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Tetrahedron Letters 46 (2005) 7495–7497
Tetrahedron Letters

Synthesis of 5-substituted pipecolic acid derivatives as new conformationally constrained ornithine and arginine analogues

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Received 18 July 2005; revised 25 August 2005; accepted 2 September 2005

Abstract—Two, orthogonally protected, constrained analogues of arginine have been synthesised in a diastereodivergent manner. The key step involved an electrophilic or radical functionalisation of methyl *N*-Boc-5,6-dehydropipecolate.

L-Arginine, a guanidino group-containing proteinogenic amino acid, which is positively charged at neutral pH, is involved in a large number of physiological and pathophysiological processes. The arginine residue, alone or as part of a peptide, constitutes an important component of substrates or inhibitors of a variety of enzymes. Various conformationally constrained analogues of arginine have been described. Most of these analogues involve a restriction by means of a bridge between the side chain atoms.[1] Little has been reported on the development of arginine mimetics wherein simultaneous restriction of χ^i and ϕ torsion angles were achieved. To the best of our knowledge, only four of such analogues, which are proline-templated have been reported[2] (Fig. 1).

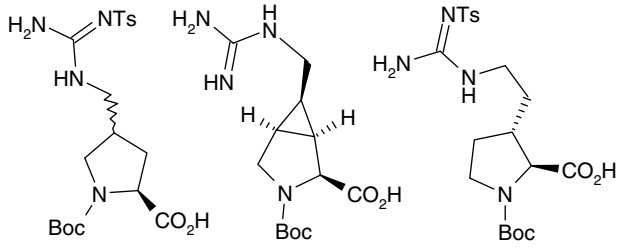
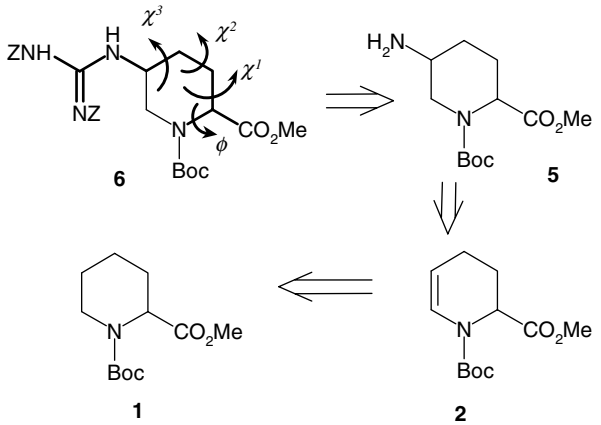


Figure 1. Proline-templated analogues of arginine.

The work disclosed in this letter describes a diastereoselective synthesis of racemic, orthogonally protected *cis* and *trans* 5-guanidino-pipecolic acids as new constrained analogues of arginine where four torsion angles (χ^1, χ^2, χ^3 and ϕ) are restricted. Variously substituted pipecolic acid derivatives have already been described;[3] some of them were designed for peptidomimetics purposes.[4] Our strategy towards the synthesis of protected 5-guanidino pipecolic acids **6** relies on diastereoselective functionalisation of 5,6-dehydropipecolic acid derivative **2**, via the corresponding ornithine analogues **5** (Scheme 1).

We started our synthesis from **2**, which we prepared in quantitative yield, from racemic *N*-Boc methylpipecolate



Scheme 1. Retrosynthesis of orthogonally protected 5-guanidino-piecolic acids.

Keywords: Arginine-mimetics; Constrained analogues; Pipecolic acid; Stereoselective synthesis.
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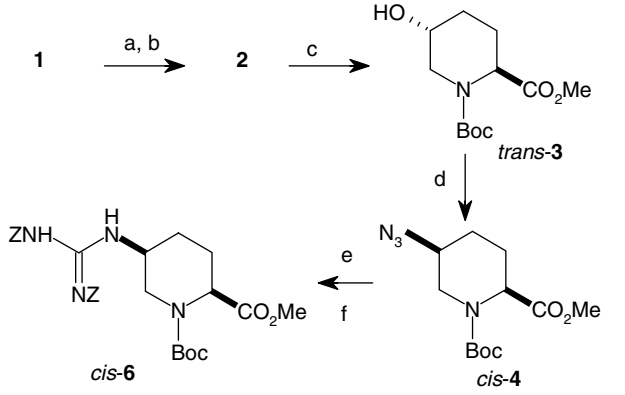
doi:10.1016/j.tetlet.2005.09.008

