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The Vinylfluoro Group as an Acetonyl Cation Equivalent: Stereoselective Synthesis of 6-Substituted 4-Hydroxy Pipecolic Acid Derivatives

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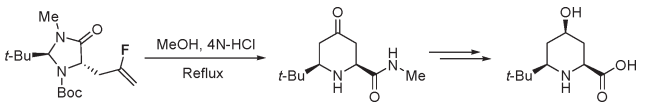

An unprecedented cascade of reactions after acid-catalyzed hydrolysis of *tert*-butyl (2*S*,5*S*)-2-*tert*-butyl-5-(2-fluoroallyl)-3-methyl-4-oxoimidazolidine-1-carboxylate **3a** leading to pipecolic acid derivative **5** is presented. The vinylfluoro group is shown to be an acetonyl cation equivalent under acidic conditions. Interestingly, vinylchloro and vinylbromo groups do not show such transformation under the same conditions. The pipecolic acid derivative **5** produced in this way is further used to synthesize (2*R*,4*R*,6*S*)-6-*tert*-butyl-4-hydroxypiperidine-2-carboxylic acid **9**.

The imposing number of known substituted pipecolic acids, along with their derivatives, clearly reflects the importance of these molecules, especially in medicinal chemistry. For example, pipecolic acid derivatives are prevalent among peptides,[1] immunosuppressants,[2] enzyme inhibitors,[3] or *N*-methyl-D-aspartic acid (NMDA) antagonists.[4] The naturally occurring (2*S*,4*R*)-4-hydroxypipecolic acid **1**[5] (Figure 1) is found as a constituent of certain cyclopeptide antibiotics (Virginiamycine)[6] and has been used as a building block in a synthesis of Palinavir **2**, a potent HIV protease inhibitor.[7] In addition, it is an interesting natural rigid amino acid for the protein design especially to study the conformational heterogeneity of the peptide bond when incorporated in polypeptides.[8]

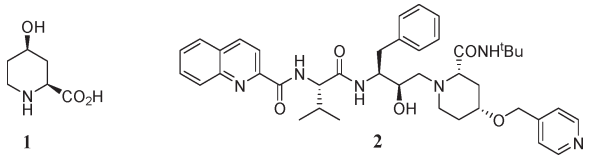

FIGURE 1. (2*S*,4*R*)-4-Hydroxypipecolic acid **1** and Palinavir **2**.

Substituted pipecolic acid derivatives[9] are interesting not only for their potential bioactivity but also as starting material for synthesizing piperidine alkaloids and medicinally relevant compounds of the palinavir type. Most of the approaches toward pipecolic acid derivatives described in the literature are based on stereoselective syntheses with chiral inductors.[10]

Continuing our efforts in the synthesis and application of fluorinated amino acids,[11] we have recently reported a novel asymmetric synthesis of γ-fluorinated α-amino acid derivatives from the Boc-protected imidazolidinone **6**, (*S*)-Boc-BMI,[12] and 2-fluoroallyltosylate with subsequent acid-catalyzed hydrolysis of the formed fluorovinyl compound **3a**.[13] In this note, we wish to disclose a novel molecular rearrangement during the acidic hydrolysis of compound **3a**. In addition to the desired fluorinated amino acid amide **4a** we also observed the formation of (2*S*,6*R*)-6-*tert*-butyl-4-oxopipecolic acid amide **5** in a minor amount (Scheme 1).

