alkylation of **1a**. Addition of magnesium bromide to the reaction mixture containing DMPU had no effect on the selectivity, but decreased the chemical yield.

Surprisingly, alkylation of **1b** is more effective than alkylation of the Schiff base derived from *p*-chlorobenzaldehyde and alanine *tert*-butyl ester, which under the same condition gave only poor yields. Moreover, elimination of HBr from 1-bromo-2-fluoroalkanes was observed.[13]

Unfortunately, the imine **3b** decomposed partially during chromatography on silica gel. Thus, the crude product **3b** was directly hydrolyzed with 15% citric acid and the analytically pure isopropyl ester **4b** was obtained in 13% overall yield. After treatment of **4b** with hydrochloric acid and subsequently with propene oxide in ethanol, crystalline (+)-(*S*)-2-amino-4-fluoro-2-methylbutanoic acid (**5b**) was obtained in 24% yield and with 85% enantiomeric excess. The configuration of **5b** should be (*S*) in analogy to the configuration of **5a** and with regard to analogous reactions.[20] The enhancement of the optical purity is due to partial resolution during crystallization.

Recently, we reported 3-bromo-2-fluoropropene (**7**) as a good alkylating reagent for glycine ester enolates.[13] The alkylation of **1a** with the fluorinated allylic bromide **7** at −78 °C occurred with 73% chemical yield and high diastereoselectivity (> 97%) (Scheme 2). During hydrolysis of the



Scheme 2

protecting imino group with aqueous citric acid partial racemization occurred and the ester **9** was isolated with 83% *ee*. The free (−)-(*S*)-2-amino-4-fluoropent-4-enoic acid (**10**) was obtained by hydrolysis of the ester function with trifluoroacetic acid and subsequent treatment of the crude product with propene oxide in ethanol. The absolute configuration of the amino acid was determined to be (*S*) by comparison of the optical rotation to that of the (+)-(*R*)-2-amino-4-fluoropent-4-enoic acid synthesized with (*R*)-camphor as the auxiliary.[15] This corresponds to the above-mentioned results with the saturated amino acid **5a**.

Based on computational studies, Matsumoto et al. doubted whether dimeric structures such as **6** suggested by Soladié-Cavallo et al.[20] are formed in solution (Figure 1).[30] Taking a closer look at **6**, it becomes obvious that there should be a strong steric interaction between the two molecules. Particularly after alkylation of one half of the dimeric enolate, the attracting interactions between the two parts of the complex become weaker as the α-proton of the alkylated molecule is directed towards the other half of the complex. This should strongly decrease the stability of the dimer.

In the C_i-symmetric dimer **11** (Figure 2), which is formed from two enantiomeric monomers, steric interactions should be weaker as the two molecules are located *side-on* to each other. Hence, the *meso* dimer **11** should be favored over the homochiral dimer **6**. Also, after alkylation of one part of the dimer **11**, the α-hydrogen atom is not directed towards the other hydroxypinanone molecule, but into the free space. In solutions of a deprotonated racemic mixture of **1a** the formation of the C_i-symmetric **11** may be favored over the formation of the C_2-symmetric **6** and its enantiomer. Assuming the formation of such different dimers the reactivity and selectivity of (*R*,*R*,*R*)- and (*rac*)-**1a** should be different.

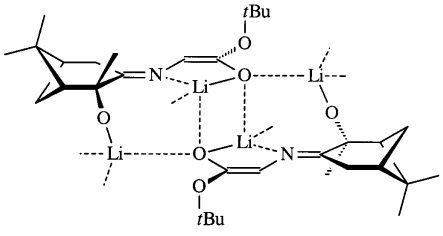
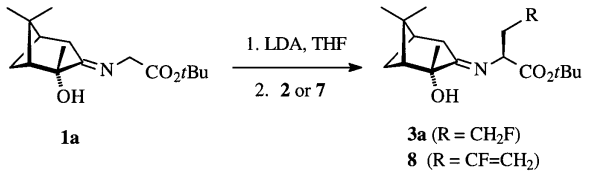


