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# Total Synthesis of (+)-Epiquinamide

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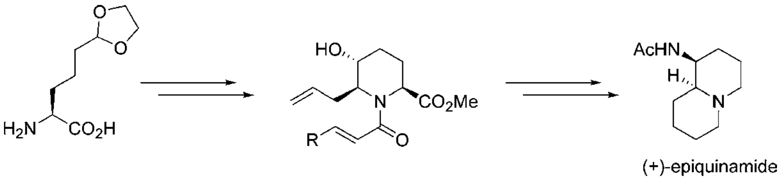
## ABSTRACT

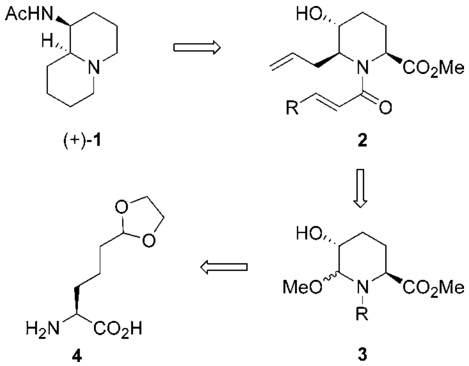


**The stereoselective total synthesis of the novel quinolizidine alkaloid (+)-epiquinamide is presented, starting from the amino acid L-allysine ethylene acetal. Key steps in the synthesis involved a highly diastereoselective *N*-acyliminium ion allylation and a ring-closing metathesis reaction to provide the bicyclic skeleton.**

The novel quinolizidine alkaloid epiquinamide **1**, recently isolated from the skin of the Ecuadorian frog *Epipedobates tricolor*, represents a new structural class of nicotinic agonists, selective for $\beta$2 receptor subtypes.[1] Similar to epibatidine, it might function as a potential lead compound for the development of new therapeutics for neuronal receptors.[1,2] Further investigations toward its biological activity are hampered by the limited availability of the natural product. In addition, the isolated amount of ~240 $\mu$g of epiquinamide proved to be sufficient for the determination of the relative stereochemistry based on MS, IR, and NMR analysis, resulting in the assignment of the (1*R**,10*R**)-1-acetamidoquinolizidine isomer. However, the absolute stereochemistry of the natural product to date remains unknown. This communication details the stereoselective total synthesis of (+)-epiquinamide, which confirms the relative stereochemistry of the natural product and allows the production of significant amounts of this biologically active compound.

As depicted in Scheme 1, we envisaged to obtain epiquinamide from (2*S*,5*R*,6*S*)-hydroxypipecolic acid derivative **2**. This key intermediate should provide the bicyclic skeleton after a ring-closing metathesis reaction. Amide **2** could be derived from *N*-acyliminium ion precursor **3** via a diastereoselective allylation reaction. For the synthesis of *N*,*O*-acetal **3** we relied on our recently developed strategy involving the cyclization of protected L-allysine ethylene acetal **4** followed by a diastereoselective epoxidation/ring-opening strategy applied on the obtained cyclic enamide.[3] In turn, L-allysine ethylene acetal can be readily obtained in enantiomerically pure form by biocatalytic resolution of the corresponding amino acid amide.[4,5]

**Scheme 1.** Retrosynthetic Analysis



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(1) Fitch, R. W.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2003**, *66*, 1345.

(2) Baker, D. D.; Alvi, K. A. *Curr. Opin. Biotechnol.* **2004**, *15*, 576.

