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Enantioselective Syntheses of 2-Amino-4-fluoropent-4-enoic Acids. Isosteres of Asparagine

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Abstract: Diastereoselective alkylation of (*R*)-(+)-camphor-based glycine or alanine esterimines with 3-bromo-2-fluoropropene after hydrolytic deprotection gave (*R*)-(+)-2-amino-4-fluoropent-4-enoic acid with 38% overall yield and 90% ee, or (*R*)-(+)-2-amino-4-fluoro-2-methylpent-4-enoic acid (19% overall yield, 59% ee), respectively. Deprotection under drastic conditions was accompanied by hydrolysis of the fluorovinyl moiety to give (*R*)-(-)-2-amino-4-oxopentanoic acid hydrochloride with 28% overall yield and >95% ee. *Ab initio* calculations of acetamide and 2-fluoropropene as models for a primary amide or a fluorovinyl group despite of their different electronic structure show a similar electrostatic potential on the van der Waals surface suggesting their isosteric behavior.

Keywords: Amino acids, Fluorinated compounds, Alkylation, Asymmetric synthesis

Introduction

The search for biological active analogs of natural products has developed considerable attention since several decades. Fluorinated compounds are of special interest since the introduction of fluorine can have a profound effect on biological activity.[1,2] Due to the similar van der Waals radii fluorine can substitute hydrogen isosterically.[1-3] Because of its high electronegativity and its ability to act as a hydrogen bond acceptor,[4,5] fluorine can also mimic oxygen of a hydroxy group.[3] Fluoroolefins are of particular interest since they have been described as isosteres of amide moieties[6] and have been used as hydrolysis stable isosteres of peptide bonds[7-12] and of proline amide.[13] In these cases the C-F group acts as a mimic for the C=O group. Thus, 2-amino-4-fluoropent-4-enoic acid (**1**) should be an isostere for asparagine (**2**). Recently we synthesized **1** and the α-methylated analogue **11a** as the racemic modification by alkylation of glycine and alanine esterimines with 3-bromo-2-fluoropropene (**4a**).[14] We now present the enantioselective preparation of (*R*)-(+)-2-amino-4-fluoropent-4-enoic acid (**1**) and

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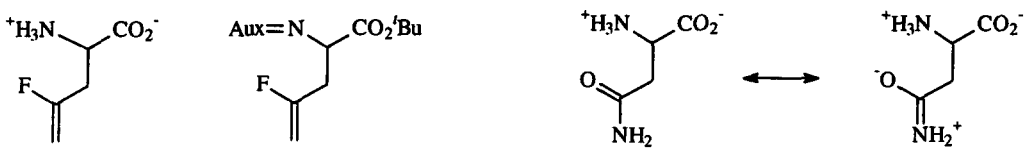
its α-methylated analogue **11a**. The results of a comparative study on the electronic structure of a primary amide group and a 2-fluoroethene group are also described.

Results and discussion

X-Ray data and dipole moment calculations suggest that fluoroolefins are excellent steric and electronic mimics for peptide bonds[6] and receptor binding studies.[8,12] It has also been recently suggested that a terminal 2-fluoroolefin moiety is a mimic for a primary amide in 5-carboxamido-tryptamine.[15] When the bond lengths of the amido group in asparagine monohydrate (C=O 1.24 Å, C–N 1.33 Å)[16] and that of a 2-fluoroolefin moiety in a fully protected[+)] 2-amino-4-fluorobutanoic acid (C=C 1.30 Å, C–F 1.36 Å)[17] are compared, the geometric similarity becomes obvious (Scheme 1). Moreover, in similar molecules having a substituted fluorovinyl moiety only small deviations from these bond lengths (C-F 1.36-1.38 Å, C=C 1.30-1.33 Å) have been found.[18-21]



1 2

bond lengths:	C–F	1.36 Å	C=O	1.22-1.24 Å
(X-Ray)	C=C	1.30 Å	C–NH_2	1.32-1.33 Å

Scheme 1

In order to illustrate the isosteric behavior of the amide and the fluorovinyl groups we performed *ab initio* calculations (B3LYP/6-31G(d,p))[22] on acetamide, 2-fluoropropene and propene. Despite the clearly different electronic structure of the amide and the 2-fluoroolefin, the electrostatic potential on the van der Waals surface (Figure 1) of both compounds is similar in shape, confirming the earlier findings obtained with semiempirical and low-level *ab initio* calculations.[6,7]

An analysis of the π orbitals in both molecules with the NBO program[23] gives an explanation for the similarity of the dipole orientation. The nitrogen in acetamide bears no significant charge because on the one hand the C-N σ bond is polarized towards nitrogen. On the other hand a substantial amount of π density (0.25 e) is delocalized from the nitrogen lone pair into

[+)] Auxiliary: 2-Hydroxypinan-3-one

the antibonding C-O π* orbital (Figure 2). Numerous studies have been published on the similar electronic structure of formamide.[24-27] The charge distribution of acetamide described here resembles earlier findings using another method.[28]

In 2-fluoropropene which has been treated in *ab initio* calculations without analysis of the charge distribution,[29] there is also a "π-back-bonding" effect from the halogen lone pair into the C-C π* orbital, but this interaction is less significant and cannot compensate the polarization of the C-F σ bond.