Figure 2. *meso*-Dimer **11** of the enolate of **1a**

The experiments proved that the alkylation of (*rac*)-**1a** with 1-bromo-2-fluoroethane (**2**) and 3-bromo-2-fluoropropene (**7**) succeeded with significantly higher chemical yield compared to the reaction with (+)-(*R*,*R*,*R*)-**1a** under the same conditions (Scheme 3, Table 4). The diastereoselectivity of the alkylation of (*R*,*R*,*R*)-**1a** or (*rac*)-**1a** is equal with **7** and almost equal with **2** (90% or 93%, respectively). The differences in yield should be due to different diastereomeric interactions between the enantiomers in the intermediary structures. Thus, aggregation of the enolates during the reactions is obvious. Such aggregations of intermediates



Scheme 3

Table 4. Alkylations of enantiopure and racemic **1a**

Starting material	R	Yield (%)	*ds*[a]
(*R*,*R*,*R*)-**1a**	CH_2F	37	90
(*rac*)-**1a**		67	93
(*R*,*R*,*R*)-**1a**	$H_2C{=}CF$	73	> 97
(*rac*)-**1a**		91	> 97

[a] Determined by ^{19}F NMR spectroscopy.

have already been suggested as an explanation of nonlinear stereochemical effects in asymmetric catalysis.[31,32] Moreover, for 2-hydroxy-3-pinanone itself, the value of optical rotation does not correlate linearly with the optical purity. This effect was explained by solute/solute interactions.[33]

Furthermore, the racemic ester imine **1a** and its alkylation products **3a** and **8** are crystalline solids [m.p.: (*rac*)-**1a**: 102−104 °C; (*rac*)-**3a**: 65−66 °C; (*rac*)-**8**: 40−44 °C], while the enantiopure compounds are oils at room temperature. All attempts to crystallize these compounds failed. X-ray analyses of single crystals of the racemic compounds show C_i-symmetric dimers, which are connected by two hydrogen bonds [2.12 Å (161°) in **1a**, 2.14 Å (158°) in **3a**, and 2.34 Å (160°) in **8**] (Figures 3−5).