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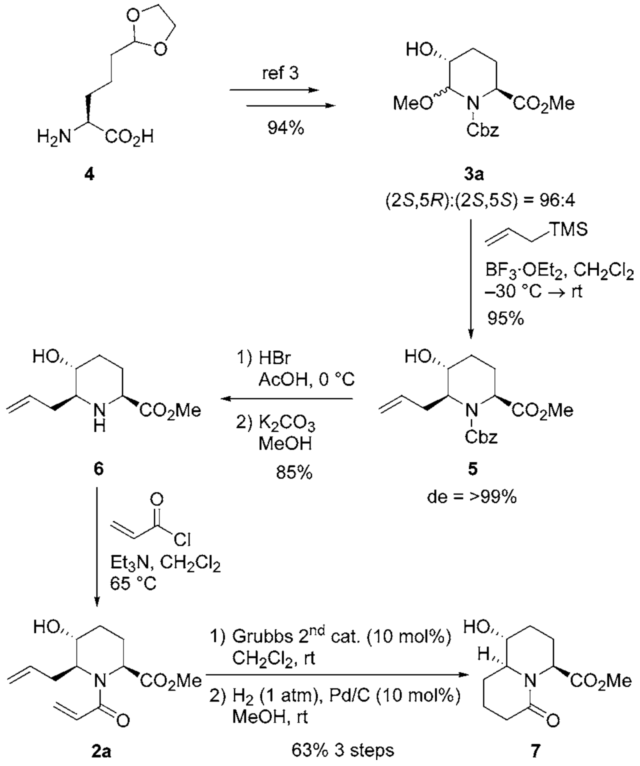
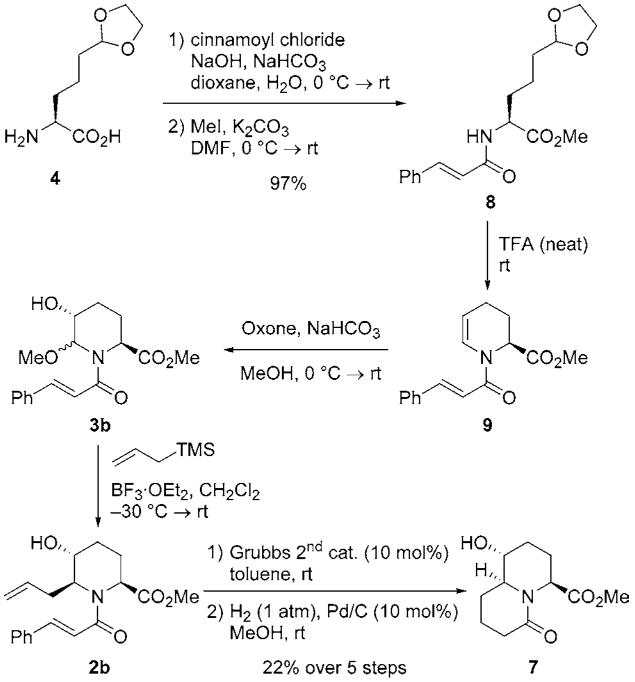
The reaction sequence to Cbz-protected pipecolic acid derivative **3a** proceeds in an excellent yield of 94% over four steps with a diastereoselectivity of 96:4 in favor of the desired (2*S*,5*R*)-isomer (Scheme 2). Treatment of *N*,*O*-acetal **3a** with $BF_3{\cdot}OEt_2$ in the presence of allyltrimethylsilane gave rise to a highly diastereoselective *N*-acyliminium ion reaction yielding the (2*S*,5*R*,6*S*)-configured product **5** as a single isolated product.[3,6] Removal of the Cbz moiety under acidic conditions[7] allowed the subsequent introduction of an acryloyl group, setting the stage for the formation of the bicyclic skeleton by ring-closing metathesis.[8] It should be noted that acrylamide **2a** is a highly reactive intermediate, prone to polymerization when treated with acid or heated above ~40 °C. To circumvent the necessity of purification of the unstable acrylamide, amine **6** was treated with exactly 1 equiv of acryloyl chloride, whereafter the crude product was used immediately for the next reaction. Indeed, treatment of **2a** with a catalytic amount of the Grubbs second generation ruthenium catalyst,[9] followed by immediate hydrogenation of the double bond, yielded the bicyclic product **7** in a yield of 63% over three steps.

**Scheme 2.** Synthesis of the Bicyclic Core[a]



We also envisaged a more direct approach to quinolizidinone **7**, by using an acrylate-type group instead of the Cbz for nitrogen protection, prior to its use as a handle for the ring-closing metathesis. However, since the acrylamide moiety was already found to be prone to polymerization, the expectedly more stable cinnamoyl group was chosen instead (Scheme 3).

**Scheme 3.** Direct Introduction of the Cinnamoyl Moiety[a]



Coupling of cinnamoyl chloride with amino acid **4** followed by methylation yielded amide ester **8** in a nearly quantitative yield. Upon treatment with TsOH in refluxing toluene the expected piperidine **9** was formed, although the reaction suffered from extensive dimerization of the enamide product. This could be circumvented by performing the reaction in neat TFA, resulting in a fast and clean cyclization. A completely selective epoxidation of the enamide double bond was observed when **9** was treated with Oxone in methanol, yielding *N*,*O*-acetal **3b**. The conversion of **3b** into lactam **7** was accomplished in a manner analogous to the protocol described in Scheme 2. Thus, *N*-acyliminium ion allylation, followed by ring-closing metathesis and subsequent reduction of the double bond, afforded the desired bicyclic product **7**. Although all transformations from amide **8** to quinolizidinone **7** proceeded with good conversions, the

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(3) Botman, P. N. M.; Dommerholt, F. J.; de Gelder, R.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org. Lett.* **2004**, *6*, 4941.

