# Asymmetric Synthesis of Unsaturated Pipecolic Acid Derivatives

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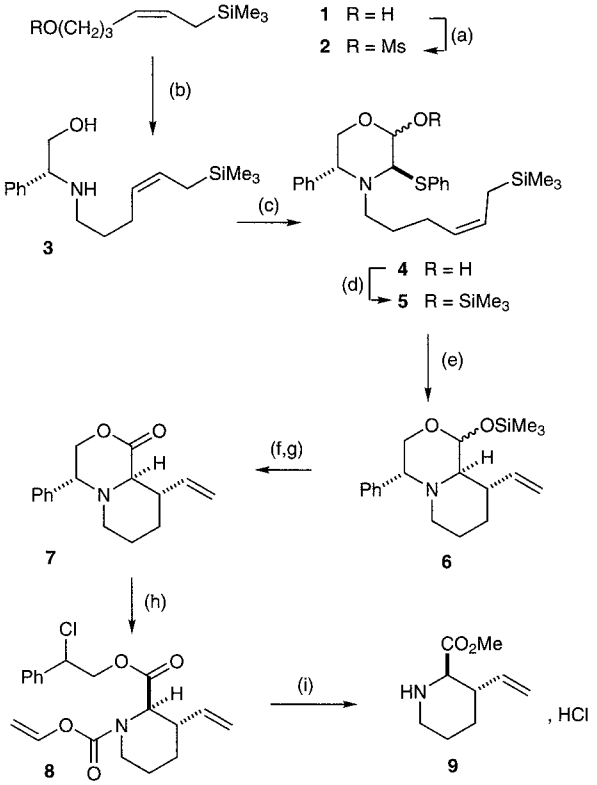
**Abstract:** Two enantiopure pipecolic acid derivatives having an olefinic moiety were synthesized from an intramolecular addition of allyl silanes on an iminium double bond. The iminium moiety was generated via a reaction of chiral β-amino alcohols with glyoxal.

Due to their central role in chemistry and biology, α-amino acids are still synthetic targets of great interest.[1] In particular, much attention has been focused on the asymmetric synthesis of substituted pipecolic acids.[2] Reports of asymmetric syntheses of unsaturated derivatives of such compounds are very scarce,[3,4] in spite of the great importance of olefinic amino acids which are interesting synthetic materials due to the possible functionalisation of the double bond.[5] We describe here an efficient synthesis of two alkenyl derivatives of (*R*)-pipecolic acid.

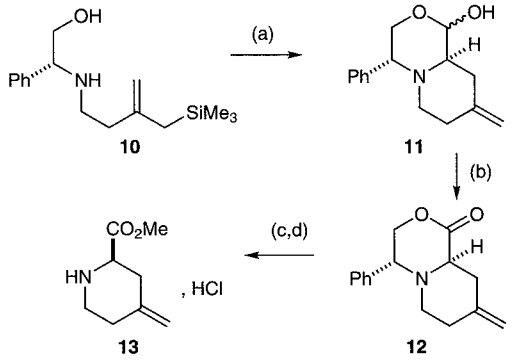
The present method is based on a totally stereoselective addition of allyl silanes on an iminium moiety,[6] which results from a condensation between glyoxal and a *N*-substituted (*R*)-phenylglycinol.[7]

Unsaturated ω-hydroxy silane **1**[8] was reacted, via its mesyl derivative **2**, with (*R*)-phenylglycinol and the resulting product **3** yielded amino thioether **4** by treatment with glyoxal in the presence of thiophenol. Protection of the hemiketal moiety of **4** was followed by Lewis acid ($ZnBr_2$) mediated formation of an intermediate iminium ion whose intramolecular reaction with the unsaturated silyl moiety, followed by a Swern oxidation, yielded lactone **7** whose debenzylation (by formation of the vinylcarbamate **8**) and methanolysis eventually furnished the unsaturated pipecolic derivative **9** (Scheme1). The structure of the diastereomerically pure lactone **7** was determined by using $^1H$ NMR measurements.[9]



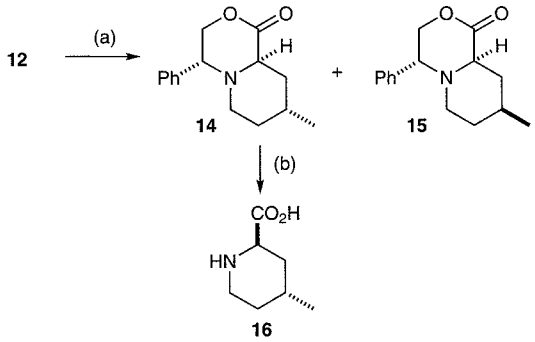

**Scheme 1.** a) MsCl, $Et_3N$, $CH_2Cl_2$, 98%; b) (*R*)-phenylglycinol, $(i\text{-Pr})_2EtN$, MeCN, 70%; c) OHC-CHO, THF:$H_2O$ (50:50), then PhSH, 98%; d) TMSCl, $Et_3N$, THF, 70%; e) $ZnBr_2$, $CH_2Cl_2$, 51%; f) *n*-$Bu_4NF$, THF, 80%; g) $(COCl)_2$, DMSO, $Et_3N$, -50 to 0°C, 70%; h) $CH_2$=CH-OCOCl, $CH_2Cl_2$, reflux, 85%; i) 5N HCl in MeOH, reflux, 95%.