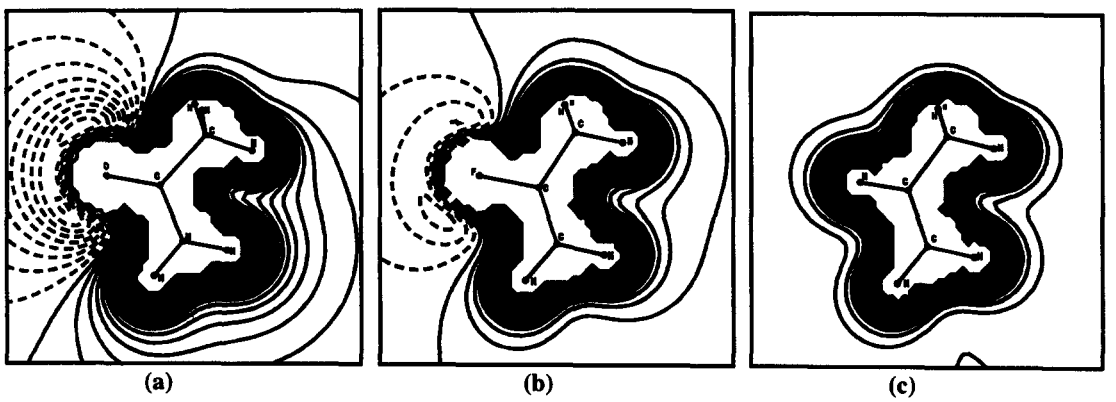


Figure 1: Electrostatic potential in the molecular plane of (a) acetamide, (b) 2-fluoropropene, and (c) propene. Dashed lines: negative potential, contour level spacing: 0.01 atomic units (B3LYP/6-31G(d,p)).

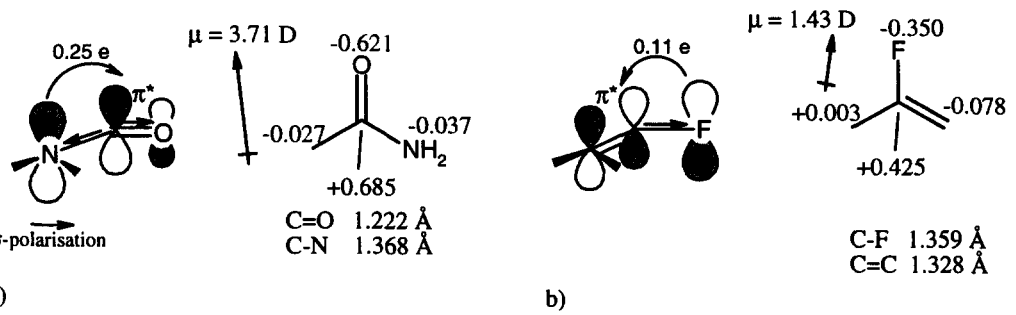


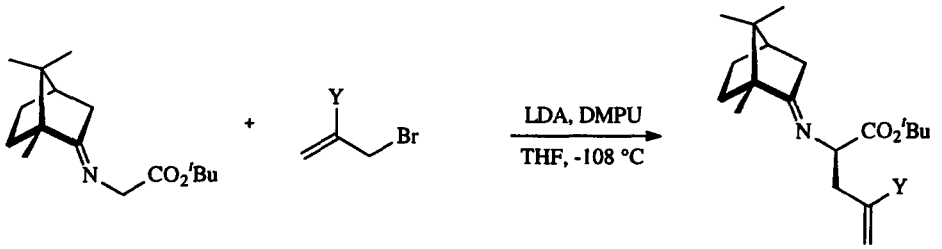
Figure 2: σ-Inductive and π-donor-acceptor interactions, dipole moments, NPA charges (hydrogens summed to the heavy atoms), and bond lengths of acetamide (a) and 2-fluoropropene (b) (B3LYP/6-31G(d,p)).