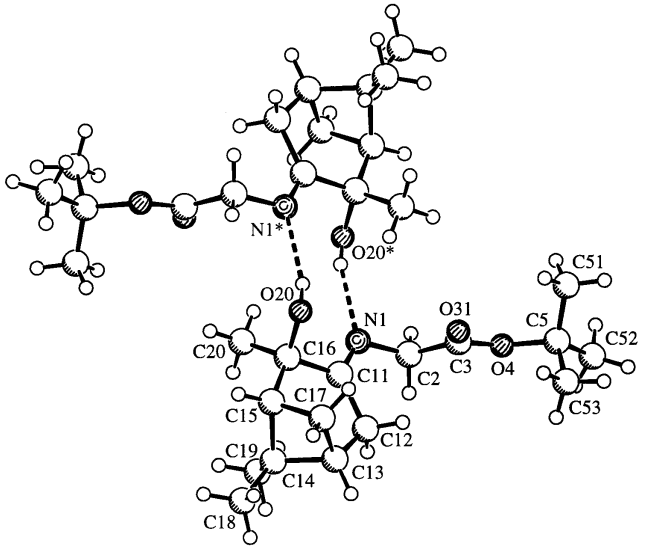


Figure 3. X-ray structure of racemic **1a**

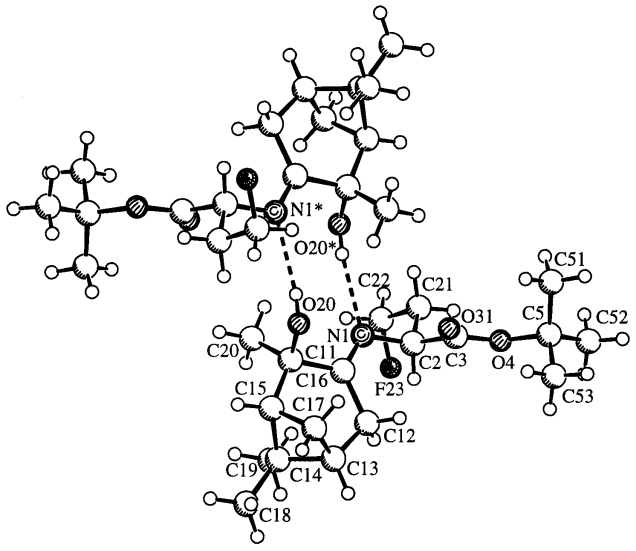


Figure 4. X-ray structure of racemic **3a**

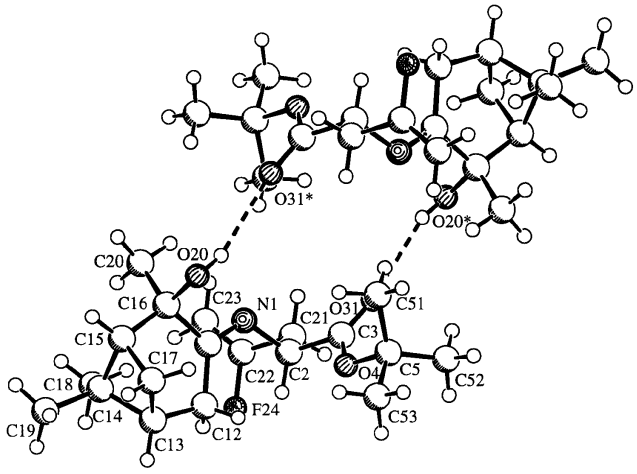


Figure 5. X-ray structure of racemic **8**

Conclusion

(+)-(*R*,*R*,*R*)-2-Hydroxy-3-pinanone has been used as an auxiliary for the enantioselective synthesis of three γ-fluorinated α-amino acids. (+)-(*S*)-2-Amino-4-fluorobutanoic acid (**5a**) of > 96% enantiomeric purity was synthesized in 3 steps and 14% overall yield using 1-bromo-2-fluoroethane (**2**) as fluorinated building block. The α-methylated analogue **5b** was isolated with 85% *ee* and 3% overall yield. 3-Bromo-2-fluoropropene (**7**) has been shown to be a very reactive and selective alkylation reagent (> 95% *ee*). However, during hydrolysis of the alkylated product **8** (> 97% *ds*) partial racemization occurred and the (−)-(*S*)-2-amino-4-fluoropent-4-enic acid (**10**) was obtained with 25% overall yield and 81% enantiomeric purity. Alkylation of the Schiff base **1a** with 1-bromo-2-fluoroethane (**2**) and 3-bromo-2-fluoropropene (**7**) succeed with different yields for the racemic and enantiomerically pure compound **1a**. In order to explain this result the formation of aggregates of intermedi-

ary enolates in solution and diastereomeric interactions of the enantiomers are suggested.

Experimental Section

General Remarks: All air- and moisture-sensitive reactions were performed under argon in flame-dried flasks using standard Schlenk techniques. 1-Bromo-2-fluoroethane (**2**) was a gift from Bayer AG, Leverkusen. All other starting materials were obtained from Acros, Merck or Fluka. Diisopropylamine and DMPU were dried over molecular sieves (4 Å) and THF was distilled from sodium/benzophenone before use. (*R*,*R*,*R*)-*tert*-Butyl [(2-hydroxypinan-3-ylene)amino]acetate (**1a**)[19] and 3-bromo-2-fluoropropene (**7**)[11] were prepared according to literature procedures. − Melting and boiling points are uncorrected. − ^{1}H (300 MHz), ^{13}C (75.5 MHz), and ^{19}F NMR (282.3 MHz): Bruker WM 300. As internal standards TMS was used for ^{1}H, $CDCl_3$ for ^{13}C and $CFCl_3$ for ^{19}F NMR spectroscopy. If not stated otherwise, $CDCl_3$ was used as solvent. The multiplicity of the ^{13}C NMR signals concerning the $^{13}C^1H$ coupling was determined by the DEPT method. Atoms marked with an asterisk belong to the pinene skeleton. − Mass spectra (70 eV): GC/MS coupling: Varian GC 3400/MAT 8230 and data system SS 300 of Finnigan MAT and Varian GC 3400/Varion Saturn IT (Ion Trap) and data system. − Elemental analysis: Mikroanalytisches Laboratorium, OC, Universität Münster. − X-ray data sets were collected with an Enraf−Nonius CAD4 diffractometer. Programs used: Data reduction Mo1EN, structure solution SHELXS-86, structure refinement SHELXL-97, graphics SCHAKAL-92.

