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# Total synthesis of (+)-epiquinamide from D-mannitol

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ABSTRACT

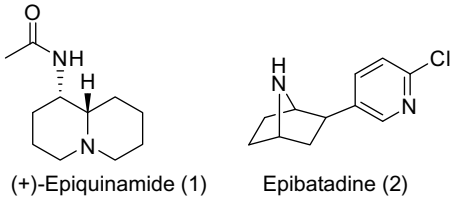
The total synthesis of (+)-epiquinamide, a novel quinolizidine alkaloid isolated from the Ecuadoran poison frog, *Epipedobates tricolor* is described. The key step includes a ring-closing metathesis reaction to construct both the six member rings. D-Mannitol was used as a chiral pool material.



Ecuadoran frog skin is an important source of interesting biologically-active alkaloids.[1] In 2003, Daly et al. isolated novel quinolizidine alkaloids epiquinamide (**1**)[2] along with known alkaloids epibatadine (**2**)[3] from the methanolic skin extracts of an Ecuadoran frog, *Epipedobates* tricolor (Fig. 1). The structure of the compound was disclosed to be **1** on the basis of detailed spectral data (MS, IR and NMR) analysis and recently the absolute stereochemistry was determined by Rutjes et al. via chiral GC.[4a] Daly et al.[2] evaluated the bioactivity of the molecule on the basis of membrane-potential fluorescence and it was found to be β2 selective. But due to the low abundance of the molecule, they could not do further biological studies with epiquinamide. Thus, low availability and potential biological activity make this molecule an attractive target for synthetic organic chemists.[4] As part of our continuing interest in stereoselective syntheses of natural products from the chiral pool[5], we report herein, an approach for the total synthesis of epiquinamide (**1**) starting from the cheap and easily-available starting material, D-mannitol.

Retrosynthetically (Scheme 1), epiquinamide could be obtained from alcohol **3**, which in turn could be obtained from bis-alkene **4** via ring-closing metathesis.[6] Again bis-alkene **4** could be obtained by means of N-allylation of **5**, which could be synthesized through ring-closing metathesis of bis-alkene **6** which in turn, could be synthesized from known compound **7**.[7]

The synthesis of bis-olefinic compound **6** (Scheme 2) commenced from **7**, which was prepared from D-mannitol according to the reported procedure.[7] N-Acylation with 3-butenoic acid using isobutylchloroformate and NMM in THF afforded compound **6** which underwent ring-closing metathesis with Grubbs' 1st generation catalyst in $CH_2Cl_2$ at 50 °C for 6 h and gave six-membered lactum **9**.[6,8] At this stage, we thought that both debenzylation and reduction of the double bond could be carried out under hydrogenation conditions. But when compound **9** was hydrogenated under atmospheric pressure using hydrogen balloons and Pd–C as a catalyst in methanol, it afforded **10** exclusively. Finally, the *N*-benzyl group was removed under Li/liq. $NH_3$ conditions[9] to get compound **5**. N-Allylation of **5** with NaH and allyl-bromide in DMF afforded compound **11**, which was converted to bis-olefinic compound **13** in five steps. Acetonide deprotection followed by routine protecting-group manipulations afforded primary alcohol **12**. Oxidation of the primary alcohol with DMP[10] followed by Wittig olefination with stable ylide $Ph_3P{=}CHCOOEt$ in $CH_2Cl_2$ at room temperature furnished bis-olefinic compound **13**. Herein, it is worth mentioning that the Wittig reaction with $Ph_3P{=}CH_2$ under different conditions failed. Now the stage was set for the crucial ring-closing metathesis reaction for the construction of the second ring. Accordingly, compound **13** was treated with 10 mol % of Grubbs'1st generation catalyst in $CH_2Cl_2$ for 24 h to give **14**[11] in 71% yield. Reduction of the double bond followed by TBS deprotection[12] afforded




(+)-Epiquinamide (1) Epibatadine (2)