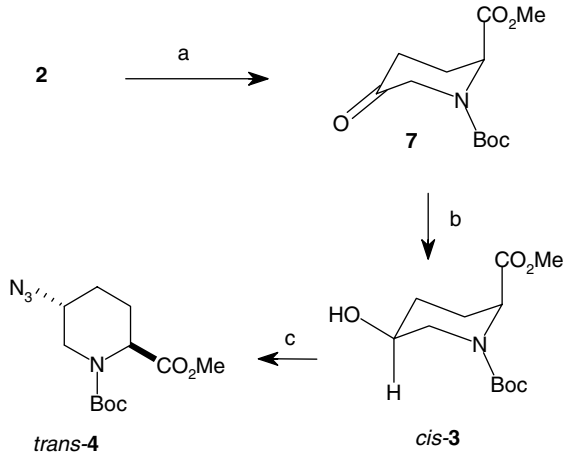
1 in two steps; α-electromethoxylation and subsequent β-elimination of methanol.[5] Our initial attempts to directly introduce the 5-amino group by hydroboration–amination sequence, based on literature examples,[6] were unsuccessful. Therefore, we sought an alternative stepwise approach to the ornithine mimetics **5** via the corresponding 5-hydroxypipecolate. Although less reactive than enamines, enecarbamates react with various electophiles[7] including boranes in the hydroboration–oxidation sequence making possible the introduction of the hydroxyl group into the β-position of the enecarbamate nitrogen atom.[7,8] As was pointed out by Plehiers and Hootelé[8a] for 1-carbomethoxy-6-alkyl-2,3-dehydropiperidines, the hydroboration of **2** does not reach the trialkylborane stage. On the other hand, even with 1 equiv of BH_3·DMS the hydroboration of **2** was very slow in THF (15 h for 1 mmol scale). Therefore, we examined the solvent effects (toluene, Et_2O, CH_2Cl_2) and dichloromethane was found to be the most effective solvent for the hydroboration step, which is completed after 2.5 h.[9] The oxidative cleavage of the C–B bond was best achieved with trimethylamine *N*-oxide (TMO) in refluxing THF. Under these conditions the desired alcohol was isolated in 62% yield as a mixture of isomers (*trans*/*cis* = 93/7)[10] with respect to the ester function. This mixture has been conveniently separated by column chromatography, and each diastereomer was obtained in a pure form.[11] Mesylation of alcohol *trans*-**3** provided the corresponding mesylate, which was reacted with sodium azide to give the azido derivative *cis*-**4** in good yield. This compound was then subjected to hydrogenolysis using 10% palladium-on-charcoal in dichloromethane affording the corresponding primary amine *cis*-**5**. To avoid lactamisation,[12] the crude ornithine analogue *cis*-**5** was allowed to react with *N*,*N*-di-(benzyloxycarbonyl)-*S*-methylthiourea in presence of triethylamine and mercury(II) chloride,[13] to give the fully protected *cis* isomer of arginine analogue *cis*-**6** with 83% yield after column chromatography (Scheme 2).

This route provides the protected unnatural α-amino acid (±)-*cis*-**6** in high diastereomeric purity. To extend this methodology to the *trans* isomer analogue, the alcohol *cis*-**3** was required. This *cis* isomer was envisioned by a stereoselective axial reduction with $NaBH_4$ of the corresponding ketone, which is taken to be locked in a conformation with the 2-carbomethoxy group axially oriented, due to the known $A^{1,3}$ allylic strain present in α-substituted *N*-acylpiperidines.[8a,14] To this end, the crude intermediate of the hydroboration step was subjected to oxidation with various oxidants in order to achieve the C–B oxidative cleavage and subsequent oxidation of the resulting alcohol to the corresponding ketone **7**. The best yield (40%) of ketone **7** was obtained by using 4 equiv of *o*-iodoxybenzoic acid (IBX)[15] in refluxing acetonitrile (Scheme 3). As anticipated, treatment of **7** with sodium borohydride gave selectively the alcohol *cis*-**3** (*cis*/*trans* > 97/3). Pure *cis*-**3** was converted into the azido compound *trans*-**4** following the procedure previously developed with the alcohol *trans*-**3**.