***tert*-Butyl (1*R*,2*R*,5*R*,2′*S*)-4′-Fluoro-2′-[(2-hydroxypinan-3-ylene)-amino]butanoate (3a):** A solution of lithium diisopropylamide was prepared by addition of 12.5 mL (20.0 mmol) of *n*-butyllithium (1.6 N in hexane) to a solution of 2.8 mL (20.0 mmol) of diisopropylamine in 20 mL of THF under argon at −78 °C. The cooling bath was removed and the mixture was stirred for 15 min. Then, 2.81 g (10.0 mmol) of Schiff base **1a** in 10 mL of THF was added to the LDA solution at −78 °C. After 90 min 1.27 g (10.0 mmol) 1-bromo-2-fluoroethane (**2**), dissolved in 10 mL of THF, was added at −78 °C. The resulting mixture was stirred for 2 h at this temperature and warmed up to room temperature within ca. 12 h. Now the reaction mixture was quenched with 25 mL of brine, the organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed with water, dried with magnesium sulfate and evaporated in vacuo. The crude product had a *ds* of 90% (^{19}F NMR). The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate, 1:1). Yield: 1.28 g (37%), > 98% *ds* (^{19}F NMR). − ^{1}H NMR: δ = 0.81 (s, 3 H, CH_3*), 1.29 (s, 3 H, CH_3*), 1.41 [s, 9 H, $C(CH_3)_3$], 1.44 (s, 3 H, CH_3*), 1.54 (d, 1 H, $^2J_{HH}$ = 10.5 Hz, CH*H**), 1.94−2.65 (m, 8 H, 5 × CH*, CH_2CH$_2$F, −OH), 4.28 (dd, 1 H, $^3J_{HH}$ = 4.3 Hz, $^3J_{HH}$ = 9.3 Hz, CHN), 4.18−4.64 (m, 2 H, CH_2F). − ^{13}C NMR: δ = 22.8 (q, CH_3*), 27.3 (q, CH_3*), 28 (q, CH_3*), 28.2 [q, C(CH_3)$_3$], 28.1 and 33.2 (t, C*), 38.3 and 50.1 (d, C*), 33.4 (dt, $^2J_{CF}$ = 17.8 Hz, CH_2CH_2F), 58.5 (s, C*), 58.5 (d, COH), 76.5 (s, CHN), 80.8 (dt, $^1J_{CF}$ = 162.8 Hz, CH_2F), 81.5 [s, $C(CH_3)_3$], 170.1 (s, C=N), 179.7 (s, COO). − ^{19}F NMR: δ = −221.0 [ddt, $^2J_{HF}$ = 47.3 Hz, $^3J_{HF}$ = 35.8 Hz, $^3J_{HF}$ = 20.7 Hz, 4′-F(2′*R*)], −222.7 [ddt, $^2J_{HF}$ = 47.3 Hz, $^3J_{HF}$ = 35.6 Hz, $^3J_{HF}$ = 17.8 Hz, 4′-F(2′*S*)]. − GC/MS; *m*/*z* (%): 328 (11) [M^+ + 1], 271 (11) [M^+ − C_4H_8, McLaff], 228 (24) [256 − C_2H_4], 226 (18) [M^+ − $CO_2C(CH_3)_3$], 166 (13) [$C_{10}H_{16}NO^+$], 57 (100). − $C_{18}H_{30}O_3NF$ (237.4): calcd. C 66.03, H 9.24, N 4.28; found C 65.49, H 9.00, N 4.22.

***tert*-Butyl (+)-(*S*)-2-Amino-4-fluorobutanoate (4a):** 1.00 g (3.06 mmol) of alkylated Schiff base **3a** was dissolved at 0 °C in 14 mL of THF and 12 mL of 15% aq. citric acid and stirred for 72 h at room temperature. THF was evaporated in vacuo and the aqueous phase was extracted with toluene (3 × 40 mL), neutralized with solid Na_2CO_3 and extracted with diethyl ether (5 × 20 mL). The combined ethereal layers were dried with $MgSO_4$. Removal of the solvent under reduced pressure gave a crude product, which was purified by bulb-to-bulb distillation. Yield: 261 mg (48%), > 96% *ee* [^{19}F NMR, 50 mol-% Eu(hfc)$_3$]. − $[\alpha]_D^{20}$ = +3.8 (*c* = 0.72, $CHCl_3$), b.p. 89−90 °C/18 Torr. − The spectroscopic data agree with published values for the racemic compound.[11]

