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Stereoselective syntheses of 4-fluoro- and 4,4-difluoropipecolic acids

Alexander S. Golubev,[a,b] Hartmut Schedel,[a] Gabor Radics,[a] Joachim Sieler[c] and Klaus Burger[a,*]

[a]*Department of Organic Chemistry, University of Leipzig, Johannisallee 29, D-04103 Leipzig, Germany*
[b]*Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov str. 28, GSP-1, V-334, Rus-117813 Moscow, Russia*
[c]*Department of Inorganic Chemistry, University of Leipzig, Linnestraße 3, D-04103 Leipzig, Germany*

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Abstract—Stereoselective syntheses of 4-fluoro- and 4,4-difluoropipecolic acids starting from Z-protected 4-hydroxy- and 4-oxopipecolates via fluorodehydroxylation and fluorodeoxygenation are described.

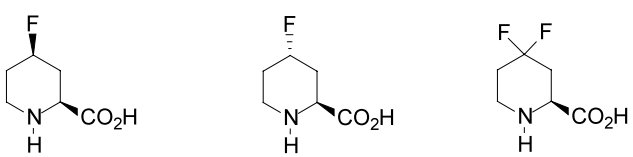
Coplanarity of peptide bonds confers partitioning of peptide chains between two energetically preferred rotational states, *cis* and *trans*. This molecular heterogeneity is particularly pronounced when imino acids like proline or pipecolic acid form peptide bonds.[1] Recent studies revealed some characteristical differences in respect to thermodynamics and kinetics of the *cis–trans* isomerism about pipecolic acid peptide bonds compared with prolines.[2]

Peculiarities of the prolyl peptide bond isomerism in 4-fluorine-containing (*S*)-prolines turned out to be of particular interest and importance rendering (2*S*,4*R*)-4-fluoro- and (2*S*,4*S*)-4-fluoroprolines an excellent tool for targeted protein design.[3] The unique nature of the element fluorine with its combination of strong electronegativity and low steric demand, and on the other hand the option to use ^{19}F NMR spectroscopy in the absence of endogenous organic fluorocompounds provide fluorine-containing molecules with a series of useful biochemical and biomedicinal characteristics.[4] Therefore, fluorine-containing pipecolic acid derivatives represent an interesting new tool for studies of the *cis–trans* isomerization of the peptide bond, for peptide and protein folding experiments, and for the design of new types of peptidomimetics.

Herein, we describe the first syntheses of 4-fluoro- and 4,4-difluoropipecolic acids. The synthetic strategy is based on DAST fluorination of 4-hydroxy- and 4-oxopipecolic acid derivatives, respectively. In contrast to the *trans*-4-hydroxy-(*S*)-proline, 4-oxygenated pipecolic acids, although present as constituent of natural products,[5] are not commercially available to the best of our knowledge (Scheme 1).

A series of synthetic approaches to enantiopure 4-oxygenated pipecolic acids have been recently described.[6] The iminium ion cyclization of homoallylic amines with glyoxylic acid attracted our interest because of its preparative elegance, the ready accessibility of reagents, and the availability of both (2*S*)- and (2*R*)-configurated 4-oxygenated pipecolic acids.

A mixture of *cis*-4-hydroxy esters (in a ratio of 2:1) was obtained according to Skiles et al.[7b] on reaction of homoallylic amine **1** with glyoxylic acid in a mixture of acetonitrile/water (1:1) followed by treatment with ammonia-containing methanol. Diastereomers **2** and **3** can be easily separated by column chromatography on silica gel even on a 20 g scale (Scheme 2).



Scheme 1.

Keywords: 4-hydroxypipecolic acid; 4-oxopipecolic acid; 4-fluoropipecolic acid; 4,4-difluoropipecolic acid; DAST; fluorodehydroxylation; fluorodeoxygenation.

* Corresponding author. Fax: (49) 341 9736599; e-mail: burger@organik.chemie.uni-leipzig.de

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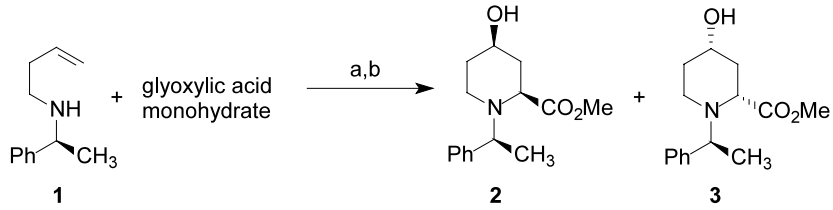


Scheme 2. *Reagents*: (a) acetonitrile–H_2O (1:1), 20°C; (b) CH_3OH, NH_3 (cat).

