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A Formal Enantioselective Synthesis of (–)-Epiquinamide by Proline-Catalyzed One-Pot Sequential α-Amination/Propargylation of Aldehyde and Asymmetric Dihydroxylation of Olefin

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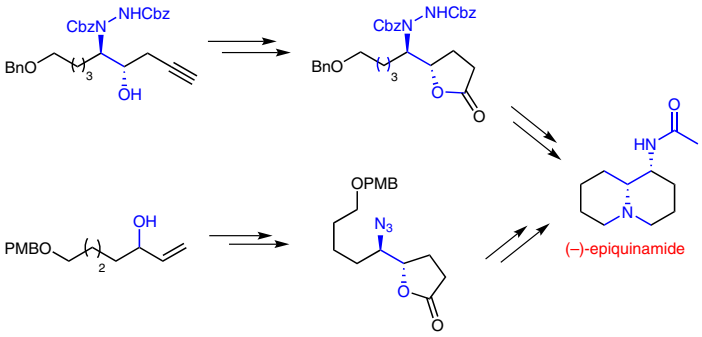

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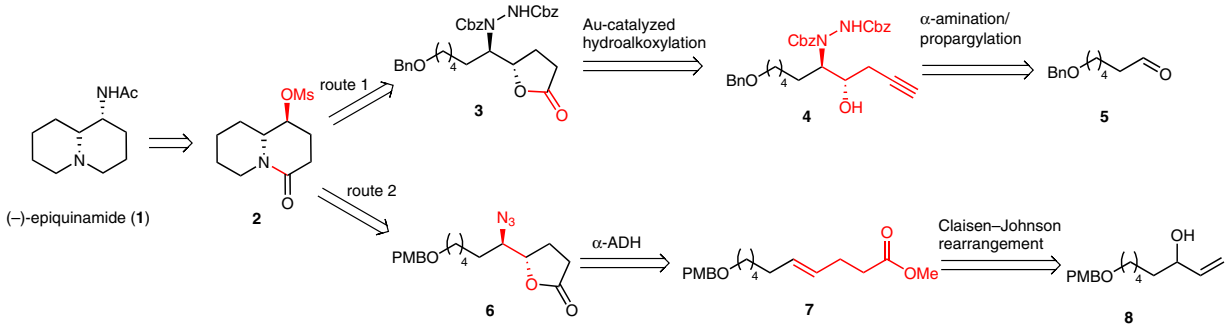
Abstract Two independent routes to the formal synthesis of (–)-epiquinamide, have been described: the first route utilizes an L-proline-catalyzed one-pot sequential α-amination/propargylation of aldehyde, while the second one employs asymmetric dihydroxylation as the key reaction to install the stereochemistry. While the first synthesis was accomplished in nine steps with 24.4% overall yield and dr 9:1, the second strategy resulted in the synthesis in eight steps with 36.4% overall yield and with perfect enantiocontrol.

Key words amination, dihydroxylation, diastereoselective, proline, quinolizidine

A diverse array of biologically active, lipid-soluble alkaloids, have been discovered in amphibian skin. Such alkaloids generally possess characteristic structural units like quinazolines, indolizidines, pyrrolidines, piperidines, etc. Epiquinamide (**1**), one of such quinazoline alkaloid, was recently isolated from the skin extracts of the Ecuadorian poison dart frog *Epipedobates tricolor*.[1] Due to its structural importance, several methods of synthesis have been reported.[2] To date only a few asymmetric syntheses of **1** have been reported involving multiple steps or enzymatic resolution as a key step.[2a–f] However, most of the reported synthesis involves the use of chiral pool resources or chiral auxiliary. Use of expensive chiral pool resources and multiple reaction sequences are some of the other limitations associated with the reported methods. In this regard, it is apt to search for a flexible and catalytic method for the synthesis of epiquinamide from inexpensive starting materials. Recently, proline-catalyzed sequential reactions have become well recognized to synthesize diverse and complex molecular architectures. In continuation of our work aimed at the development of new sequential reactions and their application in the synthesis of bioactive molecules,[3] we herein describe an efficient approach to the formal synthesis of (–)-epiquinamide (**1**) based upon either L-proline-catalyzed one-pot sequential α-amination/propargylation or regioselective asymmetric dihydroxylation (ADH) as the key chiral inducing reactions.