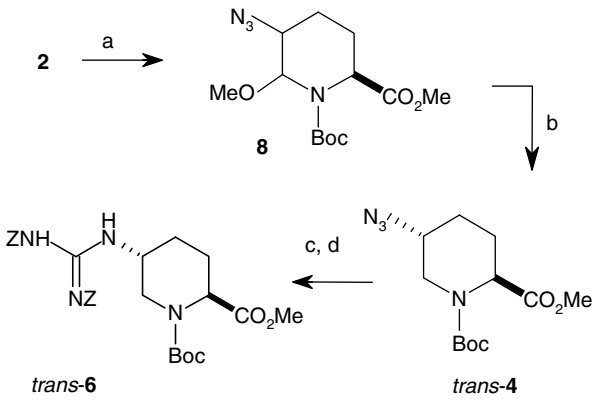
Beside this four-step route, we examined a two-step way. The azidoalkoxylation of olefins, especially electron rich ones, is a well established method for the introduction of amino group.[16] Thus, treatment of a mixture of our enecarbamate **2** and sodium azide, in acetonitrile–methanol, with cerium(IV) ammonium nitrate (CAN) at 0 °C afforded the desired α-methoxy-β-azido compound **8** in 76% yield[17] as a complex diastereomeric mixture.[18] Subsequent reduction of the α-aminoether moiety, via the corresponding iminium ion,[5b,19] afforded the 5-azidopipecolate derivative **4** as a diastereomeric mixture (*trans*/*cis*: 55/45). This ratio reflects the low selectivity of the azidomethoxylation step. To optimise the stereoselectivity, we have studied the influence of various factors and found that the diastereoselectivity in favor of the desired *trans* isomer is strongly temperature dependent. Best result (*trans*/*cis*: 92/8) was obtained when the azidomethoxylation step was carried out in acetone at −95 °C (Scheme 4). Finally, hydrogenolysis of *trans*-**4** gave quantitatively the ornithine analogue *trans*-**5**, which



Scheme 2. Reagents and conditions: (a) −2e⁻(C–C)–MeOH–*n*-Bu_4NBF_4; (b) NH_4Cl (1.4 equiv), toluene (reflux), (93% yield, two steps); (c) (i) THF–2 M BH_3·DMS (1 equiv), CH_2Cl_2, −78 °C then rt, (ii) evaporation then TMO·H_2O (5.4 equiv), THF (reflux), 15 min (62% yield); (d) (i) MsCl, NEt_3 (82%), (ii) NaN_3, DMF, 65 °C (90% yield); (e) H_2, 10% Pd–C, CH_2Cl_2, (f) ZN=C(SMe)NHZ, NEt_3, $HgCl_2$ (83% yield, two steps).



Scheme 3. Reagents and conditions: (a) (i) THF–2 M BH_3·DMS (1 equiv), CH_2Cl_2, −78 °C then rt, (ii) evaporation then IBX (4 equiv), CH_3CN (reflux) (40% yield, two steps); (b) $NaBH_4$, MeOH (85%, *cis*/*trans* > 97/3); (c) (i) MsCl, NEt_3 (78%), (ii) NaN_3, DMF, 65 °C (91%).



Scheme 4. Reagents and conditions: (a) NaN_3 (1.5 equiv), CAN (3 equiv), acetone–MeOH, −95 °C; (b) Et_3SiH (1 equiv), $BF_3{\cdot}OEt_2$ (1 equiv), CH_2Cl_2, −80 °C, (60%, *trans*/*cis*: 92/8); (c) (i) 10% Pd–C, H_2 (1 atm), CH_2Cl_2, (ii) ZN=C(SMe)NHZ, NEt_3, $HgCl_2$, CH_2Cl_2 (80% yield, two steps).

was then subjected to the guanylation procedure to afford the arginine analogue *trans*-**6** in 80% overall yield.

In summary, we have developed a diastereodivergent synthesis of the orthogonally protected unknown α-amino acid 5-guanidinopipecolic acid as new arginine analogues. The biological evaluation of each fully deprotected diastereomer (racemic) with NOS isoforms will be the subject of a later report.

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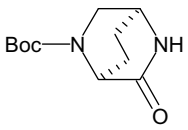
9. Similar rate enhancement of hydroboration in chlorohydrocarbon solvents was reported, see: Kanth, J. V.; Brown, H. C. *Tetrahedron Lett.* **2000**, *41*, 9361–9364.
10. Variable amounts (7–15%) of the unexpected C=C reduction compound **1** were isolated. By using BD_3 we established that both introduced hydrogen atoms were supplied by borane. We have previously observed similar results with enelactams.[5b]
11. The assignment of relative stereochemistry of *cis* and *trans* isomers is based on ^1H NMR spectra recorded at variable temperature in toluene.[4a]
12. When the hydrogenolysis was performed in methanol lactamisation took place during the evaporation of the solvent leading to a bicyclic lactam:



Therefore, we employed more volatile solvent, that is, dichloromethane. The aminoester thus obtained should be stored at low temperature (−20 °C) to avoid its lactamisation.
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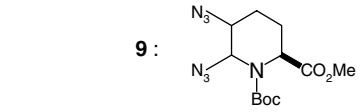
17. Variable amounts (<14%) of α,β-diazido compound **9** were obtained, depending on the dropwise addition rate of CAN solution to the encarbamate **2** and sodium azide mixture. Fast addition increased the amounts of **9**.



18. At least three diastereomers of **8** were detected by chromatography (TLC and GC).
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