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An Efficient Approach to the Family of 4-Substituted Pipecolic Acids. Syntheses of 4-Oxo-, *cis*-4-Hydroxy-, and *trans*-4-Hydroxy-L-pipecolic Acids from L-Aspartic Acid[1,2]

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Key words: 4-Oxo-L-pipecolic acid, 4-hydroxy-L-pipecolic acids, L-aspartic acid, hexafluoroacetone, intramolecular Michael addition, Stille reaction

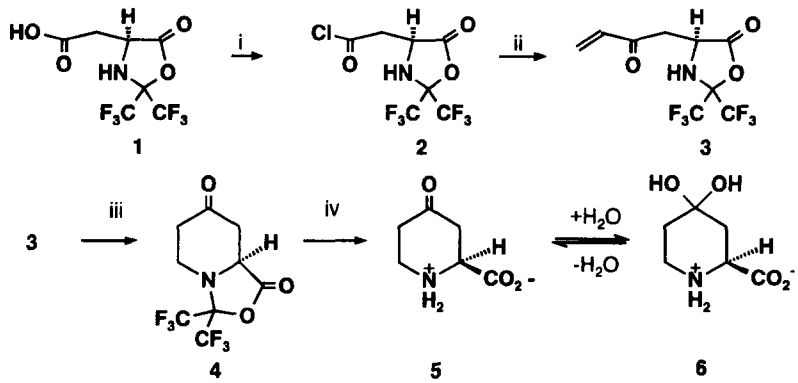
Abstract: Syntheses of 4-oxo-, *cis*-4-hydroxy-, and *trans*-4-hydroxy-L-pipecolic acids from L-aspartic acid using hexafluoroacetone as protecting reagent are described. Combination of a Stille cross-coupling reaction with subsequent Lewis acid catalyzed intramolecular Michael addition provides 4-oxo-L-pipecolic acid **5** or *trans*-6-methyl-4-oxo-L-pipecolic acid. Borohydride reduction of the protected 4-oxo-L-pipecolic acid derivative gives the corresponding *cis*-4-hydroxy-L-pipecolic acid **8**. The *trans* isomer **10** is obtained in good yield via Mitsunobu inversion.

4-Substituted pipecolic acids are of biological interest. In particular, 4-oxo-L-pipecolic acid is a constituent of the virginiamycins, a family of cyclopeptides with antibiotic activity[4]. *Trans*-4-hydroxy-L-pipecolic acid is a naturally occurring amino acid isolated from *Acacia* species[5]. The 4-phosphono derivative of *cis*-4-hydroxypipecolic acid represents a N-methyl-D-aspartate antagonist[6]. Several syntheses of racemic 4-oxopipecolic acid have been developed[7]. Enantiomerically pure 4-oxo-L-pipecolic acid was obtained on oxidation of suitably protected *cis*-4-hydroxy-L-pipecolic acid[4b,8,9]. The latter was produced by hydrogenation of pyridine derivatives followed by enzymatic or quinine resolution of the racemic *cis*-4-hydroxypipecolic acid[8].

Our approach starts from L-aspartic acid as homochiral precursor and hexafluoroacetone (HFA) as protecting reagent. Hexafluoroacetone and L-aspartic acid react to give compound **1**[10]. On reaction with thionyl chloride the acid chloride **2** is formed[11]. **2** is coupled with vinyltrimethyltin or vinyltributyltin in the presence of a palladium catalyst according to the Stille protocol[12] to give the enone **3**.