The isosteric behavior of the amide and the fluorovinyl groups can therefore be attributed mainly to the similarly polarized C=O and =C-F bonds which dominate the electrostatic potential. Recognition by enzymes, which is mainly electrostatic when the substrate is only loosely attached to a binding site, can be expected to be non-selective with respect to both moieties. At closer distances, orbital control becomes decisive and the fluorovinyl compound is inert to hydrolysis, whereas the amide is attacked by nucleophiles.[8,12]

Based on these results we expected 2-amino-4-fluoropent-4-enoic acid (**1**) to be an isostere for asparagine (**2**). Since absolute stereochemistry is essential for physiological properties, we developed a method for enantioselective preparation of (*R*)-(+)-2-amino-4-fluoropent-4-enoic acid (**1**) and its α-methylated derivative **11a** based on earlier results with (*R*)-(+)-camphor as the chiral auxiliary.[30]

The imine derivatives of glycine esters of (*R*)-(+)-camphor have already been applied to the synthesis of non-fluorinated amino acids.[31-34] The diastereomeric excess in the alkylation of this Schiff's base shows several distinct trends.[35] While alkylating agents that do not have an adjacent π-system, show low to moderate selectivity (up to 50% de) much better results were obtained with allylic and benzylic halides (up to 98% de). McIntosh et al. explained this behavior by π–π- or π–Li association between the alkylating agent and the enolate.[35] Our experience showed[36] that vinylic fluorides in comparison to the corresponding non-fluorinated parent compounds are best considered as electron rich olefins caused by hyperconjugation ($p_F \rightarrow \pi^*_{C=C}$). Thus, Schiff's bases derived from glycine esters of (*R*)-(+)-camphor should reasonably be expected to alkylate with 3-bromo-2-fluoropropene (**4a**) in high diastereomeric excess. Additionally a coordination between the fluorine and the lithium ion might also increase the selectivity.

Alkylation of the imino ester **3** with 3-bromo-2-fluoropropene (**4a**) proceeded with good selectivity (87% de), but only a 40% yield was obtained at -78°C. The yield can be significantly improved by the addition of DMPU[37] and the selectivity increased to 96% de by decreasing the temperature to -108°C.



3 **4a** Y = F, **4b** Y = H → **5a** Y = F 86% (96% de), **5b** Y = H 86% (96% de)

Scheme 2

On the other hand metal exchange of lithium by magnesium or application of other bases such as potassium *tert*-butoxide resulted in lower chemical yield and optical purity (Table 1).

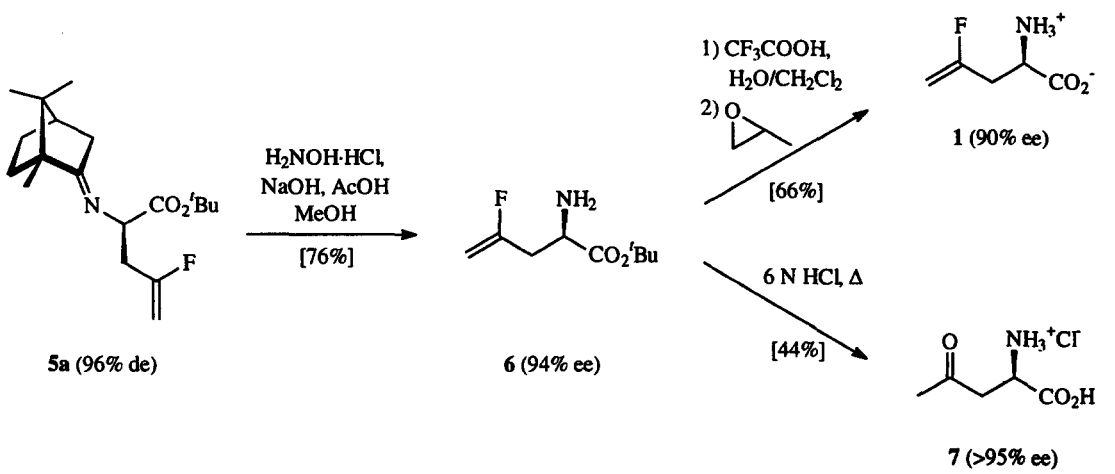
Table 1: Diastereoselective alkylation of **3**

Base	Additive	Temperature	Yield (%)	% de[a)]
LDA	--	-78 °C	40	87
LDA	1 eq DMPU	-78 °C	86	87
LDA	2 eq DMPU	-78 °C	86	87
LDA	2 eq DMPU	-108 °C	86	96
LDA	$MgBr_2 \cdot OEt_2$	-78 °C	47	70
KO^{t}Bu	--	-78 °C	14	79

[a)] The ratio of diastereomers of the crude product was determined by ^{19}F NMR spectroscopy ($\delta = -97.00$ ppm major diastereomer, $\delta = -97.95$ ppm minor diastereomer).