(+)-(*S*)-2-Amino-4-fluorobutanoic Acid (5a): A solution of 272 mg (1.54 mmol) ester **4a** in 10 mL of 6 N hydrochloric acid was heated under reflux for 6 h. The solvent was evaporated in vacuo and the residual crude amino acid hydrochloride dried over phosphorus pentoxide. The hydrochloride was dissolved in 7 mL of dry ethanol, 4−5 mL of propene oxide was added and the mixture was heated under reflux for 15 to 20 min. The precipitated product was isolated by suction and dried over phosphorus pentoxide. Yield: 146 mg (79%), > 96% *ee* [^{19}F NMR after derivatization with (*S*)-2-chloropropionic chloride]. − $[\alpha]_D^{20}$ = +10.7 (*c* = 0.79, 1 N HCl), m.p. 168 °C (dec.). − The spectroscopic data agree with published values for the racemic compound.[11]

Isopropyl (1*R*,2*R*,5*R*)-2′-[(2-Hydroxypinan-3-ylene)amino]propanoate (1b): A mixture of 7.95 g (60.0 mmol) alanine isopropyl ester and 6.15 g (36.6 mmol) of (*R*,*R*,*R*)-(+)-2-hydroxy-3-pinanone, 50 mL of toluene, and 1.5 mL of boron trifluoride−diethyl ether was heated under reflux for 3−4 h at a pressure of 210 mbar with a Dean−Stark trap. After evaporation of the solvent in vacuo, the crude product was purified by chromatography (cyclohexane/diethyl ether, 2:1, silica gel pretreated with 5% Et_3N in cyclohexane/diethyl ether). Yield: 8.77 g (86%). − **Mixture of Diastereomers:** ^{1}H NMR: δ = 0.8 (s, 3 H, CH_3*), 1.12 [d, 6 H, $^3J_{HH}$ = 6.2 Hz, CH(CH_3)$_2$], 1.23 (s, 3 H, CH_3*), 1.32 (d, 3 H, $^3J_{HH}$ = 6.7 Hz, CHNCH_3), 1.39 (s, 3 H, CH_3*), 1.45 (d, 1 H, $^2J_{HH}$ = 10.6 Hz, CH*H**), 1.95 (m, 2 H, 2 × CH*), 2.23 (ddt, 1 H, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 2.2 Hz, C*H*H*), 2.47 (m, 2 H, CH_2*), 2.75 (s, 1 H, OH), 4.15 (q, 1 H, $^3J_{HH}$ = 6.7 Hz, CHN), 4.92 [sept, 1 H, $^3J_{HH}$ = 6.2 Hz, C*H*(CH$_3$)$_2$]. − ^{13}C NMR: δ = 18.1 (q, CH_3), 21.6 [q, CH(*C*H$_3$)$_2$], 22.8 (q, CH_3*), 27.9 (t, CH_2*), 27.2/28.2 (q, CH_3*), 32.7/33.0 (t, CH_2*), 38.2/38.3 (d, CH*), 38.4 (s, C*), 50.1 (d, CH*), 57.4/57.6 (d, CHN), 68.0 [d, *C*H(CH$_3$)$_2$], 76.3/76.4 (s, COH), 171.5/171.7 (s, C=N), 177.1 (s, COO). − GC/MS; *m*/*z* (%) = 281 (2.8) [M^+], 266 (4) [M^+ − CH_3], 263 (4) [M^+ − H_2O], 238 (24) [M^+ − C_3H_7], 194 (34) [M^+ − $CO_2C_3H_7$], 114 (72) [$C_5H_8NO_2^+$], 113 (100) [$C_5H_7NO_2^+$]. − $C_{16}H_{27}NO_3$ (281.4): calcd. C 68.28, H 9.68, N 4.98; found C 68.48, H 9.77, N 5.03.