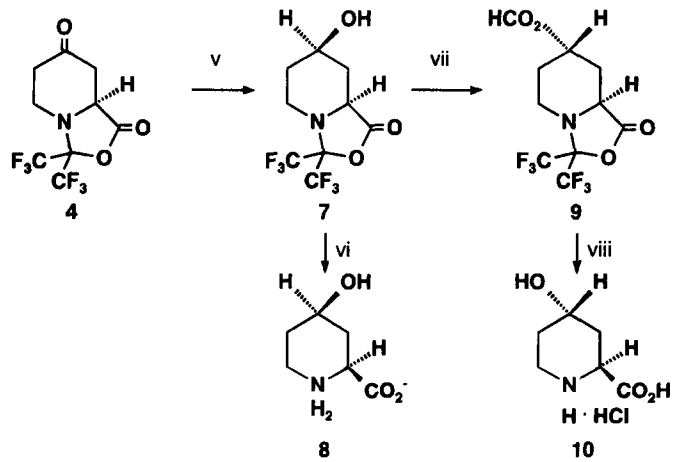
The crucial step of our strategy consists of an intramolecular Michael addition (6-endo-trig[13]) of the enone **3**, proceeding smoothly under reflux in benzene in the presence of $BF_3 \cdot Et_2O$ to give HFA-protected 4-oxo-L-pipecolic acid **4**[14] in 50-55% yield. Simultaneous deprotection of the vicinal amino and carboxylic functions proceeds under very mild conditions (*i*-PrOH/H_2O, 50:50, v/v) at room temperature to give 4-oxo-L-pipecolic acid **5**. The unprotected amino acid **5** was transformed into its

hydrochloride and purified by crystallization. According to the ^{1}H and ^{13}C NMR spectra in D_2O the free amino acid as well as its hydrochloride predominantly exist as the geminal diols **6**[15].



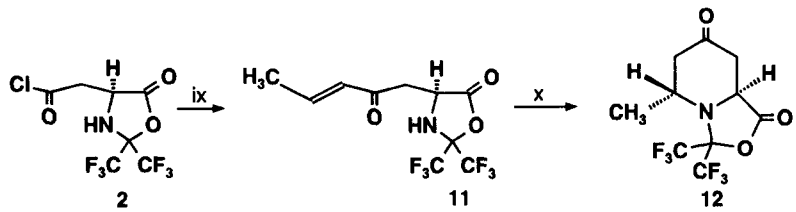
i) $SOCl_2$, reflux, 84%; ii) CH_2=CH-$SnMe_3$ or CH_2=CH-Sn(*n*-Bu)$_3$, $PhCH_2Pd(PPh_3)_2Cl$, dimethoxyethane, 67 or 58%; iii) $BF_3{\cdot}OEt_2$, benzene, reflux, 55-60%; iv) H_2O/*i*-PrOH, 100%.

The reduction of compound **4** with $NaBH_4$ in the presence of pentafluorophenol[16] exclusively gives the HFA-protected *cis*-4-hydroxy-L-pipecolic acid derivative **7**. L-*Cis*-4-hydroxy-L-pipecolic acid **8** is obtained after deprotection with *i*-PrOH/H_2O[17]. Mitsunobu reaction[18] with compound **7**, which is most favourably carried out with formic acid, affords the *trans*-4-hydroxy-L-pipecolic acid derivative **9**. Deprotection of the amino and carboxylic functions again is achieved on treatment with *i*-PrOH/H_2O. Treatment with 6N HCl is necessary to deblock the hydroxy group. *Trans*-4-hydroxy-L-pipecolic acid was characterized as hydrochloride **10**[19].



v) C_6F_5OH, $NaBH_4$, 80%; vi) H_2O/*i*-PrOH, 100%; vii) DEAD, PPh_3, HCO_2H, 78%; viii) 1. H_2O/*i*-PrOH, 2. 6N HCl, 85%.

Further, we investigated the scope and limitations of the intramolecular Michael addition using various substituted enones as starting material. The *trans* substituted α,β-unsaturated ketone **11** gives the corresponding 6-methyl-4-oxo-L-pipecolic acid derivative **12**[20]. The cyclization reaction proceeds rather slowly but highly stereoselective to give **12** in 30% yield. A cross peak in the NOESY spectrum of the bicyclic compound **12** between the signals of the methyl group and of the angular proton proves that the methyl group occupies the *trans*-position in **12**. Therefore, the absolute configuration of **12** is (5S,9R). All protons were assigned unambiguously by a DQF-COSY spectrum.
However, no cyclization products were observed when the corresponding phenyl, methoxycarbonyl or dimethyl substituted enones were treated under similar reaction conditions.



ix) R-CH=CH-Sn(*n*-Bu)$_3$, $Pd_2(DBA)_3 \cdot CHCl_3$, toluene; x) $BF_3 \cdot OEt_2$, benzene, reflux, 30%.

