ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

6-Alkynyl- and 6-Aryl-Substituted (*R*)-Pipecolic Acid Derivatives

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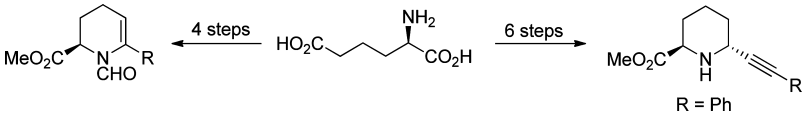
Received April 18, 2013

ABSTRACT



(*R*)-α-Aminoadipic acid is a readily available enantiomerically pure starting material for the synthesis of (*R*)-pipecolic acid and its derivatives. Sonogashira or Suzuki cross-coupling reactions of an *N*-formyl pipecolate-derived vinyl bromide furnish 6-alkynyl or aryl derivatives. Reduction with sodium cyanoborohydride and subsequent *N*-deformylation provide 6-alkynyl substituted (*R*)-pipecolic acid derivatives, valuable building blocks for amino acid and peptide chemistry.

Amino acids are versatile chiral pool building blocks in peptide chemistry, organic synthesis, and organocatalysis.[1] D-Amino acids are not as abundant in Nature as the L-configured counterparts. However, D-amino acids significantly influence the conformation of e.g. cyclic peptides.[2] α-Aminoadipic acid, the homologue of glutamic acid, is a naturally occurring amino acid found in green plants and microorganisms.[3,4] It is an intermediate in lysine metabolism.[5] (*R*)-α-Aminoadipic acid **1** constitutes the acyl substituent present in penicillin N and cephalosporin C. It is cleaved in the semisynthesis of β-lactam antibiotics to give 7-aminocephalosporanic acid (7-ACA), which is subsequently acylated in order to introduce different side chains. Only recently, an enzymatic process was developed, which provides (*R*)-α-aminoadipic acid in large quantities by cleavage from the fermentation product cephalosporin C using cephalosporin acylase.[6]

(*R*)-α-Aminoadipic acid has been proven to be a convenient chiral pool starting material for the synthesis of (*R*)-pipecolic acid and its derivatives.[7] Pipecolic acid, also known as homoproline or piperidine-2-carboxylic acid, is a component of several secondary metabolites in plants and fungi. (*S*)-Pipecolic acid occurs in many natural products with interesting biological activities, like the anticancer agent VX710,[8] the antibiotic sandramycin,[9] the immunosuppressants FK 506[10] and rapamycin,[11] the histone deacetylase (HDAC) inhibitors WF-3161 and Cyl-2,[12] and the ATPase inhibiting efrapeptins and neo-efrapeptins.[13] (*R*)-Pipecolic acid is a constituent of the HDAC inhibitors trapoxin A and apicidin.[14] Substituted derivatives of pipecolic acid are valuable building blocks for

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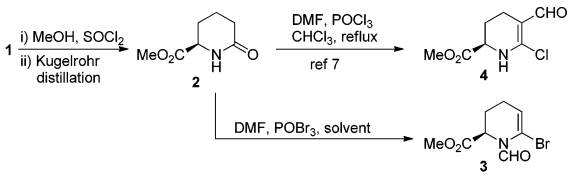
10.1021/ol4010728

structure–activity relationship studies. It is assumed that 6-substituted derivatives of pipecolic acid can act as mimics of *cis*-prolyl peptide bonds as compared to the 5-substituted proline derivatives.[15] They exhibit potential bioactivity and also serve as starting material for the synthesis of biologically active piperidine alkaloids.[16] However, only a few routes are available for the synthesis of 6-substituted pipecolic acid derivatives.[17] Therefore, it was of interest to synthesize 6-substituted derivatives of pipecolic acid which could be further incorporated into peptides for conformational studies.