The retrosynthetic analysis for the asymmetric synthesis of (–)-epiquinamide (**1**) is shown in Scheme 1. We envisioned that epiquinamide (**1**) can be easily prepared from the key intermediate quinolizidine **2** by substitution of mesyl group with azide followed by the reduction of azide and amide groups. We further envisaged that the key intermediate **2** can be prepared by two routes: (i) Route 1 shows that the quinolizidine **2** could be synthesized from hydrazino lactone **3** via hydrogenation over Raney Ni followed by N-alkylation of the resulting amide. The hydrazino lactone **3** could be prepared by intramolecular hydroalkoxylation of the alkyne **4**, which in turn can be obtained by L-proline-catalyzed one-pot sequential α-amination/propargylation of aldehyde **5**. (ii) Route 2 shows that the quinolizidine **2** could be synthesized from azido lactone **6** via hydrogenation over Pd/C followed by N-alkylation of the resulting amide. The azido lactone **6c** can be obtained by asymmetric dihydroxylation of homoallylic ester **7**, which in turn can be prepared by the Claisen–Johnson rearrangement of allylic alcohol **8**.

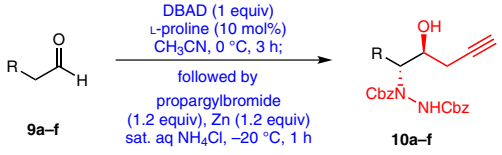
Before starting the synthesis of (–)-epiquinamide, as shown in route one, we examined the feasibility of proline-catalyzed 'one-pot' sequential α-amination/propargylation of aldehydes for the first time.[3a] As a model study, propanaldehyde (**9a**) was α-aminated[4] with dibenzyl azadicarboxylate catalyzed by L-proline (15 mol%) in MeCN at 0 °C for three hours that produced the corresponding α-aminated aldehyde, in situ, followed by the sequential addition of Zn powder (1.2 equiv), propargylic bromide (1.2 equiv) and saturated aqueous NH_4Cl at –20 °C to give *anti*-vicinal amino alcohol **10a** in 84% yield (dr 99:1). To generalize this



Scheme 1 Retrosynthetic analysis of epiquinamide (**1**)

one-pot reaction, a series of aliphatic aldehydes bearing different functionalities (alkyl, arylalkyl, benzoyloxy or TBS ether) were examined under the same protocol. We observed complete diastereoselectivity in propargylation reaction when R group was small (entry 1, Table 1). However, as R group was changed to a bulky group, we observed a decrease in the diastereoselectivity (entries 2–6, Table 1).

Table 1 L-Proline-Catalyzed Asymmetric Sequential α-Amination/Propargylation Reaction of Aldehydes[a]



Entry	Aldehydes (*R*) (**9a–f**)	Products (**10a–f**) Yield (%)[b]	ee (%)[c]	dr[c]
1	Me (**1a**)	84	93	99:1
2	*n*-Bu (**1b**)	86	95	90:10
3	4-(TBS)-propyl (**1c**)	79	93	87:13
4	3,4,5-trimethoxybenzyl (**1d**)	87	93	79:21
5	4-methoxybenzyl (**1e**)	81	96	80:20
6	4-chlorobenzyl (**1f**)	83	95	81:19

[a] Reaction conditions: propanaldehyde (5 mmol), DBAD (5 mmol), L-proline (10 mol%), propargyl bromide (7.5 mmol), Zn (7.5 mmol), sat. aq NH_4Cl (10 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

The stereochemical assignment of this sequential reaction was made based on the previously established absolute configuration of α-amino aldehydes.[4a] The relative stereochemistry of vicinal amino alcohol **10a**, was determined by transformation into the oxazilidinone, which upon NOE experiment showed amino alcohols in *anti*relationship.[5] To rationalize the observed high *anti* stereochemistry relationship, a Felkin–Ahn transition state[6] model (Figure 1) has been proposed, in which Zn atom of propargyliczinc reagent is coordinated to the carbonyl oxygen and the nucleophilic attack of the corresponding reagent takes place at the '*Si*' face predominantly perpendicular to the bulky CbzN-NHCbz group to deliver *anti*-amino alcohols **10a–f**.