The construction of *trans*-configured 6-alkyl substituted L-pipecolic acid derivatives is of current interest since they represent a key precursor to the family of several antibiotic compounds like solenopsin A[21].
Experiments to transform the HFA-protected 4-oxo-D-pipecolic acid (optical antipode of **4**) into *cis*-4-(phosphonomethyl)-D-pipecolic acid and *cis*-4-(1H-tetrazol-5-yl-methyl)-D-pipecolic acid - both selective NMDA antagonists[22] - are under way.

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14. **4**: m.p. 63°C; $[\alpha]_D^{22}$ -31.2 (c 1.0; $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): 3.89 (dd, J = 11.8, 2.6 Hz, 1H, H5); 3.74 (dd, J = 11.6, 7.4 Hz, 1H, H9); 3.16 (m, 1H, H9); 2.86 (ddd, J = 14.7, 3.4, 1.6 Hz, 1H, H8); 2.68-2.48 (m, 3H, H8, H6); ^{13}C NMR (50.3 MHz, $CDCl_3$): 201.9 (C7); 166.7 (C4); 121.4 (q, J = 293.9 Hz, CF_3); 120.2 (q, J = 286.9 Hz, CF_3); 88.6 (sept, J = 33.5 Hz, C2); 55.5 (C5); 42.7; 42.3; 40.1 (C6, C8, C9); ^{19}F NMR (235.3 MHz, $CDCl_3$): 3.07 (q, J = 8.4 Hz, 3F, CF_3); -0.30 (q, J = 8.4 Hz, 3F, CF_3); IR (KBr, cm^{-1}) 1847 (C=O); 1721 (C=O). Anal. Calcd for $C_9H_7F_6NO_3$: C, 37.13; H, 2.42; N, 4.81. Found: C, 37.30; H, 2.39; N, 4.87.
15. **6**·HCl: m.p. 194°C (dec); lit[4a] 194°; $[\alpha]_D^{22}$ +4.1 (c 0.55; H_2O); lit[5] $[\alpha]_D^{21}$ +3.8 (2%, H_2O); The ^1H NMR spectrum (360 MHz, D_2O) consists of two sets of signals. The first set essentially coincides with the ^1H NMR spectra given for **6**·HBr (ref. 7d) and corresponds to the geminal diol form **6**·HCl (97.4% as evaluated from ^1H NMR spectrum); the second set of signals corresponds to the keto form **5**·HCl (2.6%); ^{13}C NMR (50.3 MHz, D_2O): 172.6 (COOH); 92.4 (C4); 56.5 (C2); 42.5 (C6); 38.7 (C3); 35.2 (C5) (geminal diol form); 206.7 (C4); 171.7; 57.4; 42.8; 41.2; 37.9 (keto form). Anal. Calcd for $C_6H_9NO_3 \cdot HCl \cdot H_2O$: C, 36.47; H, 6.12; N, 7.09. Found: C, 36.75; H, 5.92; N, 7.42. Some examples of an equilibrium between the keto form and the geminal diol form in 4-oxo-2-aminoacids are described, see: Whitten, J.P.; Barney, C.L.; Huber, E.; Bey, P.; McCarthy, J.R. *Tetrahedron Lett.* **1989**, *30*, 3649.
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20. **12**: m.p. 48°C; $[\alpha]_D^{22}$ -35.2 (c 1.25; $CHCl_3$); ^1H NMR (360 MHz, acetone-d_6): 4.69 (dd, J = 8.2, 7.6 Hz, 1H, H5); 4.27 (dq, J = 6.8, 6.5 Hz, 1H, H9); 2.79 (dd, J = 14.1, 6.5 Hz, 1H, H8); 2.68-2.64 (m, 2H, H6); 2.27 (br. d, J = 14.1 Hz, 1H, H8); 1.24 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): 202.5 (C7); 167.5 (C4); 120.5 (q, J = 289.4 Hz, CF_3); 120.2 (q, J = 289.4 Hz, CF_3); 50.2; 47.5; 46.7; 42.3 (C5, C6, C8, C9); 17.3 (CH_3); ^{19}F NMR (235.3 MHz, $CDCl_3$): 1.32 (q, J = 8.4 Hz, 3F, CF_3); -0.22 (q, J = 8.4 Hz, 3F, CF_3). Anal. Calcd for $C_{10}H_9F_6NO_3$: C, 39.36; H, 2.97; N, 4.59. Found: C, 39.20; H, 2.97; N, 4.55.
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