**Figure 1.**

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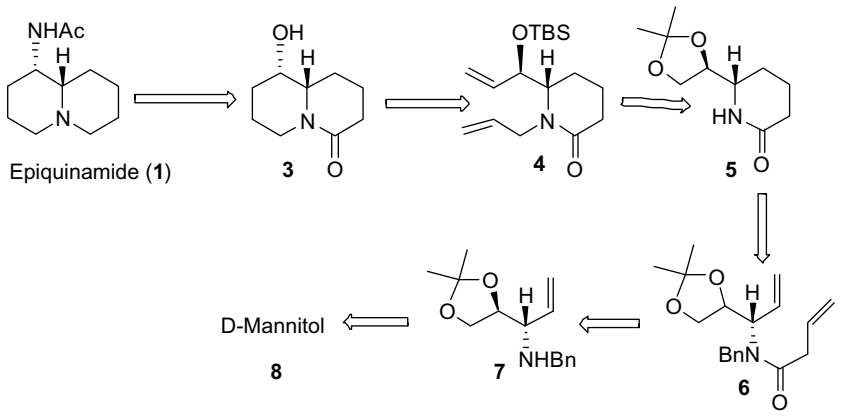
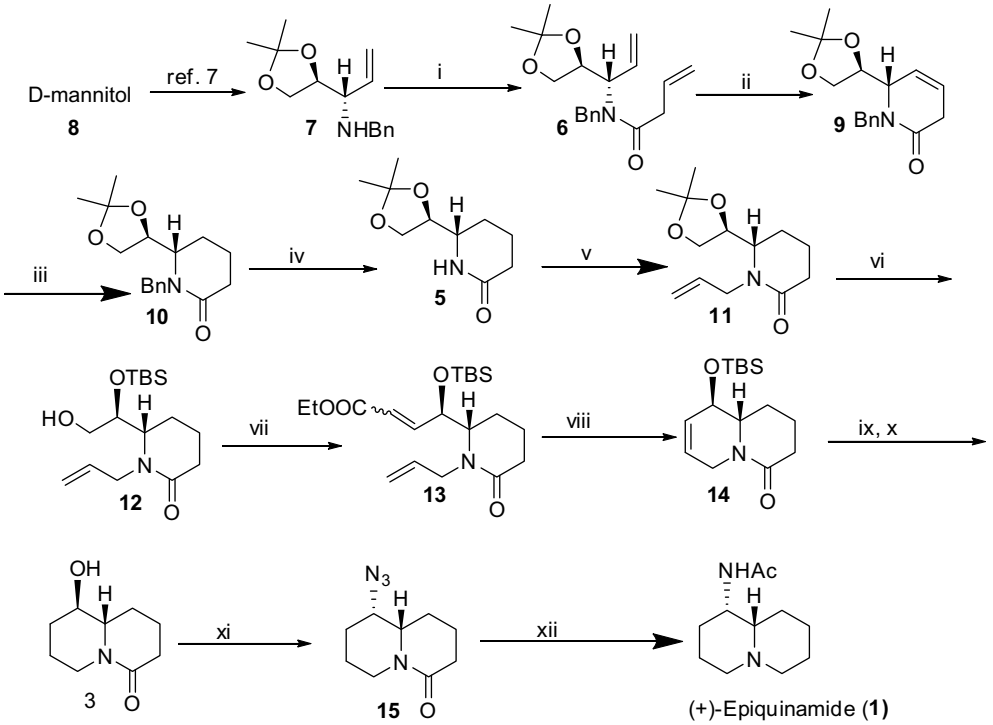



**Scheme 1.** Retrosynthetic analysis of **1**.




**Scheme 2.** Reagents and conditions: (i) 3-butenoic acid, isobutylchloroformate, NMM, THF, 0 °C to rt, 8 h, 87%; (ii) 5 mol % Grubbs' 1st generation catalyst, $CH_2Cl_2$, 50 °C, 5 h, 92%; (iii) $H_2$, Pd–C, MeOH, rt, 0.5 h, 90%; (iv) Li, liq. $NH_3$, THF, −78 °C, 1 h, 64%; (v) NaH, ally bromide, DMF, 0 °C to rt, 2 h, 83%; (vi) (a) CSA, MeOH, rt, 4 h, 77%; (b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 0.5 h, 96%; (c) HF–Py, THF, rt, 14 h, 86%; (vii) (a) DMP, $CH_2Cl_2$, 0 °C to rt, 1.5 h; (b) $Ph_3P{=}CHCOOEt$, $CH_2Cl_2$, rt, 1 h, 84% over two steps; (viii) 10 mol % Grubbs' 1st generation catalyst, $CH_2Cl_2$, 50 °C, 24 h, 71%; (ix) Pd–C, $H_2$, MeOH, 0.5 h, 90%; (x) TBAF, THF, rt, 7 h, 89%; (xi) (a) Ms–Cl, $Et_3N$, $CH_2Cl_2$, 0.5 h; (b) $NaN_3$, DMF, 100 °C, 24 h, 50% over two steps; (xii) (a) $LiAlH_4$, THF, reflux, 24 h; (b) $Ac_2O$, 1 N NaOH, dioxane, 2 h, 79% over two steps.