For the alkylation of the imino ester **3** with 3-bromopropene (**4b**) McIntosh et al. reported a diastereomeric excess of 76% (-78 °C, HMPA as an additive)[31,35] which is slightly lower than we obtained in our experiments with DMPU as an additive at -78°C (87% de). Alkylation with both the fluorinated and the non-fluorinated allylic bromides **4** gave the same chemical yield and optical purity at -108°C (Scheme 2).

Deprotection of the alkylation product **5a** was achieved in two steps (Scheme 3). The ester **6** was prepared in 76% yield by transamination with hydroxylamine. The thus formed camphor oxime was isolated by extraction (81% yield). The optically active 2-amino-4-fluoropent-4-enoic acid (**1**) was liberated by hydrolysis of the ester function with trifluoroacetic acid and subsequent treatment of the crude product with propene oxide in ethanol. The optical purity of **1** was determined by ^{19}F NMR after derivatization with (*S*)-2-chloropropionic acid.[38]

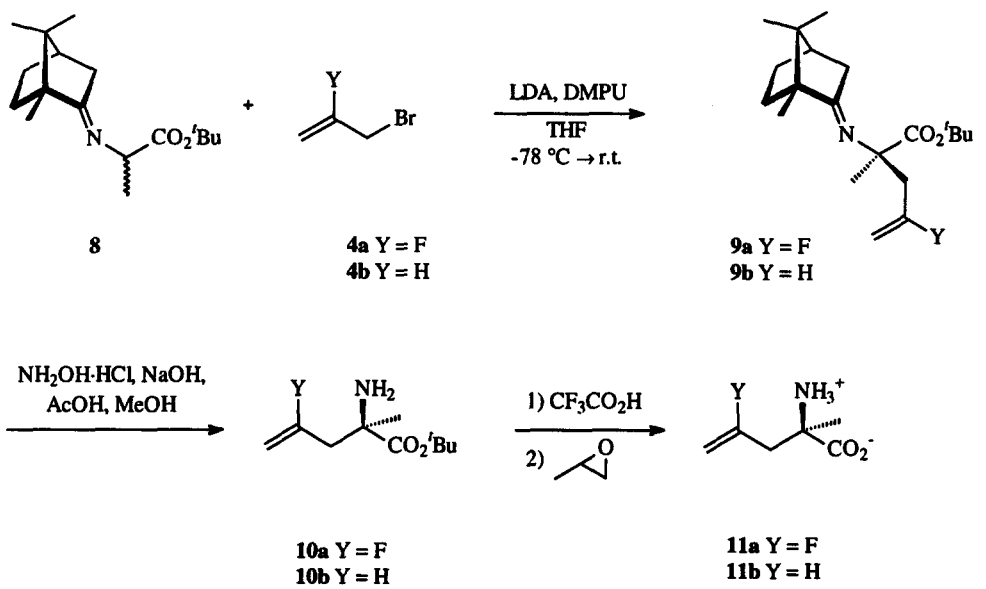


Scheme 3

Both the *tert*-butyl ester and the fluorovinyl moiety were hydrolyzed by refluxing the ester **6** in 6 N HCl for six hours[14] to give (*R*)-(−)-2-amino-4-oxopentanoic acid hydrochloride (**7**). The absolute configuration of **7** was determined to be (*R*) by comparison of the optical rotation to that of the recently synthesized (*S*)-(+)-2-amino-4-oxopentanoic acid hydrochloride.[39] The optical purity (>95%) of the acid was specified by ^{19}F NMR of the amide prepared with Mosher's acid.

It is well known in the non-fluorinated series that α-methyl-α-amino acids can be synthesized by alkylation of Schiff's bases of alanine esters and 2-hydroxypinan-3-one.[40] Under the conditions shown in Scheme 4 we synthesized 2-amino-4-fluoro-2-methylpent-4-enoic acid (**11a**) in four steps from Schiff's base **8**.

The enolate of the imine **8** is less reactive than that of the glycine derivative **3**. Alkylation with 3-bromo-2-fluoropropene (**4a**) at room temperature gave **9a** in 64% yield while 52% of **9b** were isolated from the alkylation with 3-bromopropene (**4b**). In both cases the diastereomeric excess was moderate (Table 2). The amino acids were obtained by deprotection of the imines in two steps. Transamination with hydroxylamine gave the esters **10a** (57%) and **10b** (75%), respectively. The *tert*-butyl groups were hydrolyzed with trifluoroacetic acid. The absolute configuration of the unfluorinated amino acid **11b** was determinated to be (*R*) by comparison of the optical rotation to literature data.[41] Analogously, the configuration of the fluorinated amino acid **11a** should also be (*R*).