First, we tried the direct fluorodehydroxylation of *cis*-4-hydroxypipecolic esters **2** and **3** with DAST in CH_2Cl_2. We found that fluorodehydroxylation of (2*S*,4*R*)-4-hydroxypipecolic ester **2** gave a mixture of two fluorine-containing compounds in modest yields. Based on 2D NMR measurements, these compounds were assigned the structure of (2*S*,4*S*,2′*S*)-4-fluoropipecolate **4** and (2*R*,4*R*,2′*S*)-4-fluoropipecolate **5**. Surprisingly, a mixture of the same compounds was obtained on DAST fluorodehydroxylation of (2*R*,4*S*)-4-hydroxypipecolic ester **3** (Scheme 3).

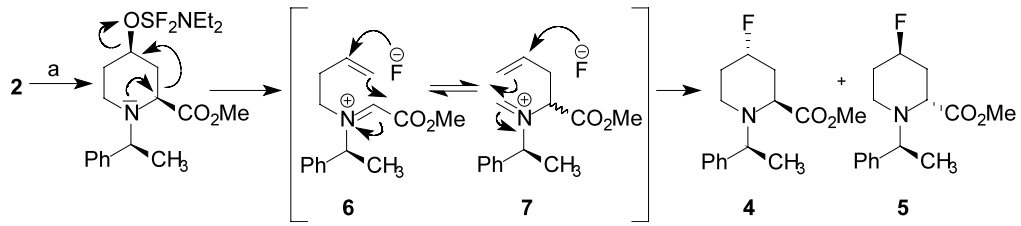
A fragmentation process of the Grob type seems to be a plausible explanation for the experimental facts.[8] Formation of the iminium ions **6** and **7** accounts for the observed epimerization at C-2 of the piperidine ring.[9] The anchimeric assistance of the methoxycarbonyl group is responsible for the exclusive formation of the *trans* fluoroderivatives **4** and **5**. This effect only operates when the methoxycarbonyl group is placed in axial position favoring an equatorial attack of the fluoride ion. Therefore, compounds **2** and **3** are of no use for a direct stereoselective fluorodehydroxylation with DAST.

Consequently, we changed the *N*-protection group, regarding Z-protected 4-hydroxypipecolic acids being more suitable for a DAST fluorination. The electron-withdrawing effect of both the Z-group and the methoxycarbonyl group should reduce the tendency to undergo a Grob fragmentation during the fluorination step in favour of the desired S_N2 substitution process. The Z-protected methyl *cis*-4-hydroxy-(*S*)-pipecolate **8** was obtained from ester **2** on catalytic hydrogenation and Z-protection in 84% yield. Mitsunobu inversion in THF with DEAD and formic acid and subsequent methanolysis gave *trans*-4-hydroxy-(*S*)-pipecolate **10** in 53% yield.[10] The standard Mitsunobu protocol was successfully applied without modifications recommended in the literature (Scheme 4).[11]

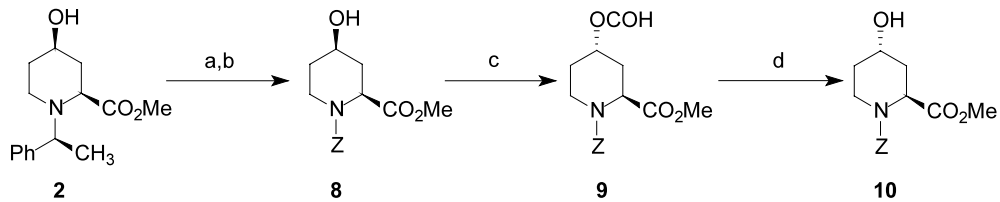
DAST fluorodehydroxylation of Z-protected *cis*-4-hydroxypipecolate **8** in THF afforded *trans*-4-fluoro-(*S*)-pipecolate **11** in 60% yield. The latter was deprotected to give *trans*-4-fluoro-(*S*)-pipecolic acid **13**.[12] Likewise, Z-protected *trans*-4-hydroxy-(*S*)-pipecolate **10** was transformed into *cis*-4-fluoro-(*S*)-pipecolate **14** and subsequently into *cis*-4-fluoro-(*S*)-pipecolic acid **16** (Scheme 5).[13]

Z-Protected methyl 4-oxo-(*S*)-pipecolate **17** was obtained from *cis*-4-hydroxypipecolate **8** by Swern oxydation in 85% yield. DAST fluorodeoxygenation of γ-ketoester **17** afforded 4,4-difluoroderivative **18** in 39% yield, which was deprotected to give 4,4-difluoro-(*S*)-pipecolic acid **20** (Scheme 6).[14]