secondary alcohol **3**. Compound **3** was converted to **15** in two steps; mesylation followed by mesyl displacement with $NaN_3$ gave **15**. Finally **15** was converted to epiquinamide (**1**) according to the reported procedures.[4a,e,f] The spectral data of compounds **15**[13] and **1**[14] are in full agreement with the literature data.[4f]

In conclusion, we have achieved the stereoselective total synthesis of epiquinamide from the commercially available, cheap starting material D-mannitol, with an overall yield of 4.6% from compound **7**, using ring-closing metathesis as a key step. The functionalization of ring-closing metathesis products could provide a large number of analogues of this molecule. Work is going on in that direction, and will be reported in due course.

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8. *Analytical and spectral data of* **9**: $[\alpha]_D^{27}$ −38 (*c* 0.6, $CHCl_3$); IR (neat): $\nu_{max}$ 2984, 2928, 2539, 1643 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.34–7.20 (m, 5H), 5.97 (dt, *J* = 9.8, 3.7 Hz, 1H), 5.75 (ddd, *J* = 9.8, 4.5, 2.3 Hz, 1H), 5.59 (d, *J* = 15.8 Hz, 1H), 4.36 (dt, *J* = 3, 6.8 Hz 1H), 4.20 (d, *J* = 15.8 Hz, 1H), 4.0 (dd, *J* = 8.3, 6.8 Hz, 2H), 3.70 (dd, 8.3, 6.8 Hz, 1H), 3.08 (dd, *J* = 8.3, 3.0 Hz, 2H), 1.42 (s, 3H), 1.32 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 169.1, 136.9, 128.6, 127.7, 127.3, 126.2, 122.1, 109.8, 65.1, 57.8, 47.7, 33.3, 25.8, 25.0; MS (ESIMS): *m*/*z*: 288 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$ 288.1594. Found 288.1596.
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13. *Analytical and spectral data of* **15**: $[\alpha]_D^{27}$ +16.1 (*c* 0.38, $CH_2Cl_2$); IR (neat): $\nu_{max}$ 2925, 2884, 2098, 1655 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 4.81 (m, 1H), 3.63 (m, 1H), 3.39 (m, 1H), 2.47–2.22 (m, 3H), 2.16 (m, 1H), 1.93–1.82 (m, 3H), 1.77–1.71 (m, 2H), 1.68–1.57 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 170.3, 60.7, 58.2, 41.8, 32.7, 28.6, 26.6, 19.5, 19.0; MS (ESIMS): *m*/*z*: 195 $[M+H]^+$; HRMS (ESI) calcd for $C_9H_{15}N_4O$ $[M+H]^+$: 195.1243. Found 195.1238.
14. *Analytical and spectral data of* **1**: $[\alpha]_D^{27}$ +25 (*c* 0.1, $CHCl_3$), reported[4f] +28 (*c* 0.23, $CHCl_3$); IR (neat): $\nu_{max}$ 3354, 2933, 2858, 2356, 1652 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 6.50 (br s, 1H), 3.99 (m, 1H), 2.97–2.75 (m, 2H), 2.02 (s, 3H), 1.91–1.72 (m, 6H), 1.64–1.44 (m, 5H), 1.37–1.26 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 150 MHz) $\delta$ 169.9, 64.6, 56.7, 56.6, 47.9, 29.5, 28.8, 25.3, 23.9, 23.4, 20.4; MS (ESIMS): *m*/*z*: 197.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{11}H_{21}N_2O$ $[M+H]^+$ 197.1653. Found 197.1651.