SCHEME 1. Hydrolysis of Fluorovinyl Compound 3a

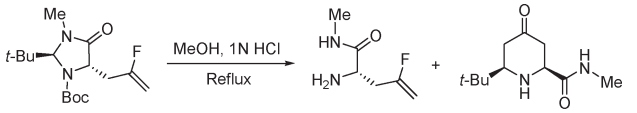

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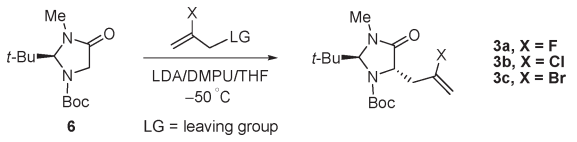
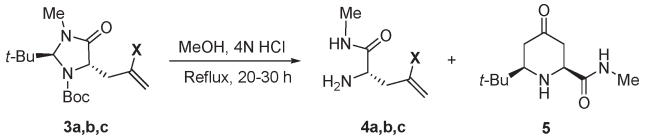
TABLE 1. Asymmetric Alkylation of (*S*)-Boc-BMI 6 with Different Electrophiles



entry	X	LG	product	yield (%)[a]	ds (%)[b]
1	F	OTs	**3a**	95	99
2	Cl	Cl	**3b**	45	99
4	Cl	OTs	**3b**	78	99
4	Br	Br	**3c**	85	99

[a]Isolated yields. [b]ds calculated from ^{19}F or ^{1}H NMR spectra.

TABLE 2. Reaction of 3a,b,c with 4 N HCl



entry	substrate	X	product (yield (%))	
1	**3a**	F	**4a** (21)	**5** (57)[a]
2	**3b**	Cl	**4b** (72)	
3	**3c**	Br	**4c** (63)	

[a]Yield after chromatographic purification.

We optimized the reaction conditions for the formation of **5** and used it further in the synthesis of (2*R*,4*R*,6*S*)-6-*tert*-butyl-4-hydroxypiperidine-2-carboxylic acid **9**.

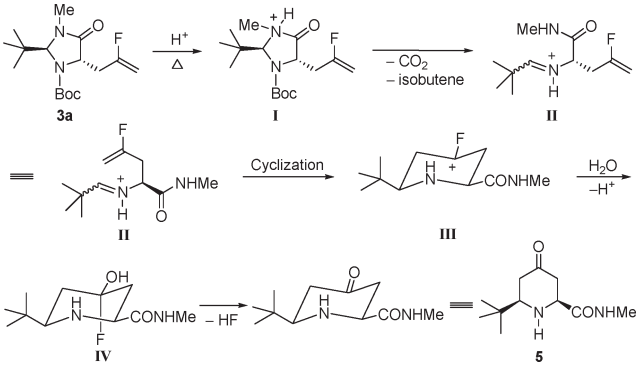
For comparative studies, the chloro and bromo derivatives **3b** and **3c** were prepared analogous to a protocol described by Seebach et al.[12] The asymmetric alkylation of **6** with different electrophiles gave the products **3a**,**b**,**c** with good yield and excellent stereoselectivity (Table 1).

Subsequently, the vinyl compounds **3a**,**b**,**c** were dissolved in methanol, treated with 4 N aqueous HCl, and allowed to reflux for 20 h. Under these conditions, compound **3a** beside **4a** gave the 4-oxo-pipecolic acid derivative **5** as the major product via cascade of reactions (entry 1, Table 2). Increasing the reaction time from 20 to 30 h does not make any change to the product yield. The absence of a fluorine resonance in ^{19}F NMR, a pair of olefinic carbons at 93.4 and 163.6 ppm in ^{13}C NMR, and the appearance of a pair of methylene groups in the ^{1}H NMR spectrum strongly pointed toward a major skeletal change and fit the assigned structure **5**. Unequivocal proof for the structural assignment was established through careful 2D-NMR investigations.

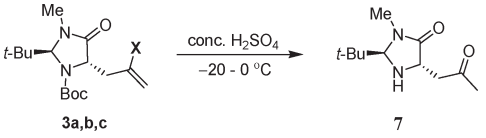
A plausible mechanism for the formation of **5** is depicted in Scheme 2. We believe that the presence of a vinylfluoro group in **3a** triggers the cascade of events.