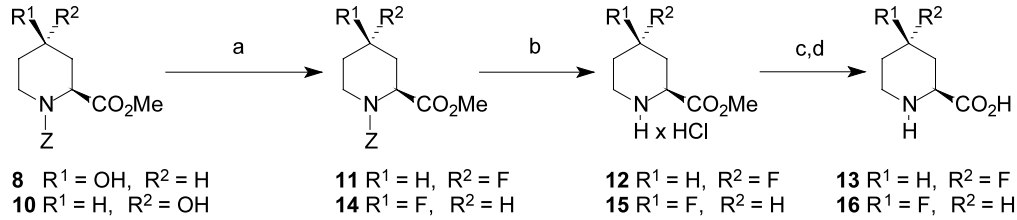
The configuration of compound **15** was determined by X-ray structural analysis of the Mosher derivative **21**[15] synthesized from (*R*)-α-methoxy-α-trifluoromethyl phenylacetic acid chloride (Fig. 1). Using the chiral center of the substructure introduced by Mosher's



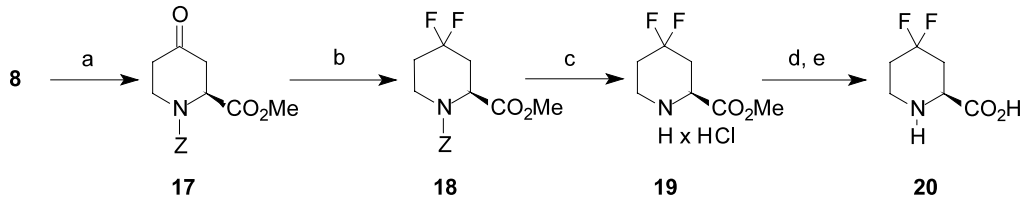
Scheme 3. *Reagents*: (a) DAST, dichloromethane.



Scheme 4. *Reagents*: (a) $Pd(OH)_2/C$, H_2, HCl in methanol; (b) Z-Cl, 1 M Na_2CO_3, 0°C; (c) DEAD, Ph_3P, HCO_2H, THF, 5°C; (d) CH_3OH, HCl (cat.).



Scheme 5. *Reagents*: (a) DAST, THF, −50°C to rt; (b) $Pd(OH)_2/C$, H_2, HCl in methanol; (c) 6N HCl, 90°C; (d) propylene oxide.



Scheme 6. *Reagents*: (a) DMSO, $(COCl)_2$, Et_3N; (b) DAST, THF; (c) $Pd(OH)_2/C$, H_2, HCl in methanol; (d) 6N HCl, 90°C; (e) propylene oxide.

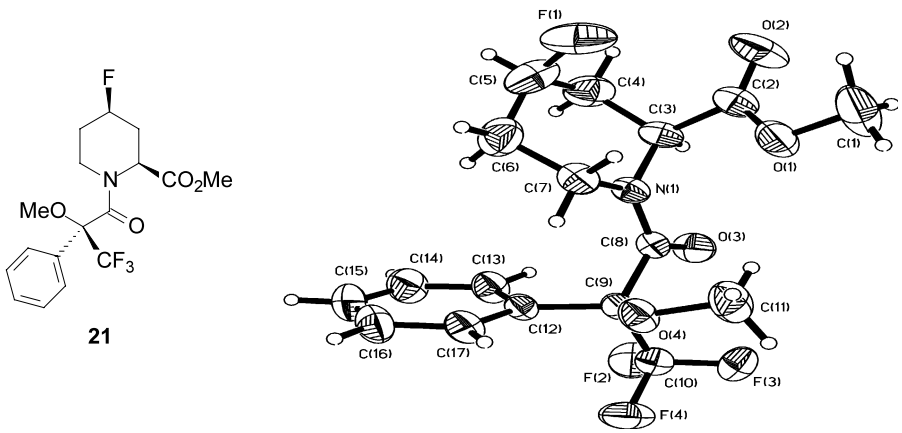


Figure 1. ORTEP plot of **21** showing the (*S*)-configuration of C(2) and (*R*)-configuration of C(4).

reagent—which is (*S*)-configurated as a reference—we unequivocally can assign C-2 (*S*) and C-4 (*R*) configuration. Thus, the configuration of compound **15** determined by hetero NOE experiments was confirmed by X-ray structural analysis.