8 **4a** Y = F, **4b** Y = H

9a Y = F, **9b** Y = H

10a Y = F, **10b** Y = H

11a Y = F, **11b** Y = H

Scheme 4

Table 2: Yields and optical purity of **9**, **10** and **11**

Alkylating agent	Yield of **9** [%]	de [%]	Yield of **10** [%]	ee [%]	Yield of **11** [%]	ee [%]
4a (Y=F)	64	56	57	59	52	61
4b (Y=H)	52	49	75	48	46	70

Experimental

General Remarks: All air- and moisture-sensitive reactions were performed under an argon atmosphere in flame dried flasks using standard Schlenk technique. 3-Bromo-2-fluoropropene (**4a**) was prepared according to the procedure given in ref.[14] All other starting materials were obtained from Acros, Merck and Fluka chemicals. Diisopropylamine and DMPU were dried over molecular sieves (4 Å) and THF was distilled from sodium/benzophenone before use. 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. TMS for ^{1}H, $CDCl_3$ for ^{13}C and $CFCl_3$ for ^{19}F NMR were used as internal standards. If not stated otherwise $CDCl_3$ was the solvent. The multiplicity of the ^{13}C NMR signals regarding the $^{13}C^1H$ coupling was determined by the DEPT method. – IR spectra: Nicolet 5DXC-FT-IR spectrometer. – 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.

Alkylation of Glycine Ester Imines: To a stirred solution of 0.23 ml (3.0 mmol) diisopropylamine in 7.5 ml of dry THF, 1.86 ml of *n*-butyllithium (1.6 N in hexane, 3.0 mmol) was added dropwise, followed by the dropwise addition of 0.6 ml (5mmol) DMPU at -78°C. The cooling bath was removed for 5 min. A solution of 700 mg (2.5 mmol) imino ester **3**, dissolved in 7.5 ml of dry THF was added at -78°C. After 1 h the temperature was reduced to -108°C and 3.0 mmol of the corresponding allylic bromide **4** was added dropwise (syringe), and stirring was continued for 5 h at -108°C. Then 1 ml of methanol followed by 30 ml of H_2O were added at this temperature and the reaction mixture was warmed up to room temperature. The organic layer was separated and the aqueous layer extracted with Et_2O (3 x 10 ml). The combined organic phases were washed twice with 10 ml of H_2O, once with saturated aqueous $NaHCO_3$ solution, once with saturated aqueous NaCl solution and dried over $MgSO_4$. The solvent was evaporated. Filtration of the product through a short silica gel column (cylohexane/Et_2O 2:1) and evaporation of the solvent in vacuum gave colorless oils.

tert-Butyl (R,R,R)-(+)-4'-Fluoro-2'-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylideneamino)pent-4'-enoate (**5a**): Yield 700 mg (86%). - $[\alpha]_D^{20}$ = + 91.6 (c = 2.67, CH_2Cl_2), 96% de (^{19}F NMR). - ^{1}H NMR: δ = 4.45 [dd, 1H, $^2J_{HH}$ = 2.6 Hz, $^3J_{HF}$ = 17.2 Hz, =CH(*Z*)], 4.19 [ddd, 1H, $^2J_{HH}$ = 2.6 Hz, $^3J_{HF}$ = 50.1 Hz, $^4J_{HH}$ = 1.0 Hz, =CH(*E*)], 4.02 (dd, 1H, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 4.5 Hz, CHN), 2.77 (dddd, 1H, $^2J_{HH}$ = 15.0 Hz, $^3J_{HF}$ = 12.2 Hz, $^3J_{HH}$ = 4.5 Hz, $^4J_{HH}$ = 1.0 Hz, C*H*H), 2.56 (ddd,

1H, $^2J_{HH}$ = 15.04 Hz, $^3J_{HF}$ = 26.7 Hz, $^3J_{HH}$ = 9.1 Hz, CH*H*), 2.36 - 1.53 (m, 6H, camphor skeleton), 1.35 [s, 9H, $C(CH_3)_3$], 0.91 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.74 (s, CH_3). - ^{13}C NMR: δ = 186.0 (s, C=O), 170.3 (s, C=N), 163.6 (ds, $^1J_{CF}$ = 256.8 Hz, CF), 92.1 (dt, $^2J_{CF}$ = 20.3 Hz, $=CH_2$), 81.2[s, $C(CH_3)_3$], 61.5 (d, CHN), 54.2 (s, C), 47.2 (s, C), 43.9 (d, CH_2), 35.6 (dt, $^2J_{CF}$ = 12.7 Hz, CH_2CF), 32.5 (t, CH_2), 31.9 (t, CH_2), 27.4 (t, CH_2), 28.0 [q, $C(CH_3)_3$], 19.5 (q, CH_3), 18.9 (q, CH_3), 11.5 (q, CH_3). - ^{19}F NMR: δ = -97.00 (m, main diastereomer); -97.95 (m, minor diastereomer). - GC/MS, *m/z* (%): 323 (7) [M^+], 267 (2) [M^+-C_4H_8, McLafferty], 222 (100) [M^+-$CO_2C_4H_9$], 208 (30), 57 (8) [$C_4H_9^+$]. - $C_{19}H_{30}FNO_2$ (323.45): calcd. C 70.55, H 9.44, N 4.33; found C 70.49, H 9.40, N 4.39.