Under the acidic condition, protonation of compound **3a** should give the ammonium ion **I**. Subsequent loss of CO_2 and isobutene from **I** should give the intermediate iminium ion **II**, which is a strong electrophile. The fluoroolefin side

SCHEME 2. Plausible Mechanism for the Formation of 5



SCHEME 3. Hydrolysis of Vinyl halides 3 to the Methyl Ketone 7



chain in **II** undergoes a cyclization reaction to form **III** where the carbocationic center is stabilized by the fluorine atom.[14] Intermediate **III** upon hydration gives the unstable geminal fluorohydrin **IV**, which eliminates HF to yield the 6-substituted 4-oxo-pipecolic acid derivative **5**, bearing both substituents in the energetically preferred equatorial position.

The outcomes of the reaction alter completely when it was carried out with the chloro- or bromovinyl compounds **3b** and **3c** (entry 2 and 3, Table 2). To our surprise these compounds did not lead to product **5** under the same condition. Even under more drastic conditions, namely concd HCl under reflux, or perchloric acid, hydrolysis of the vinylchloro or the vinylbromo moiety did not occur.

When **3a**,**b**,**c** were treated with concd H_2SO_4 following a literature method[15] for the hydrolysis of vinylhalides to methyl ketones, compound **7** was formed (Scheme 3).

With respect to the chemical reactivity, fluorinated compounds behave in a unique manner owing to inductive and resonance effects caused by fluorine.[14,16] Allen and Tidwell have shown that 2-fluoropropene is hydrolyzed to acetone in sulfuric acid[17] and *tert*-butyl 2-amino-4-fluoropent-4-enoate was hydrolyzed to 2-amino-4-oxopentanoic acid with 6 N HCl under reflux.[11d] The formation of **7** from **3a** (Scheme 3) suggests that the electron-rich vinylfluoro group in intermediate **II** triggers the cyclization reaction to form the pipecolic acid derivative under the reaction conditions of Scheme 2.

To further support the above mechanism, compound **4a** was treated with 4 N HCl in the presence of 5 equiv of pivaldehyde under reflux for 20 h to obtain **5** in 73% yield (Scheme 4). Enolizable aldehydes or benzaldehydes did not give the expected products.

In a logical application of this stereoselective cascade reaction approach to 4-oxo-pipecolic acid derivative **5**, we

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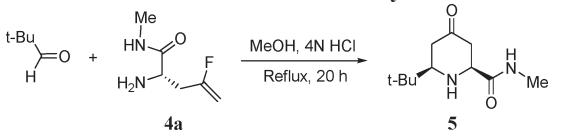
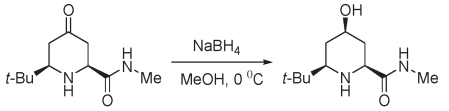
SCHEME 4. Reaction of 4a with Pivaldehyde



4a 5

SCHEME 5. $NaBH_4$ Reduction of 4-Oxo-pipecolic Acid Amide 5



5 8

were interested in synthesizing (2*S*,4*R*,6*R*)-6-*tert*-butyl-4-hydroxypiperidine-2-carboxylic acid (**9**). Initially, treatment of **5** with $NaBH_4$ in methanol at 0 °C for 3 h afforded almost exclusively the *all-cis*-diastereomer **8**, which was contaminated with 4% (^{1}H NMR) of the diastereomer having 4*S*-configuration (overall yield 86%) (Scheme 5).

The configuration of the newly created stereocenter at C-4 was established by analysis of a 600 MHz ^{1}H NMR spectrum of compound **8**. The large coupling constants of 12 Hz clearly indicate the 1,2-diaxial proton interactions of H-4 and H-3_{axial} as well as H-4 and H-5_{axial}. This fact suggests an axial attack of the hydride ion upon the carbonyl group. In the most stable conformation of **5** the substituents in positions 2 and 6 are placed in an equatorial position. The observed preference of isomer **8** is attributed to an easier approach of the hydride reagent to the carbonyl group from the axial side. In particular, the equatorial attack is hindered by repulsive interactions with the axial hydrogens H-3_{axial} and H-5_{axial}.[18] In addition to the spectroscopic data, X-ray crystallography of a colorless racemic[19] crystal of **8** (Figure 2) (see the Supporting Information for details) unambiguously confirmed the *cis*-configuration of all substituents.