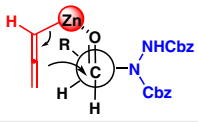
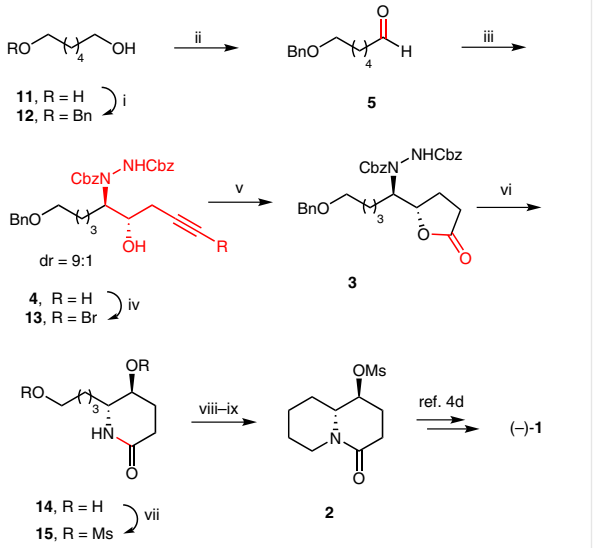


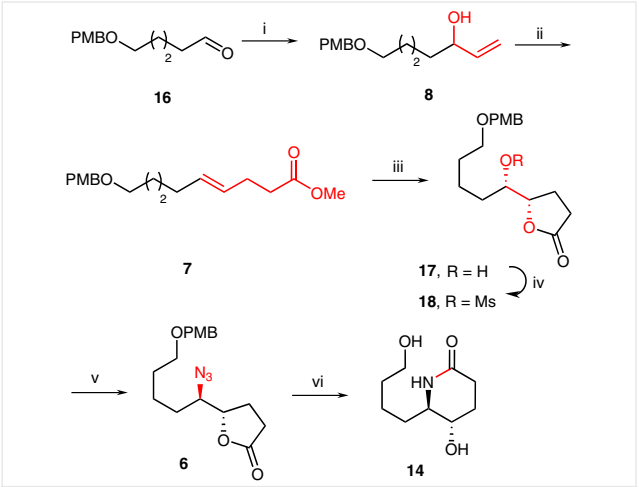
Figure 1 Felkin–Ahn transition state

After finding the feasibility of one-pot sequential reaction, the synthesis of (–)-epiquinamide (**1**) commenced with the commercially available 1,6-hexanediol (**11**), which was protected as monobenzyl ether followed by selective oxidation with PCC to give the corresponding aldehyde **5** in 87% yield. Aldehyde **5** was then subjected to L-proline-catalyzed sequential α-amination/propargylation protocol to afford the *anti*-amino alcohol **4** in 79% yield (94% ee, dr 9:1). Bromination[7] of amino alcohol **4** [$AgNO_3$ (10 mol%), NBS (1 equiv), acetone] gave the terminal alkyne bromide **13** in 82% yield, which was subjected to intramolecular hydroalkoxylation[8] with $AuCl_3$ (10 mol%) as catalyst in toluene/water (10:1) to furnish γ-butyrolactone **3** in 78% yield. The γ-butyrolactone **3** was subjected over Raney Ni to the hydrogenation condition to cleave N–N bond giving free amine in situ as well as to deprotect benzyl ether. The free amine underwent intramolecular opening with lactone to give the stable six-membered amide **14**, thus releasing the free alcohol moiety. The diol **14** was mesylated completely with two equivalents of mesyl chloride in the presence of Et_3N in THF to give the dimesylate **15** in 91% yield. Finally, the N-alkylation of the amide using sodium hydride in THF was carried out to construct the bicyclic ring, i.e. quinalizidine **2**. The quinalizidine **2** can be readily converted to the desired (–)-epiquinamide (**1**), as reported by previous works[2a] (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) BnBr, NaH, DMF, 0 °C, 4 h, 78%; (ii) PCC, CH_2Cl_2, r.t., 3 h, 87%; (iii) L-proline (10 mol%), DBAD (1 equiv), MeCN, 0 °C, 3 h followed by propargylic bromide (1.2 equiv), Zn (1.2 equiv), sat. aq NH_4Cl, –20 °C, 79%; (iv) $AgNO_3$ (8 mol%), NBS (1.2 equiv), acetone, r.t., 82%; (v) $AuCl_3$ (10 mol%), toluene–H_2O (9:1), r.t., 78%; (vi) Raney Ni, H_2 (80 psig), MeOH, acetic acid (cat.), r.t., 24 h, 92%; (vii) MsCl (2 equiv), Et_3N, CH_2Cl_2, 0 °C, 1 h, 91%; (viii) NaH, THF, reflux, 86%.