Methyl 6-oxopipecolate **2** was prepared from (*R*)-α-aminoadipic acid by esterification and subsequent lactamization during Kugelrohr distillation in excellent yield according to a protocol published for (*S*)-6-oxopipecolic acid.[18] Vilsmeier–Haack reaction of amides or lactams is reported to give compounds like the 5-formyl-6-halogenated derivative **4**.[7,19] Treatment of **2** with DMF and $POBr_3$ under different conditions gave **3** (Scheme 1). Interestingly, similar compounds, e.g. triflates, are obtained in much more complicated procedures.[22a] *N*-Formylated products have been reported[20] as intermediates that are deformylated upon addition of excess $POCl_3$. However, in our case the *N*-formyl compound **3** was formed as the only product as confirmed by DEPT and HSQC experiments.

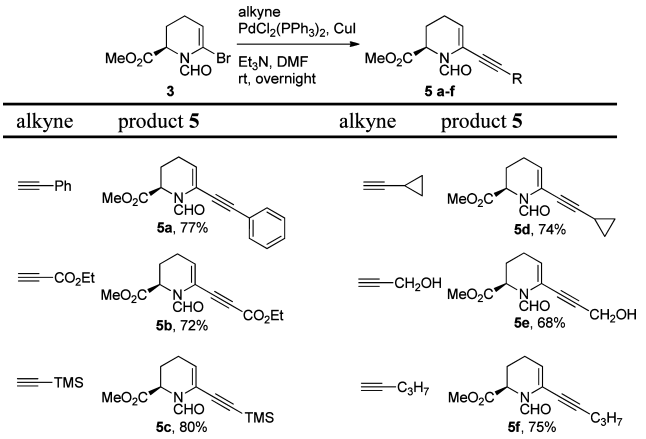
Scheme 1. Bromo-*N*-formylation vs Vilsmeier–Haack Formylation of (*R*)-Methyl 6-Oxopipecolate



	solvent	equiv $POBr_3$	*t* (h)	temp (°C)	yield **3** (%)
1.	CH_2Cl_2	2	18	rt	70
2.	CH_2Cl_2	2.5	2	40	84
3.	$CHCl_3$	3	18	rt	60
4.	$CHCl_3$	2.5	3	70	74
5.	$C_2H_4Cl_2$	3	3	90	78

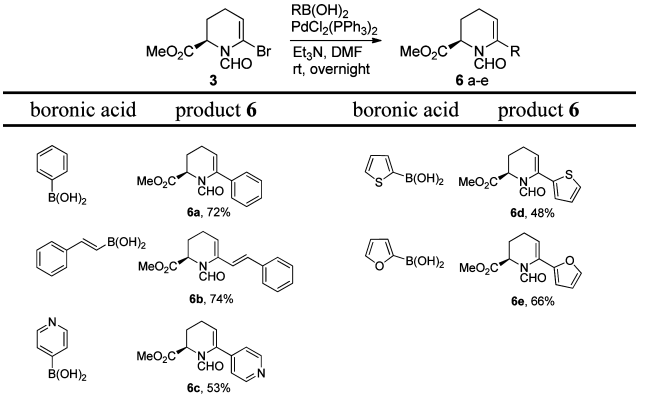
The vinyl bromide **3** turned out to be a favorable starting material for Sonogashira and Suzuki cross-coupling reactions (Schemes 2 and 3). Sonogashira cross-coupling combines, e.g., a vinyl bromide and a terminal alkyne. An array of alkyne substituted derivatives of (*R*)-pipecolic acid was prepared using catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI in the presence of Et_3N as the base. The coupled products were obtained in good-to-high yields.

Scheme 2. Synthesis of (*R*)-Pipecolic Acid Derivatives by Sonogashira Cross-Coupling Reaction



The high enantiomeric purity (*ee* > 99%) of **5a** was verified by chiral HPLC (CHIRALPAK AD).

Scheme 3. Synthesis of (*R*)-Pipecolic Acid Derivatives via Suzuki Cross-Coupling Reactions



Application of Suzuki cross-coupling reactions with compound **3** and suitable boronic acids in the presence of $PdCl_2(PPh_3)_2$ as the catalyst gave an array of 6-aryl or 6-*trans*-β-styryl substituted derivatives of (*R*)-pipecolic acid under mild conditions in good yields (Scheme 3). Exemplarily, compound **6a** was shown to be enantiomerically pure (*ee* > 99%) by chiral HPLC (CHIRALPAK AD).