The synthesis of 6-*tert*-butyl-4-hydroxy pipecolic acid **9** was completed by amide hydrolysis of **8** in refluxing 6 N aqueous HCl. After purification on a cation-exchange resin (Dowex 50W), **9** (96:4) was isolated in 65% yield (Scheme 6).

In conclusion, a novel acid catalyzed cascade of reactions leading from the fluorovinylic compound **3a** to the rearranged 4-oxo-pipecolic acid derivate **5** was discovered. The vinylfluoro group was shown to be an acetonyl cation equivalent under acidic conditions. The vinylchloro and vinylbromo groups remain unaffected under the same conditions. Compound **5** was further used to synthesize (2*S*,4*R*,6*R*)-6-*tert*-butyl-4-hydroxypiperidine-2-carboxylic acid (**9**) (30% over four steps starting from **3a**).

Experimental Section

General Procedure for Asymmetric Alkylation (3a as an example). A solution of diisopropyl amine (0.13 mL, 0.94 mmol) in anhydrous THF (2 mL) was cooled to −50 °C and a 1.6 M hexane solution of *n*-BuLi (0.6 mL, 0.94 mmol) was added dropwise, then the reaction mixture was stirred for 30 min. The cosolvent DMPU (1 mL) was added and then the reaction mixture was stirred for 10 min. (*S*)-Boc-BMI (Me) (0.2 g, 0.78 mmol) in anhydrous THF (2 mL) was added to the reaction mixture, which was then stirred for 1 h. The corresponding allylic compound was added to the above reaction mixture, which was allowed to stir overnight at −50 °C. Saturated NH_4Cl solution was added to quench the reaction and extracted with ether (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under vacuum. The pure product was obtained upon column chromatography purification (ethyl acetate/cyclohexane, 1:4).

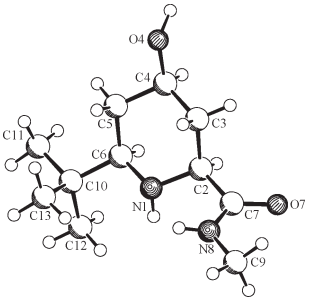
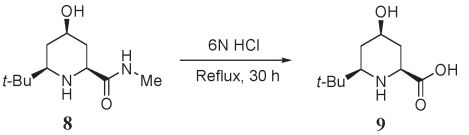


FIGURE 2. X-ray structure of racemic **8**.

SCHEME 6. Synthesis of (2*S*,4*R*,6*R*)-6-*tert*-Butyl-4-hydroxy-pipecolic Acid (9)



8 9

Compound **3a** was isolated as white solid, which was crystallized from pentane: yield 233 mg (95%); mp 79 °C (pentane); $[\alpha]^{20}_D$ −16.5 (*c* 0.515, Et_2O); NMR shows carbamate dynamics with 1:1.5 ratio from ^{19}F NMR; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 9 H), 1.46 (s, 9H), 2.72−2.90 (m, 1H), 2.98 (s, 3H), 3.38 (br s, 1H), 4.08 (d, $^3J_{HH}$ = 5.4 Hz, 1H), 4.23 (dd, $^3J_{HH}$ = 2.4 Hz, $^3J_{HF}$ = 50.1 Hz, 1H *trans*), 4.54 (dd, $^3J_{HH}$ = 2.7, $^3J_{HF}$ = 17.9, 1H *cis*), 4.92 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.8, 28.4, 32.0 (d, $^2J_{CF}$ = 25.9 Hz), 32.3, 41.2, 57.9, 81.4, 81.5, 93.7 (d, $^2J_{CF}$ = 19.4 Hz), 152.9, 162.7 (d, $^1J_{CF}$ = 258.0 Hz), 171.3; ^{19}F NMR (282 MHz, $CDCl_3$) for major rotamer δ −97.05 (m, 1F), for minor rotamer δ −93.20 (m, 1F); MS-ESI, *m*/*z* calcd 315.2084 $[M + H]^+$, 337.1903 $[M + Na]^+$, *m*/*z* found 315.2079 $[M + H]^+$, 337.1900 $[M + Na]^+$; GC-MS, *m*/*z* 257 (32), 201 (79), 157 (52), 57 (100). Anal. Calcd for $C_{16}H_{27}FN_2O_3$ (314.4): C 61.12, H 8.66, N 8.91. Found: C 61.14, H 8.91, N 9.01.