Despite the short and efficient synthetic route as described above, we could not enhance the diastereoselectivity (dr 9:1) of the α-amination/propargylation reaction. Therefore, we have decided to employ asymmetric dihydroxylation for stereoinduction. According to route 2 the synthesis of intermediate **14** commenced from allylic alcohol **8**, prepared by addition of vinyl magnesium bromide onto aldehyde **16**. Allylic alcohol **8** upon Claisen–Johnson [3,3]-sigmatropic rearrangement[9] (trimethyl orthoacetate, catalytic amount of propionic acid, xylene, 135 °C) produced (*E*)-homoallylic ester **7** exclusively in 85% yield (Scheme 3). The dihydroxylation of the (*E*)-homoallylic ester **7** was carried out under the Sharpless asymmetric dihydroxylation[10] (SAD) conditions, using catalytic amounts of $K_2OsO_4{\cdot}2H_2O$, and $K_3Fe(CN)_6$ as a co-oxidant in the presence of $(DHQ)_2AQN$ ligand to give the hydroxylactone **17** in 89% yield (98% ee). Under the basic condition the diol formed, in situ, underwent lactonization with the ester regioselectively to form the stable five-membered lactone **17**. The formation of lactone helps to differentiate the two hydroxyl groups and stepwise introduction of the heteroatoms into the molecule. The hydroxyl group in **17** was protected as its mesylate **18** (MsCl, Et_3N, CH_2Cl_2,0 °C) followed by its SN_2 displacement with NaN_3 to give the azidolactone **6** in 85% yield over two steps with complete inversion. The reduction of azide as well as the deprotection of PMB group was carried out under hydrogenation conditions [10% Pd/C, H_2 (1 atm), Et_3N] to give the free amine, which, in situ, underwent intramolecular ring-closing lactonization forming a stable six-membered hydroxyimide **14** with the release of free alcohol in 97% yield. Finally, by essentially following the same reaction sequence developed for the first strategy the desired quinazoline intermediate **2** was obtained.



Scheme 3 *Reagents and conditions*: (i) vinyl magnesium bromide, THF, 3 h, 73%; (ii) $EtC(OMe)_3$, $EtCO_2H$, xylene, 135 °C, 4 h, 85%; (iii) $K_2[Fe(CN)_6]$, K_2CO_3, $(DHQ)_2AQN$, $K_2OsO_4{\cdot}2H_2O$, *t*-BuOH–H_2O (1:1), 89%; (iv) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 98%; (v) NaN_3, DMF, 60 °C, 5 h, 87%; (vi) 10% Pd/C, H_2, MeOH, 25 °C, 99%.

In summary, we have developed two independent synthetic methods to access the synthetic precursor quinazoline **2** of (–)-epiquinamide. In the first strategy L-proline-catalyzed one-pot sequential α-amination/propargylation of aldehyde afforded the *anti*-amino alcohol **4** from which intermediate quinazoline **2** was derived. The second strategy used Sharpless asymmetric dihydroxylation for the introduction of stereochemistry to obtain the target compound **2**. The first synthesis was accomplished in nine steps with 24.4% overall yield while the second one resulted in eight steps with 36.4% overall yield. The synthetic strategy described herein has significant potential for further extension to quinazolizidine-based bioactive molecules containing *anti*-vicinal amino alcohol or *syn*-vicinal diamines moieties.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561956.

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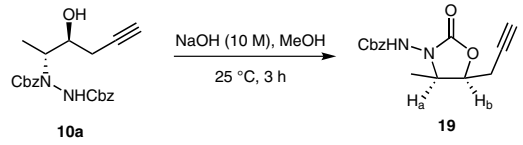
(5) To determine the relative stereochemistry of vicinal amino alcohol **10a**, it was reacted with NaOH (10 M) in MeOH to convert it into oxazilidinone **19** which upon NOE experiment shows that H_a and H_b are in correlation so amino alcohols are in *anti* relationship (Scheme 4).



Scheme 4

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