Isopropyl (+)-(*S*)-2-Amino-4-fluoro-2-methylbutanoate (4b): A lithium diisopropylamide solution was prepared by adding 10.0 mL (16.0 mmol) of *n*-butyllithium (1.6 N in hexane) to a solution of 2.2 mL (16.0 mmol) of diisopropylamine in 20 mL of THF under argon at −78 °C. The cooling bath was removed and the mixture was stirred for 15 min. Then 2.7 mL (21.5 mmol) of DMPU and 2.10 g (7.5 mmol) of Schiff base **1b** in 17 mL of THF were added to the LDA solution at −78 °C and stirred for 1 h. Next, 1.08 g (8.5 mmol) 1-bromo-2-fluoroethane (**2**) was added and the solution was stirred at this temperature for 2 h. Stirring was continued for about 12 h while the solution warmed up to room temp. Workup

was done analogously to that of *tert*-butyl (1*R*,2*R*,5*R*,2′*S*)-4′-fluoro-2′-[(2-hydroxypinan-3-ylene)amino]butanoate (**3a**). The crude product showed 88% *ds* [^{19}F NMR: δ = −217.9 (2′*S*); δ = −218.2 (2′*R*)]. Hydrolysis of the imine bond was performed analogously to *tert*-butyl (+)-(*S*)-2-amino-4-fluorobutanoate (**4a**). Final purification was achieved by MPLC (diethyl ether/methanol, 19:1, Li Chroprep Si60). Yield: 169 mg (13%), 76% *ee* [^{19}F NMR, 80 mol-% Eu(hfc)$_3$]. − $[\alpha]_D^{20}$ = +1.4 (*c* = 2.56, CH_2Cl_2), b.p. 50 °C/15 Torr. − ^{1}H NMR: δ = 1.23 [d, 6 H, $^3J_{HH}$ = 6.2 Hz, CH(C*H*$_3$)$_2$], 1.34 (s, 3 H, CH_3), 1.71 (s, 2 H, NH_2), 2.26−1.90 (m, 2 H, CH_2), 4.57 (ddd, 2 H, $^2J_{HF}$ = 47.2 Hz, $^3J_{HH}$ = 6.0 Hz, $^3J_{HH}$ = 5.7 Hz, CH_2F), 5.03 [sept, 1 H, $^2J_{HH}$ = 6.2 Hz, C*H*(CH$_3$)$_2$]. − ^{13}C NMR: δ = 21.6 [q, C(*C*H$_3$)$_2$], 26.8 (q, CH_3), 40.5 (dt, $^2J_{CF}$ = 17.8 Hz, CH_2), 56.0 (s, *C*NCH$_3$), 68.6 [d, *C*H(CH$_3$)$_2$], 80.5 (dt, $^1J_{CF}$ = 162.8 Hz, CH_2F), 176.9 (s, COO). − ^{19}F NMR: δ = −219.35 (tdd, $^2J_{HF}$ = 47.2 Hz, $^3J_{HF}$ = 26.7 Hz, $^3J_{HF}$ = 24.8 Hz). − GC/MS; *m*/*z* (%): 162 (0.15) [$M^+ - CH_3$], 130 (1.1) [$M^+ - CH_2CH_2F$], 90 (100) [$M^+ - CO_2C_3H_7$]. − $C_8H_{16}FNO_2$ (163.2): calcd. C 54.22, H 9.10, N 7.90; found C 54.02, H 8.94, N 7.72.

(+)-(*S*)-2-Amino-4-fluoro-2-methylbutanoic Acid (5b): Ester hydrolysis was achieved analogously to *tert*-butyl 2-amino-4-fluorobutanoate (**4a**). Treatment with propene oxide was performed in *n*-propanol. Yield: 26.0 mg (24%), 85% *ee* [^{19}F NMR, after derivatization with (*S*)-2-chloropropionyl chloride]. − $[\alpha]_D^{20}$ = +1.3 (*c* = 0.50, 2 N HCl), m.p. 165 °C (dec.). − The spectroscopic data agree with published values of racemic **5b**.[10]