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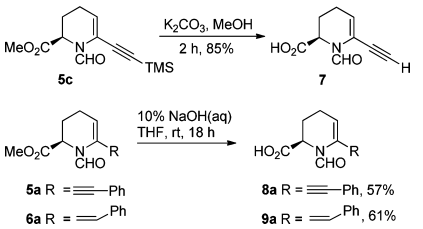
Scheme 4. Desilylation of **5c** and Ester Hydrolysis of **5a** and **6a**



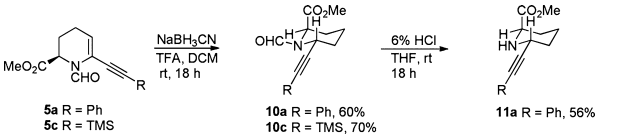
Desilylation of **5c** was performed under basic conditions using K_2CO_3 in MeOH to give **7** in 85% yield. Cleavage of the methyl ester[21] was carried out exemplarily on compounds **5a** and **6a** using 10% aq NaOH in THF to give the free carboxylic acids **8a** and **9a** (Scheme 4).

N-Acyl substituted 2,3-dehydropiperidines can be reduced with $NaCNBH_3$ in the presence of TFA according to Toyooka et al.[22] The acyliminium salt initially formed by protonation is attacked by the hydride. Likewise, the 6-alkynyl substituted *N*-formyl enamines of type **5** can be reduced in the presence of 8 equiv of TFA and 4 equiv of $NaCNBH_3$ at ambient temperature to stereoselectively give the 2,6-*trans*-disubstituted pipecolic acid derivatives **10** in 60−70% yield. Noteworthy, the reduction requires higher TFA concentrations and reaction temperatures than similar conversions described.[22]

The assignment of the NMR signals was achieved using COSY and HMBC experiments, while the (2*R*,6*R*)-configuration of **10** was established on the basis of ^{1}H NMR coupling constants and supported by NOESY experiments. H-2 gives rise to a dd with very similar coupling constants (**10a**: 5.9 Hz, 2.2 Hz; **11a**: 4.0 Hz, 4.0 Hz, whereas H-6 resonates as a dd with largely different coupling constants (**10a**: 11.8 Hz, 3.2 Hz; **11a**: 11.8 Hz, 3.2 Hz). This supports an equatorial−axial and an equatorial−equatorial relationship for H-2 and an axial−axial relationship together with an axial−equatorial one for H-6, which establishes the *trans*-configuration for the two protons and substituents, respectively (Scheme 5). The de was determined by ^{1}H NMR to be >98%, while the enantiomeric purity was complete according to chiral HPLC (CHIRALPAK AD).

Cleavage of the *N*-formyl group in **10a** was investigated under both acidic[23] and basic[24] conditions. The *N*-formyl group resisted basic conditions but was smoothly cleaved under acidic conditions. Treatment with 6% HCl solution in the presence of MeOH as solvent gave the target (2*R*,6*R*)-pipecolic acid derivative **11a** in 56% yield (Scheme 5).

Scheme 5. Reduction of the *N*-Formyl Enamine and *N*-Deformylation



In conclusion, we have developed an efficient protocol for the synthesis of 6-substituted (2*R*,6*R*)-pipecolic acid derivatives starting from (*R*)-α-aminoadipic acid by Sonogashira and Suzuki cross-coupling reactions, respectively, followed by diastereoselective *N*-formyl iminium reduction with $NaCNBH_3$ and *N*-deformylation.

Acknowledgment. The authors acknowledge the German Academic Exchange Service (DAAD) for the award of a PhD fellowship to Amina Sadiq. Sandoz GmbH, Kundl, Austria, and Trend Materials GmbH, Linz, Austria, provided the starting material (*R*)-α-aminoadipic acid.

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.