(2*S*,6*R*)-6-*tert*-Butyl-*N*-methyl-4-oxopiperidine-2-carboxamide (5). A solution of compound **3a** (2 g, 6.37 mmol) in a minimum amount of MeOH was treated with a 4 N solution of HCl in water (5 mL) and allowed to reflux for 20 h. The reaction mixture was cooled to room temperature and then extracted with CH_2Cl_2 (2 × 15 mL). The aqueous phase was neutralized (pH 7−8) with a 2 M solution of NaOH and extracted with CH_2Cl_2 (6 × 25 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under vacuum. Column chromatography purification (EtOAc/cyclohexane, 80:20) afforded **5** as white solid: yield 0.77 g (57%); mp 96−97 °C (CH_2Cl_2/MeOH); $[\alpha]^{20}_D$ −22.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.58 (s, 1H), 2.10 (ddd, *J* = 1.0, 12.2, 13.9 Hz, 1H), 2.30 (ddd, *J* = 1.0, 11.8, 14.5 Hz, 1H), 2.46 (ddd, *J* = 1.9, 2.8, 14.1 Hz, 1H), 2.59 (dd, *J* = 2.8, 12.2 Hz, 1H), 2.75 (ddd, *J* = 1.9, 3.8, 14.5 Hz, 1H), 2.86 (d, *J* = 5.0 Hz, 1H), 3.46 (dd, *J* = 3.8, 11.8 Hz, 1H), 6.67 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.3, 26.4, 33.9, 43.7, 45.1, 59.9, 65.1, 172.5, 208.7; MS-ESI, *m*/*z* calcd 213.1603 $[M + H]^+$, 235,1422 $[M + Na]^+$, *m*/*z* found 213.1598 $[M + H]^+$, 235.1414 $[M + Na]^+$; GC-MS, *m*/*z* 212 (10), 155 (55), 154 (50), 112 (60), 96 (100). Anal.

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(19) We were unable to get suitable crystals of enantiopure **8**.

Calcd for $C_{11}H_{20}N_2O_2$ (212.3): C 62.24, H 9.50, N 13.20. Found: C 61.92, H 9.43, N 12.93.

Preparation of Compound 7. Compounds **3a**,**b**,**c** were added to precooled H_2SO_4 at −20 °C and the mixture was allowed to stand for 2 days with occasional shaking. Cold water was added to the reaction flask and neutralized with solid $NaHCO_3$ and then extracted with CH_2Cl_2 (6 × 25 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under vacuum. Column chromatography purification (cyclohexane/acetone, 70:30) afforded **7** as a yellow liquid: yield 412 mg (73%): $[\alpha]^{20}_D$ −27.4 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (s, 9H), 1.97 (s, 3H), 2.43 (dd, J = 8.6, 17.8 Hz, 1H), 2.69−2.85 (m, 4H), 3.75−3.82 (m, 1H), 3.85 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 30.15, 31.3, 37.7, 46.6, 54.2, 83.6, 174.6, 206.9; MS-ESI, m/z calcd 213.1603 $[M + H]^+$, 235.1422 $[M + Na]^+$, m/z found 213.1597 $[M + H]^+$, 235.1414 $[M + Na]^+$; GC-MS, m/z 155 (100), 110 (40), 86 (50), 57 (27).