***tert*-Butyl (−)-(1*R*,2*R*,5*R*,2′*S*)-4′-Fluoro-2′-[(2-hydroxypinan-3-ylene)amino]pent-4-enoate (8):** A lithium diisopropylamide solution was prepared by addition of 6.25 mL (10 mmol) of *n*-butyllithium (1.6 N in hexane) to a solution of 1.4 mL (10 mmol) of diisopropylamine in 7.5 mL of THF under argon at −78 °C. The cooling bath was removed and the mixture was stirred for 15 min. Then 9.3 mL (7.7 mmol) of DMPU and 600 mg (2.14 mmol) of Schiff base **1b** in 7.5 mL of THF were added at −78 °C. After 60 min, 3.50 g (2.5 mmol) of 3-bromo-2-fluoropropene (**7**) was added. The resulting mixture was stirred for 2 h at this temperature and warmed up to room temperature for about 12 h. The workup was done analogously to *tert*-butyl (1*R*,2*R*,5*R*,2′*S*)-4′-fluoro-2′-[(2-hydroxypinan-3-ylene)amino]butanoate (**3a**). The residue was purified by chromatography on silica gel (cyclohexane/ether, 1:1). Yield: 530 mg (73%), > 97% *ds* (^{19}F NMR). − $[\alpha]_D^{20}$ = −60.1 (*c* = 2.28, CH_2Cl_2). − ^{1}H NMR: δ = 0.81 (s, 3 H, CH_3*), 1.29 (s, 3 H, CH_3*), 1.41 [s, 9 H, C(CH$_3$)$_3$], 1.43 (s, 3 H, CH_3*), 1.53 (d, 1 H, $^2J_{HH}$ = 10.5 Hz, CH*H**), 1.98 (m, 1 H, C*H*H*), 2.03 (dd, 1 H, $^3J_{HH}$ = 6.0 Hz, $^3J_{HH}$ = 6.0 Hz, CH*), 2.30 (dddd, 1 H, $^2J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 6.0 Hz, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 2.4 Hz, CH*), 2.75−2.48 (m, 3 H, CFC*H*H, CH_2*), 2.85 (dddd, 1 H, $^2J_{HH}$ = 18.6 Hz, $^3J_{HF}$ = 11.4 Hz, $^3J_{HH}$ = 4.0 Hz, $^4J_{HH}$ = 0.72 Hz, CFCH*H*), 4.25 [ddd, 1 H, $^2J_{HH}$ = 2.8 Hz, $^3J_{HF}$ = 49.8 Hz, $^4J_{HH}$ = 0.7 Hz, =CH(*E*)], 4.35 (dd, 1 H, $^3J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 4.0 Hz, CHN), 4.50 [dd, 1 H, $^2J_{HH}$ = 2.8 Hz, $^3J_{HF}$ = 17.2 Hz, =CH(*Z*)]. − ^{13}C NMR: δ = 22.7 (q, CH_3*), 27.4, 28.4 (q, CH_3*), 28.0 [q, C(*C*H$_3$)$_3$], 28.1, 33.0 (t, CH_2*), 35.6 (dt, $^2J_{CF}$ = 13.4 Hz, CF*C*H$_2$), 38.2 (s, C*), 38.3 (d, CH*), 50.1 (d, CHN), 59.5 (d, COH*), 81.7 [s, *C*(CH$_3$)$_3$], 92.3 (dt, $^2J_{CF}$ = 20.3 Hz, CF=*C*H$_2$), 163.3 (ds, $^1J_{CF}$ = 256.8 Hz, CF), 169.5 (s, C=N), 179.3 (s, COO). − ^{19}F NMR: δ = −97.4 (m, 4-F). − $C_{19}H_{30}NO_3F$ (339.4): calcd. C 67.33, H 8.91, N 4.13; found C 67.33, H 9.03, N 4.05.

***tert*-Butyl (−)-(*S*)-2-Amino-4-fluoropent-4-enoate (9):** Hydrolysis of the imine bond was performed analogously to *tert*-butyl (+)-(*S*)-2-amino-4-fluorobutanoate (**4a**). Yield: 453 mg (64%), 83% *ee* [30 mol-% Eu(hfc)$_3$]. − $[\alpha]_D^{20}$ = −12.9 (*c* = 2.15, CH_2Cl_2), b.p. 79 °C/12 Torr. − The spectroscopic data agree with published values of the racemic compound.[11]

(−)-(*S*)-2-Amino-4-fluoropent-4-enoic Acid (10): Ester **9** (96 mg, 0.5 mmol) was dissolved in 5 mL of CH_2Cl_2, 1 mL of H_2O, and 2 mL of trifluoroacetic acid. The mixture was stirred for 2 d. The phases were separated. The organic layer was extracted with 2 N HCl (3 × 3 mL). The combined aqueous phases were washed with diethyl ether, the solvent was evaporated in vacuo and the residue dried over phosphorus pentoxide. The protonated amino acid was dissolved in 7 mL of dry ethanol, 4−5 mL of propene oxide was added and the mixture was heated under reflux for 40 min. The precipitated product was isolated by suction and dried over phosphorus pentoxide. Yield: 35.6 mg (54%), 81% *ee*. − $[\alpha]_D^{20}$ = −18.0 (*c* = 1.78, H_2O). m.p. 181−182 °C. − The spectroscopic data agree with published values.[11]