tert-Butyl (R,R,R)-(+)-2'-(1,7,7-Trimethylbicyclo[2.2.1]hept-2-ylideneamino)pent-4'-enoate (**5b**): Yield: 660 mg (86%). - $[\alpha]_D^{20}$ = +100.5 (c = 3.20, CH_2Cl_2), 96% de (^1H NMR). - ^{13}C NMR: δ = 184.6 (s, C=O), 171.0 (s, C=N), 134.9 (d, =CH), 115.9 (t, $=CH_2$), 80.7 [s, $C(CH_3)_3$], 63.9 (d, CHN), 53.9 (s, C), 47.2 (s, C), 43.9 (d, CH_2), 37.3 (t, CH_2), 36.2 (t, CH_2CHN), 32.4 (t, CH_2), 28.0 [q, $C(CH_3)_3$], 27.4 (t, CH_2), 19.5 (q, CH_3), 18.9 (q, CH_3), 11.4 (q, CH_3). - GC/MS, *m/z* (%). 305 (15) [M^+], 304 (12) [M^+-H], 249 (8) [M^+-C_4H_8, McLafferty], 204 (100) [M^+-$CO_2C_4H_9$], 162 (8) [$C_{11}H_{16}N^+$]. ^1H NMR data agree with published values.[31]

Alkylation of Alanine Ester Imines: To a stirred solution of 0.46 ml (6.0 mmol) diisopropylamine in 15 ml of dry THF, 3.30 ml of *n*-butyllithium (1.6 N in hexane, 6.0 mmol) and 1.20 ml (10 mmol) of DMPU were added at -78°C. The cooling bath was removed for 5 min. A solution of the imino ester **8**[31] (prepared from (*R*)-(+)-camphor and racemic alanine *tert*-butyl ester in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$), 1.52 g (5 mmol) dissolved in 15 ml dry THF was added at -78°C. After 1 hour 6.0 mmol of the corresponding allylic bromide **4** was injected, stirring was continued for 4 h at -78°C, than the reaction mixture was slowly warmed up to room temperature overnight and worked up as described above. The crude product was purified by chromatography (ether/cyclohexane 1:4).

tert-Butyl (R,R,R)-(+)-4'-Fluoro-2'-methyl-2'-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylideneamino)pent-4'-enoate (**9a**): Yield: 1.02 g (64%, additionally 470 mg, 35%, of **8** were re-isolated), $[\alpha]_D^{20}$ = +9.6 (c = 2.33, CH_2Cl_2), 56% de (^{19}F NMR). - ^1H NMR: δ = 4.61 [dd, 1H, $^2J_{HH}$ = 2.39 Hz, $^3J_{HF}$ = 17.2 Hz, =CH(*Z*)], 4.35 [dd, 1H, $^2J_{HH}$ = 3.29 Hz, $^3J_{HF}$ = 49.6, =CH(*E*)], 2.78 (AB, 2H, $^2J_{HH}$ = 14.5 Hz, CH_2), 2.25-1.12 (m, 7H, camphor skeleton), 1.45 [s, 9H, $C(CH_3)_3$], 0.95 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.79 (s, 3H, CH_3, main diastereomer), 0.75 (s, 3H, CH_3, minor diastereomer). - ^{13}C NMR: δ = 181.3 (s, C=O), 173.9 (s, C=N), 163.5 (ds, $^1J_{CF}$ = 256.8 Hz, CF), 93.4 (dt, $^2J_{CF}$ = 20.3 Hz, $=CH_2$), 81.2 [s, $C(CH_3)_3$], 64.5 (s, CN), 55.0 (s, $CNCH_3$), 46.6 (d, CH), 44.7 (dt, $^2J_{CF}$ = 28.0 Hz, $CFCH_2$), 36.8 (t, CH_2), 32.0 (t, CH_2), 27.4 (t, CH_2), 27.9 [q, $C(CH_3)_3$], 21.6 (q, CH_3), 19.7(q, CH_3), 19.1 (q, CH_3), 11.5 (q, CH_3). - ^{19}F NMR: δ = 88.9 (m, minor diastereomer), -89.2 (m, main diastereomer). - GC/MS, *m/z* (%): 337 (7) [M^+], 282 (3) [M^++H-C_4H_8, McLafferty], 236 (100) [M^+-$CO_2C_4H_9$], 222 (10) [236-CH_2, McLafferty]. - $C_{20}H_{32}FNO_2$ (337.47): calcd.: C 71.18, H 9.56, N 4.15; found: C 71.14, H 9.57, N 4.17.