Methyl (*R*)-4-methylene pipecolate **13** was obtained[10] in a similar way (Scheme 2) starting from substrate **10**. Reaction of this compound[11] with glyoxal directly afforded bicyclic derivative **11** which was submitted to a Swern oxidation. The resulting diastereomerically pure lactone **12** was then treated as described above in the case of lactone **7**.



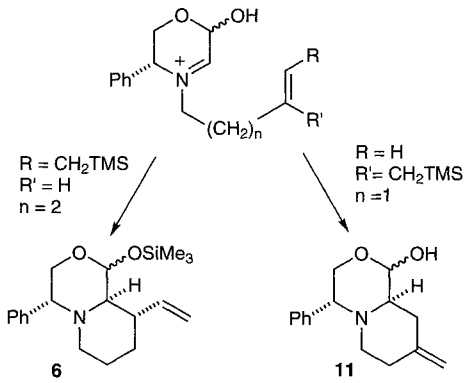

**Scheme 2.** a) OHC-CHO, THF:$H_2O$ (50:50),rt, 97%; b) $(COCl)_2$, DMSO, $Et_3N$, -50 to 0°C, 85%; c) $CH_2$=CH-OCOCl, $CH_2Cl_2$, reflux, 70%; i) 5N HCl in MeOH, reflux, 95%.

The absolute configuration of pipecolic derivative **13** was deduced from a chemical correlation with compound **16** which has already been described in enantiopure form.[12] (2*R*,4*R*)-Methylpipecolic acid **16** was obtained from compound **14** (Scheme 3) which is the major (75%) isomer produced by the hydrogenation of lactone **12**.




**Scheme 3.** a) $H_2$, $PtO_2$, AcOEt, 96%; b) $H_2$, $Pd(OH)_2$, EtOH, 98%.

As regards the cyclisation steps, it turns out (Scheme 4) that, in both cases, attack of the silane double bond on the iminium shows an identical stereoselectivity, corresponding to what was already observed in similar condensations:[7] chiral induction by the phenyl-bearing stereocenter directs the addition of the olefinic double bond to occur from the β-face of the cyclic structure.




**Scheme 4**

In conclusion, we have developed a novel and totally stereoselective method for the asymmetric synthesis of olefinic pipecolic acid derivatives.

## References and Notes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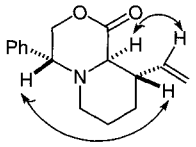
9 Data for compound 9: $[\alpha]_{20}^{D}$: -10 (*c* 0.5, $H_2O$); $^1H$ NMR (250 MHz, $D_2O$): 1.35-1.82 (m, 4H), 2.39 (dq, J=3.1 and 11.2 Hz, 1H), 2.87 (td, J=3.2 and 12.5 Hz, 1H), 3.21-3.33 (m, 1H), 3.62 (s, 3H), 3.71 (d, J=11.2 Hz, 1H), 4.81-5.04 (m, 2H), 5.50-5.65 (m, 1H); $^{13}C$ NMR (63 MHz, $D_2O$): 22.3, 29.8, 43.6, 45.0, 54.6, 62.3, 119.2, 142.4, 170.9. $^1H$ DIFNOE NMR (250 MHz) data of intermediate lactone 7 are as follows:



10 Data for compound 13: $[\alpha]_{20}^{D}$: -26 (*c* 1.5, $H_2O$); $^1H$ NMR (250 MHz, $D_2O$): 2.30-2.48 (m, 3H), 2.77 (dd, J=4.1 and 14.5 Hz, 1H), 2.98 (td, J=4.1 and 11.8 Hz, 1H), 3.35-3.43 (m, 1H), 3.72 (s, 3H), 4.02 (dd, J=4.1 and 11.4 Hz, 1H), 4.91 (bs, 2H); $^{13}C$ NMR (63 MHz, $D_2O$): 30.8, 34.5, 45.6, 54.9, 58.5, 114.9, 139.0, 170.7.

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12 Data for compound 16: $^1H$ NMR (250 MHz, $D_2O$): 0.89 (d, J=6.4 Hz, 3H), 1.28-1.76 (m, 4H), 1.94-2.02 (m,1H), 3.10-3.14 (m, 2H), 3.78 (dd, J=4.7 and 3.1 Hz, 1H); $^{13}C$ NMR (63 MHz, $D_2O$): 20.2, 26.5, 30.2, 33.8, 41.9, 56.7, 175.4; $[\alpha]_{20}^{D}$: -20 (*c* 0.25, $H_2O$); [lit.[13] $[\alpha]_{20}^{D}$: -18 (*c* 1, 2N HCl)].

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