(4) For a racemic synthesis of L-allysine ethylene acetal, see: Rumbero, A.; Martín, F. C.; Lumbreras, M. A.; Liras, P.; Esmahan, C. *Bioorg. Med. Chem.* **1995**, *3*, 1237.

(5) (a) Boesten, W. H. J.; Broxterman, Q. B.; Plaum, M. J. M. EP0905257, 1999; *Chem. Abstr.* **1999**, *130*, 251283. (b) Wolf, L. B.; Sonke, T.; Tjen, K. C. M. F.; Kaptein, B.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2001**, *343*, 662.

(6) For a recent review on *N*-acyliminium ion chemistry, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(7) The HBr salt of product **7** was treated with $K_2CO_3$ in MeOH in order to liberate the partially acetylated 5-hydroxyl group.

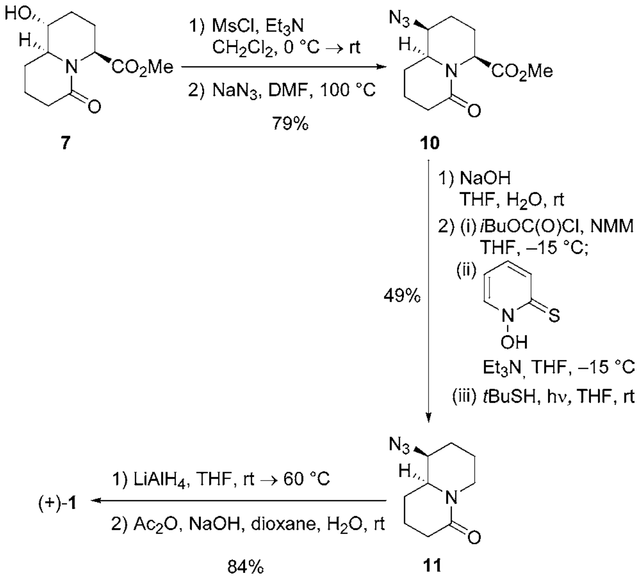
(8) For a recent example of quinolizidine formation by RCM, see: Kinderman, S. S.; de Gelder, R.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Am. Chem. Soc.* **2004**, *126*, 4100.

(9) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

purification of the intermediates by column chromatography over silica gel gave rise to substantial decomposition. For this reason the products were taken through the five-step sequence without intermediate purification, yielding **7** as a single diastereomer in a reproducible yield of 22%.

The synthesis was completed as depicted in Scheme 4. Mesylation of the alcohol, followed by treatment with sodium azide, resulted in the formation of azide **10**, in 79% yield. After saponification of the methyl ester, a decarboxylation was performed according to the method developed by Barton.[10] This involved the formation of the mixed anhydride, followed by coupling with 2-mercaptopyridine-*N*-oxide. This activated ester was then irradiated in the presence of 2-methylpropane-2-thiol, to afford **11** in 49% yield. The sequence was completed by a $LiAlH_4$-mediated reduction of both the lactam as well as the azide, followed by acylation of the primary amine yielding (+)-epiquinamide in a yield of 84% over the last two steps.

**Scheme 4.** Completion of the Synthesis



X-ray structure analysis of the corresponding HCl salt unequivocally proved the expected relative stereochemistry of the final product (Figure 1).

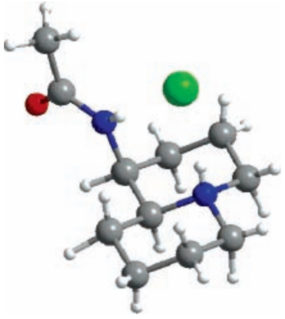


**Figure 1.** Chem3D representation of the crystal structure of (+)-**1**·HCl.

In conclusion, a stereoselective total synthesis of (+)-epiquinamide has been accomplished starting from L-allysine ethylene acetal **4**, confirming the structure and the relative stereochemistry of the natural product. Key steps in the synthesis involved a highly diastereoselective *N*-acyliminium ion allylation and a ring-closing metathesis reaction to provide the bicyclic skeleton. This synthesis allows the generation of appreciable quantities of enantiomerically pure epiquinamide, in 15 steps with an overall yield of 15.5%, from readily available L-allysine ethylene acetal. Furthermore, this pathway is amenable to the synthesis of potentially biologically active epiquinamide derivatives. Currently, we are aiming at the elucidation of the absolute configuration of natural epiquinamide, by comparison of the isolated natural product with our synthetic material. The results of these efforts will be detailed in due course.

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**Supporting Information Available:** Experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0515715

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[10] Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479.