Reduction of the Ketone 5 to the Alcohol 8. $NaBH_4$ (22 mg, 0.6 mmol) was added at 0 °C to a solution of piperidone **5** (0.25 mmol) in methanol (3 mL). After the solution was stirred for 3 h at 0 °C water (25 mL) was added. The solution was then extracted with CH_2C1_2 three times. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the residue (CH_2C1_2/MeOH, 85:15) yielded the (4*R*)-4-hydroxypipecolic acid amide **8** (contaminated with 4% of 4*S*-diastereomer) as a white solid: yield 46 mg (86%); mp 171−172 °C (EtOAc/pentane); $[\alpha]^{20}_D$ −16.4 (*c* 1.04, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93 (s, 9H), 1.01−1.07 (m, 1H), 1.12−1.18 (m, 1H), 2.01 (ddt, J = 2.2, 4.3, 12.0 Hz, 1H), 2.29 (dd, J = 2.3, 11.5 Hz, 1H), 2.39−2.34 (m, 1H), 2.83 (d, J = 5.0 Hz, 3H), 3.23 (dd, J = 2.8, 11.9 Hz, 1H), 3.70 (tt, J = 4.4, 11.0 Hz, 1H), 6.84 (s, 1H, N*H*Me); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.8, 26.4, 33.3, 35.5, 39.3, 59.2, 63.2, 69.2, 174.3; MS-ESI, m/z calcd 215.1759 $[M + H]^+$, 237.1579 $[M + Na]^+$, m/z found 215.1754 $[M + H]^+$, 237.1569 $[M + Na]^+$; EI-MS, m/z 157 (42), 156 (63), 139 (69), 112 (35), 80 (100), 57 (14).

Hydrolysis of the Amide 8 to the Pipecolic Acid 9. Crude **8** from the previous step was dissolved in 6 N aqueous HCl (20 mL) and the resulting solution was refluxed for 30 h. After concentration under vacuum, the product was treated with saturated aqueous Na_2CO_3 and washed with EtOAc to remove neutral impurities. The aqueous solution was acidified to pH 1 with 6 N HCl and then the solvent was completely removed under reduced pressure. The residue was dissolved in a minimum amount of H_2O and adsorbed on a column of cation-exchange resin (Dowex 50W). The resin was washed with distilled water until neutral and then the amino acid was eluted with 6% aqueous ammonia. The collected solution was concentrated under reduced pressure to give a yellow solid, which was washed with EtOH and lyophilized to give **9** as a yellow solid: yield 147 mg (65%); $[\alpha]^{20}_D$ −32.4 (*c* 1.05, D_2O); ^{1}H NMR (400 MHz, D_2O) δ 1.05 (s, 9H), 1.41−1.54 (m, 1H), 1.58−1.73 (m, 1H), 2.35−2.20 (m, 1H), 2.59−2.41 (m, 1H), 3.05 (dd, J = 2.4, 12.6 Hz, 1H), 3.71 (dd, J = 3.2, 13.4 Hz, 1H), 3.91−4.06 (m, 1H); ^{13}C NMR (101 MHz, D_2O) δ 26.6, 32.8, 33.6, 35.3, 60.2, 65.1, 67.4, 174.1; MS-ESI, m/z calcd 202.1443 $[M + H]^+$, 224.1262 $[M + Na]^+$, m/z found 202.1442 $[M + H]^+$, 224.1258 $[M + Na]^+$; EI-MS, m/z 144 (60), 100 (40), 80 (100).

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Supporting Information Available: Experimental procedures, characterization data, as well as ^{1}H, ^{13}C, and ^{19}F NMR spectra for all new compounds, and crystallographic data of compound **9**. This material is available free of charge via the Internet at http://pubs.acs.org.