tert-Butyl (R,R,R)-(+)-2'-Methyl-2'-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylideneamino)pent-4'-enoate (**9b**): Yield: 830 mg (52%), $[\alpha]_D^{20}$ = +9.7 (c = 0.91, CH_2Cl_2), 49% de (^{1}H NMR). - ^{1}H NMR: δ = 5.87 (m, 1H, =CH), 5.05 (m, 2H, =CH_2), 2.59 (m, 2H, CH_2), 2.28 - 1.12 (m, 7H, camphor skeleton), 1.44 [s, 9H, $C(CH_3)_3$], 0.95 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.80 (s, 3H, CH_3, main diastereomer), 0.75 (s, 3H, CH_3, minor diastereomer). - ^{13}C NMR: δ = 180.9 (s, C=O), 174.8 (s, C=N), 134.4 (d, =CH), 117.3 (t, =CH_2), 80.5 [s, $C(CH_3)_3$], 65.2 (s, CN), 54.9 (s, C), 46.9 (t, CNCH_2), 44.5 (d, CH), 37.0 (t, CH_2), 32.1 (t, CH_2), 27.5 (t, CH_2), 28.0 [q, $C(CH_3)_3$], 22.1 (q, CH_3), 19.8 (q, CH_3), 19.1 (q, CH_3), 11.6 (q, CH_3). - GC/MS, *m/z* (%): 319 (4) [M^+], 278 (2) [M^+-C_3H_5], 218 (100) [M^+-$CO_2C_4H_9$]. - $C_{20}H_{33}NO_2$ (319.48) calcd. C 75.25, H 10.42, N 4.39; found C 74.94, H 10.38, N 4.54.

Synthesis of the Amino Acid tert-Butyl Esters: A solution of 3.7 mmol alkylated imine in 12 ml of dry methanol was added to a solution of 0.15 g (3.7 mmol) NaOH, 0.27 g (3.7 mmol) of hydroxylamine hydrochloride and 0.23 g (3.7 mmol) of acetic acid in 25 ml of dry methanol at 0°C and the resulting mixture was stirred at room temperature for three days. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 10 ml of 2 N HCl and 10 ml of Et_2O. The organic layer was separated and the aqueous layer was extracted with ether (3 x 10 ml). The combined organic phases were washed with water and dried over $MgSO_4$. Removal of the solvent gave 500 mg (81%) of camphor oxime. The aqueous layer was treated with concentrated ammonia, extracted with methylene chloride (3 x 10 ml) followed by ether (3 x 10 ml) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by bulb-to-bulb distillation.

tert-Butyl (R)-(+)-2-Amino-4-fluoropent-4-enoate (**6**)*:* Yield: 529 mg (76%), 79°C/16 mbar, $[\alpha]_D^{20}$ = +7.6 (c = 2.05, CH_2Cl_2), 94% ee (^{19}F NMR, 30 mol% $Eu(hfc)_3$). Analytical and spectroscopic data agree with published values for racemic **6**.[14]

tert-Butyl (R)-(+)-2-Amino-4-fluoro-2-methylpent-4-enoate (**10a**): Preparation from 1.02 g (3.18 mmol) *tert*-butyl (*R,R,R*)-(+)-4'-fluoro-2'-methyl-2'-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylideneamino)pent-4'-enoate (**9a**) (56% de). Yield: 365 mg (57%), 45°C /15 mbar, $[\alpha]_D^{20}$ = +6.2 (c = 2.20, CH_2Cl_2), 59% ee (^{19}F NMR, 75 mol% $Eu(hfc)_3$). Analytical and spectroscopic data agree with published values for the racemic compound.[14]

