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A Convenient Synthesis of 3-Substituted Pipecolic Acid Methyl Esters

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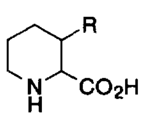
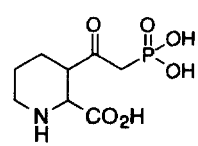
Abstract: A practical synthesis of the title compounds (**3a-c, e**) from commercially available 3-hydroxy-2-pyridine carboxylic acid (**4**) is reported. The key step in the synthetic sequence involves a Pd-catalyzed cross coupling reaction of the triflate **6** with the appropriate alkyl or aryl derivatives to generate the substituted picolinic acid esters **7a-b, 8** and **11**. Catalytic reduction of these picolinic acid esters provided the title compounds in good yields.

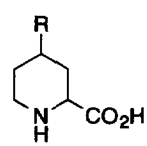
As a part of ongoing efforts to develop conformationally-constrained analogs of peptide based protease inhibitors,[2,3] we required a number of 3-substituted pipecolic acids **1**. Although a number of methods are available for the synthesis of 4-substituted pipecolic acids **2**,[4] only a few reports on the synthesis of the corresponding 3-substituted analog **1** have been published.[4,5,6] More importantly, these reports are mainly directed towards the synthesis of the methyl analog **1a** and the β-ketophosphonate **1b**.[6] Hampered by the lack of success in extending these methodology for the synthesis of other 3-substituted analogs, we pursued alternate methods for the synthesis of them. Herein, we report the successful synthesis of the title compounds from commercially available starting materials.



1a

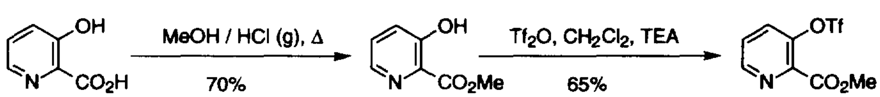


1b



2

Our synthesis began with readily available 3-hydroxy-2-pyridinecarboxylic acid (**4**). Esterification of **4** (methanolic HCl, reflux) gave the corresponding methyl ester **5** in >70 yield.[7] Treatment of **5** with Tf_2O and Et_3N (CH_2Cl_2, rt., 2 h) provided triflate **6** in 65% yield, which served as the common intermediate for the synthesis of all the target compounds.

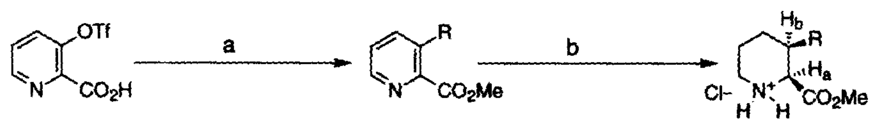


4 **5** **6**

The preparation of 3-methyl and 3-ethyl (compounds **3a-b**) derivatives is shown in **Scheme 1**. Thus, treatment of **6** with either tetramethyltin or vinyl tributylstannane in the presence of 3 mole% $PdCl_2(PPh_3)_2$ and 3 eq. LiCl in DMF at 100 °C, gave the desired Stille coupling adducts **7a, b** in 50 and 80% yield respectively.[8]

Catalytic hydrogenation of **7a, b** (60 psi H_2, PtO_2, EtOH/4N HCl)[4] gave the pipecolic acid methyl esters **3a, b** as their hydrochloride salts in quantitative yields. The cis stereochemistry between the 2 and 3 substituents in **3a, b** was established by the observed coupling constant of 4.1 Hz between H_a and H_b in the ^1H NMR (D_2O) spectra. A similar assignment of cis stereochemistry between the substituents in the corresponding 3-methylpipecolic acid (**1**, R = Me) has been reported by Shuman et al.[4]

Scheme 1

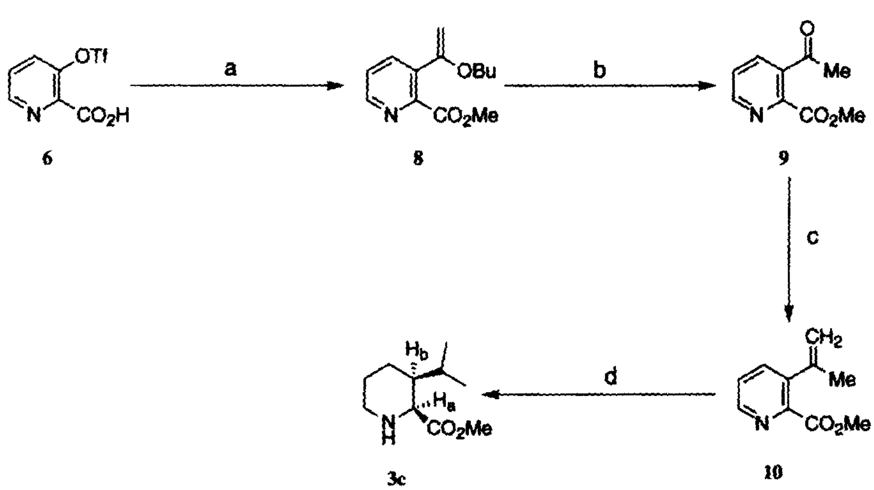


6   **7a**, R = Me; **b**, R = CH=CH$_2$ **3a**, R = Me; **b**, R = Et

a) Me_4Sn or n-Bu_3SnCH=CH2, $PdCl_2(PPh_3)_2$, LiCl, DMF, 100 °C b) H_2 (60 pSi), PtO_2, EtOH, 4N HCl.