X-ray Structures

***tert*-Butyl (1*RS*,2*RS*,5*RS*)-2′-[(2-Hydroxypinan-3-ylene)amino]-ethanoate (1a):** Formula $C_{16}H_{27}NO_3$, *M* = 381.39, colorless crystal, 0.50 × 0.40 × 0.20 mm, *a* = 12.878(2), *b* = 12.018(1), *c* = 10.741(2) Å, β = 94.68(1)°, *V* = 1656.8(4) Å^3, $\rho_{calcd.}$ = 1.128 g cm^{-3}, *F*(000) = 616 e, μ = 6.13 cm^{-1}, empirical absorption correction by scan data (0.869 ≤ *C* ≤ 0.998), *Z* = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, *T* = 223 K, ω/2θ scans, 3552 reflections collected (±*h*, −*k*, +*l*), (sin θ)/λ = 0.62 Å^{-1}, 3364 independent and 2672 observed reflections [$I \geq 2\ \sigma(I)$], 189 refined parameters, *R* = 0.060, wR^2 = 0.165, max. residual electron density 0.35 (−0.41) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

***tert*-Butyl (1*RS*,2*RS*,5*RS*,2′*SR*)-4′-Fluoro-2′-[(2-hydroxypinan-3-ylene)amino]butanoate (3a):** Formula $C_{18}H_{30}NO_3F$, *M* = 327.43, colorless crystal, 0.40 × 0.30 × 0.15 mm, *a* = 10.642(2), *b* = 11.770(1), *c* = 16.182(3) Å, α = 72.06(1), β = 79.14(1), γ = 88.31(1)°, *V* = 1892.9(5) Å^3, $\rho_{calcd.}$ = 1.149 g cm^{-3}, *F*(000) = 712 e, μ = 6.81 cm^{-1}, empirical absorption correction by scan data (0.944 ≤ *C* ≤ 0.999), *Z* = 4, triclinic, space group $P\bar{1}$ (No. 2), λ = 1.54178 Å, *T* = 223 K, ω/2θ scans, 8103 reflections collected (±*h*, +*k*, ±*l*), (sinθ)/λ = 0.62 Å^{-1}, 7707 independent and 6066 observed reflections [$I \geq 2\ \sigma(I)$], 429 refined parameters, *R* = 0.049, wR^2 = 0.143, max. residual electron density 0.38 (−0.54) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms, two chemical identical molecules with different conformation in the asymmetric unit.

***tert*-Butyl (1*RS*,2*RS*,5*RS*,2′*SR*)-4′-Fluoro-2′-[(2-hydroxypinan-3-ylene)amino]pent-4-enoate (8):** Formula $C_{19}H_{30}NO_3F$, *M* = 339.44, colorless crystal, 1.20 × 1.00 × 0.50 mm, *a* = 9.128(1), *b* = 11.033(1), *c* = 11.135(1) Å, α = 106.06(1), β = 104.74(1), γ = 105.77(1)°, *V* = 969.0(2) Å^3, $\rho_{calcd.}$ = 1.163 g cm^{-3}, *F*(000) = 368 e, μ = 6.83 cm^{-1}, empirical absorption correction by scan data (0.959 ≤ *C* ≤ 0.999), *Z* = 2, triclinic, space group $P\bar{1}$ (No. 2), λ = 1.54178 Å, *T* = 223 K, ω/2θ scans, 4161 reflections collected (±*h*, ±*k*, +*l*), (sinθ)/λ = 0.62 Å^{-1}, 3950 independent and 3747 observed reflections [$I \geq 2\ \sigma(I)$], 225 refined parameters, *R* = 0.053, wR^2 = 0.146, max. residual electron density 0.28 (−0.24) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

Crystallographic data (excluding structure factors) for the reported structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-136198, -136199, -136200. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, CambridgeCB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033, E-mail: deposit@ccdc.cam.ac.uk].

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