tert-Butyl (R)-(+)-2-Amino-2-methylpent-4-enoate (**10b**): Preparation from 830 mg (2.6 mmol) (*R,R,R*)-(+)-2'-methyl-2'-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylideneamino)pent-4'-enoate (**11b**) (49% de). Yield: 358 mg (75%), bp 45°C / 21 mbar, $[\alpha]_D^{20}$ = +1.7 (c = 2.18, CH_2Cl_2), 48% ee (^{1}H NMR, 80 mol% $Eu(hfc)_3$). - IR (NaCl): $\tilde{\nu}$ = 3380 (m, ν-N-H), 1728 (s, ν-C=O), 1672 (s, ν-C=C). ^{1}H NMR: δ = 5.74 (m, 1H, =CH), 5.13 (m, 2H, =CH_2), 2.49 (ddt, 1H, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 6.7 Hz, $^4J_{HH}$ = 1.2 Hz, C*H*H), 2.24 (ddt, 1H, $^2J_{HH}$ = 13.4, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 0.9 Hz, CH*H*), 1.73 (s br, 2H, NH_2), 1.45 [s, 9H, $C(CH_3)_3$], 1.29 (s, 3H, CH_3). - ^{13}C NMR: δ = 176.3 (s, C=O), 133.1 (d, =CH), 118.9 (t, =CH_2), 80.8 [s, $C(CH_3)_3$], 57.5 (s, CN), 45.2 (t, CH_2),

27.9 [q, C(CH_3)$_3$], 26.3 (q, CH_3). - GC/MS, *m/z* (%): 185 (0) [M^+], 184 (1) [M^+-H], 129 (10) [M^+-C_4H_8, McLaff], 84 (100) [M^+-$CO_2C_4H_9$]. - $C_{10}H_{19}NO_2$ (185.26): cald. C 64.36, H 10.26, N 7.50; found C 64.12, H 10.51, N 7.37.

Hydrolysis of Amino Acid tert-Butyl Esters: To 2.0 mmol of the *tert*-butyl esters dissolved in 20 ml of CH_2Cl_2, 4 ml of H_2O and 5 ml of CF_3COOH were added. The mixture was stirred at room temperature for two days. Then 10 ml of H_2O was added, the layers were separated and the organic phase was extracted with aqueous 2 N HCl (3 x 5 ml). The combined aqueous layers were evaporated and the residual amino acid hydrochloride was dried over phosphorus pentoxide. The hydrochloride was dissolved in 10 ml of dry ethanol, 2 ml of propene oxide was added and the solution was refluxed for 30 min. The precipitated product was isolated by suction and recrystallized from EtOH/Et_2O (1:1).

(R)-(+)-2-Amino-4-fluoropent-4-enoic acid (**1**): Preparation from 325 mg (1.72 mmol) *tert*-butyl (*R*)-(+)-2-amino-4-fluoro-2-methylpent-4-enoate (**6**) (94% ee). Yield: 134 mg (59%), mp 180-182°C (dec.), $[\alpha]_D^{20}$ = +16.3 (c = 1.10, 1N HCl), 90% ee (^{19}F NMR, after derivatization with (*S*)-2-chloropropanoic chloride[38]). Analytical and spectroscopic data agree with published values for the racemic compound.[14]

(R)-(+)-2-Amino-4-fluoro-2-methylpent-4-enoic acid (**11a**): Preparation from 353 mg (1.74 mmol) *tert*-butyl (*R*)-(+)-2-amino-4-fluoro-2-methylpent-4-enoate (**10a**) (59% ee). Yield: 134 mg (52%), mp 210°C (dec.), $[\alpha]_D^{20}$ = +6.9 (c = 2.09, H_2O), 61% ee (^{19}F NMR, after derivatization with (*S*)-2-chloropropanoic chloride[38]). Analytical and spectroscopic data agree with published values for the racemic **11a**.[14]

(R)-(+)-2-Amino-2-methylpent-4-enoic acid (**11b**): Preparation from 248 mg (1.53 mmol) *tert*-butyl (*R*)-(+)-2-amino-2-methylpent-4-enoate (**10b**) (48% ee). Yield: 91 mg (46%), $[\alpha]_D^{20}$ = +13.8, (c = 2.01, H_2O). Analytical and spectroscopic data agree with published values.[41]

(R)-(-)-2-Amino-4-oxopentanoic acid hydrochloride (**7**): 400 mg (2.11 mmol) of *tert*-butyl 2-amino-4-fluoropent-4-enoate (**6**) were refluxed in 15 ml of aqueous 6 N HCl for 6 h. The solvent was evaporated and the residue recrystallized from ether/ethanol (1:1). Yield: 141 mg (40%), $[\alpha]_D^{20}$ = –11.1 (c = 2.09, H_2O), >95% ee (^{19}F NMR, after derivatization with Mosher's acid); ref.[39]: $[\alpha]_D^{23}$ = +8.05, (c = 0.9, H_2O) for the (*S*)-(+) enantiomer. Analytical and spectroscopic data agree with published values.[39]

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