The synthesis of the 3-isopropyl analog **3c** (**Scheme 2**) employed a Pd(II) catalyzed Heck reaction[9] between **6** and n-butylvinylether. Heating a DMF solution of **6** and n-butylvinyl ether in the presence of Et_3N and 3 mole% $Pd(OAc)_2$ and 1,3-bis(diphenylphosphino)propane (dppp) resulted in the exclusive formation of α-coupled adduct **8**.[10] Hydrolysis of **8** gave the intermediate methyl ketone **9**, which underwent Wittig methylenation to yield the desired olefin **10**. Hydrogenation of **10** gave the isopropyl analog **3c** in near quantitative yield, which was isolated as the free amine. Again, the cis stereochemistry between the C-2 and C-3 substituents was established via ^1H NMR data.

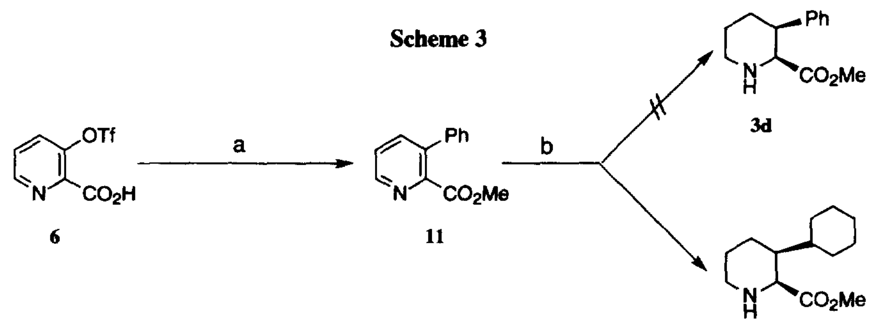
Scheme 2



a) n-BuOCH=CH2, $Pd(OAc)_2$, dppp, DMF, 70 °C b) 4N HCl, HOAc, c) Ph_3P=CH2
d) H_2 (60 pSi), PtO_2, EtOH, 4N HCl.

Synthesis of the cyclohexyl substituted derivative **3e** (**Scheme 3**) began with a Suzuki coupling[11] of **6** with phenyl boronic acid (3 mole% $Pd(PPh_3)_4$, K_2CO_3, Toluene, 90 °C)[12] to give methyl-3-phenyl-picolinate (**11**) in 80% yield. Hydrogenation of **11** gave the cyclohexyl derivative **3e** as the only isolable product.[13] Compound **3e** is a conformationally constrained analog of the important unnatural amino acid cyclohexyl alanine (*Cha*) used widely in peptidomimetic inhibitor design.

Scheme 3



6 11 3d 3e

a) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, $PhCH_3$, 90 °C b) H_2 (60 pSi), PtO_2, EtOH, 4N HCl.

In conclusion, we have developed a novel and practical method for the synthesis of 3-substituted pipecolic acid esters. Work is underway to hydrolyze the esters **3a-c, e** and incorporate them into peptide-based protease inhibitors.[14] The results of these studies will be reported in due course.

References and Notes:

1. Address all Correspondence to the author at Affymax Research Institute, 3410 Central Expressway, Santa Clara, CA 95051-0703
2. The incorporation of conformationally-constrained amino acids into peptide based inhibitors of proteases have been shown to improve their stability towards proteolytic enzymes and hence improve their biological half life. e.g.: see Thaisrivongs, S.; Pals, D.T.; Turner, S.R.; Kroll, L.T. *J. Med. Chem.* **1988**, *31*, 1369.
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4. Shuman, R.T.; Ornstein, P.L.; Paschal, J.W.; Gesellchen, P.D. *J. Org. Chem.* **1990**, *55*, 738 and references therein.
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6 The synthesis and use of optically pure 3-substituted (and 3,3-disubstituted) pipecolic acids as conformationally constrained glutamate antagonists have been reported. For e.g.: see, (a) Whitten, J.P.; Muench, D.; Cube, R.V.; Nyce, P.L.; Baron, B.M.; McDonald, I. *BioMed. Chem. Lett.* **1991**, *1*, 441. (b) Whitten, J.P.; Cube, R.W.; Baron, B.M.; McDonald, I. *ibid*, **1993**, *3*, 19. (c) Claesson, et al. *ibid*, **1992**, *2*, 1247.

7. Esterification of acid **4** using diazomethane to give **5** has been reported. However, the authors report that they obtained only very low yields of 5 under other esterification conditions. cf. Drummond, J. et al. *J. Med. Chem.* **1989**, *32*, 2116.

8. Echavaren, A.M.; Stille, J.K. *J. Am. Chem. Soc.* **1987**, *109*, 5478

9. Heck, R.F. *Org. React. 1982*, **27**, 345

10. Pendrak, I.; Chambers, P.A. *J. Org. Chem.* **1995**, *60*, 3249

11. Suzuki, A.; Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh. *J. Am. Chem. Soc.* **1989**, *111*, 314.

12. Shieh, W.C.; Carlson, J.A. *J. Org. Chem.* **1992**, *57*, 379.

13. All new compounds reported here were characterized via a combination of ^{1}H NMR, IR and electrospray mass spectra.

14. Hydrolysis of the Cbz-protected derivatives of esters **3a, c** could be cleanly achieved using 2N NaOH in MeOH at 70 °C. The resulting pipecolic acids were a 1:1 mixture of the cis and trans isomers. This result is not surprising, because it has been reported by Shuman et al (ref. 4), that when the hydrogenation of the pyridine ring was carried out in the presence of 1M KOH, a 60:40 mixture of the corresponding DL cis and DL trans substituted pipecolic acids were obtained.

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