The three enantiomers of amino acids **13**, **16**, and **20**, namely *trans*-4-fluoro-, *cis*-4-fluoro- and 4,4-difluoro-(*R*)-pipecolic acid are obtainable from (2*R*,4*S*,2′*S*)-4-hydroxypipecolate **3** using the same synthetic strategy.

Investigations of the effects induced by the incorporation of the new 4-fluoropipecolic acids into peptides and proteins on the energetics of the isomerization of the pipecolic peptide bond and the consequences on peptide and protein folding are in progress.

Acknowledgements

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12. *trans*-4-Fluoro-(*S*)-pipecolic acid (**13**): colorless crystals; mp 260–264°C (dec.); $[\alpha]_D=-21$ ($c=1$, H_2O); IR (KBr) ν 3431, 2967, 1632, 1398 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 1.70–1.96 (m, 2H), 2.07 (m, 1H), 2.43 (m, 1H), 3.11–3.48 (m, 2H), 3.73–3.79 (dd, $J=13$, 3 Hz, 1H), 5.03 (dm, $J=48$ Hz, 1H); ^{13}C NMR (D_2O, 75 MHz) δ 26.28 (d, $J_{CF}=21$ Hz), 31.11 (d, $J_{CF}=21$ Hz), 38.48, 53.91, 85.40 (d, $J_{CF}=168$ Hz), 173.92; ^{19}F NMR (D_2O, 280 MHz) δ −108.60 (m).
13. *cis*-4-Fluoro-(*S*)-pipecolic acid (**16**): white powder; mp 269–271°C (dec.); $[\alpha]_D=-11$ ($c=1$, H_2O); IR (KBr) ν 3427, 2951, 1630, 1385 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 1.90 (m, 1H), 2.02–2.28 (m, 2H), 2.51 (m, 1H), 3.09 (m, 1H), 3.53 (m, 1H), 3.94 (ddd, $J=10$, 4, 1 Hz, 1H), 4.92 (dm, $J=47$ Hz, 1H); ^{13}C NMR (D_2O, 75 MHz) δ 27.67 (d, $J_{CF}=22$ Hz), 31.27 (d, $J_{CF}=22$ Hz), 39.54 (d, $J_{CF}=10$ Hz), 54.88 (d, $J_{CF}=8$ Hz), 86.70 (d, $J_{CF}=172$ Hz), 171.96; ^{19}F NMR (D_2O, 280 MHz) δ −99.87 (d, $J=43$ Hz).
14. 4,4-Difluoro-(*S*)-pipecolic acid (**20**): white powder; mp 274–276°C (sealed tube, dec.); $[\alpha]_D=-20$ ($c=1$, H_2O); IR (KBr) ν 3435, 2976, 2474, 1611 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 2.05–2.35 (m, 3H), 2.59 (m, 1H), 3.15 (td, $J=14$, 3 Hz, 1H), 3.50 (m, 1H), 3.81 (ddd, $J=12$, 4, 2 Hz, 1H); ^{13}C NMR (D_2O, 75 MHz) δ 29.98 (t, $J_{CF}=26$ Hz), 34.12 (t, $J_{CF}=26$ Hz), 40.12 (d, $J_{CF}=10$ Hz), 56.33 (d, $J_{CF}=8$ Hz), 120.03 (dd, $J_{CF}=245$, 240 Hz), 172.02; ^{19}F NMR (D_2O, 280 MHz) δ −17.18 (d, $J_{FF}=241$ Hz, 1F), −23.99 (dm, $J_{FF}=241$ Hz, 1F).
15. X-Ray crystallographic data for **21**: Single crystals were grown from diethyl ether/hexane as colorless crystals; mp 131–133°C; $[\alpha]_D=-74$ ($c=1$, $CHCl_3$); monoclinic space group $P2_1$; $T=223$ K; $a=8.057(10)$, $b=12.011(1)$, $c=9.072(1)$ Å, $\beta=97.07(1)°$; $V=871.3(2)$ $Å^3$; $Z=2$; $D_{calcd}=1.438$ g/cm^{-3}; (STADI 4 Vierkreisdiffraktometer STOE); omega-theta-scans (0.3°); 4850 data collected; 4639 independent reflections; ($R_{int}=0.012$); for structure solution and anisotropic refinement SHELXL-97 and SHELXS-93 (Sheldrick, G. M., Göttingen, 1997) were used; $R_1=0.0385$; $wR_2=0.0989$ [$I>2\sigma(I)$]; $R_1=0.0570$; $wR_2=0.1086$ for all data. Crystallographic data for the structural analysis in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 167289. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).