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# Stereoflexible total synthesis of (−)-epiquinamide

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ABSTRACT

Hydroxy propiolate rearrangement to conjugated diene, Sharpless asymmetric dihydroxylation and one-pot quinolizine construction have been used as key steps in the total synthesis of (−)-epiquinamide.



Alkaloids isolated from the amphibian skin have shown interesting biological profiles especially relevant to neurology.[1] The skin of the Ecuadorian frog *Epipedobates tricolor* has provided novel quinolizidine alkaloid epiquinamide **1**, albeit in minute quantities (240 μg from 183 frogs) representing a new class of nicotinic agonists in CNS disorders (Fig. 1).[2] The scarcity of this natural product did not permit researchers to identify the absolute configuration and thus total synthesis was warranted.[3] Neither the absolute configuration nor optical rotation was reported by the group which isolated this natural product. The total synthesis of either enantiomer did not provide any lead on the absolute configuration. However, more recently, the Gallagher group synthesized the racemate and found no nicotinic activity.[4]

As part of a programme aimed at building a natural product library with alkaloid scaffolds as the back bone, we desired an efficient route to larger quantities of key natural products and also their intermediates.[5] Herein, we disclose a practical synthesis of (−)-epiquinamide **1a** following the retrosynthetic planning shown in Scheme 1. We have devised the plan in such a way that by changing the chiral reagents while following the same synthetic route we will be able to synthesize both the enantiomers. The key steps included the propargyl alcohol rearrangement to all trans diene ester **4**,[6] Sharpless asymmetric dihydroxylation[7] (involving

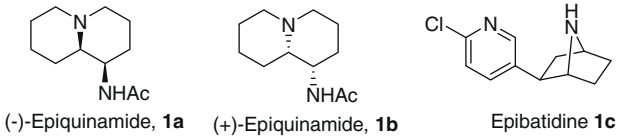
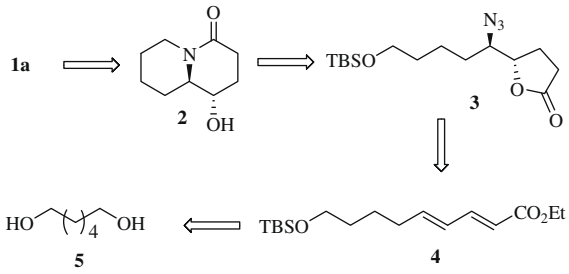
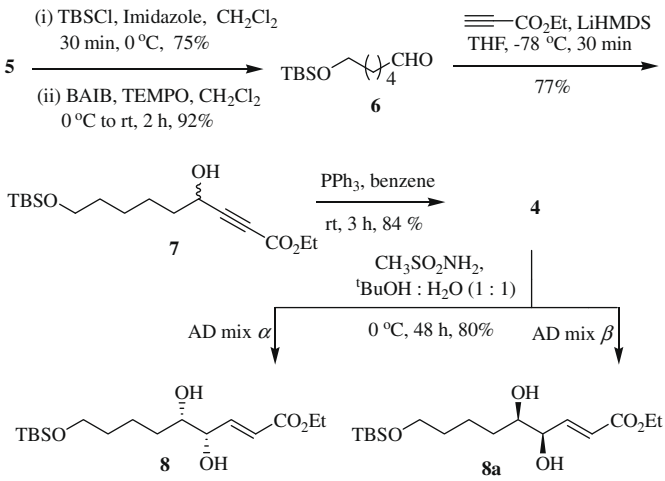



**Figure 1.** Neurologically relevant alkaloids from *Epipedobates*.




**Scheme 1.** Retrosynthesis of (−)-epiquinamide.




**Scheme 2.**

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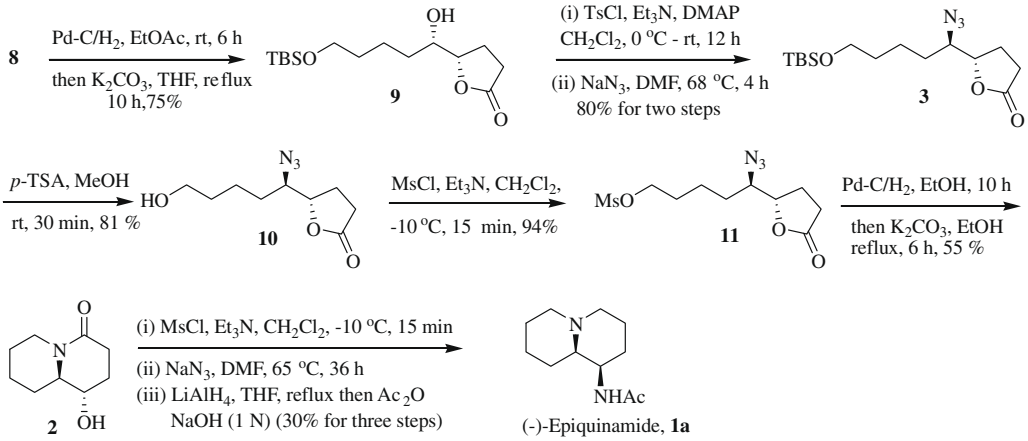


**Scheme 3.**

both ADmix α and ADmix β as reagents) and one-pot reduction-lactamization.

Thus, the forward synthesis was initiated with the commercially available 1,6-hexane-diol **5** as the starting material. The selective monosilylation of diol **5** followed by oxidation of alcohol using bis(acetoxy)iodobenzene (BAIB) and 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) afforded aldehyde **6**. Aldehyde **6** was subjected to the next crucial step to append the ethyl propiolate group (Scheme 2). The lithiated ethyl propiolate was added to aldehyde **6** at −78 °C to yield the hydroxy ethyl propiolate **7** which is ready for an 'allene'-type rearrangement in the presence of $PPh_3$. Hydroxy ethyl propiolate **7** was thus stirred in benzene in the presence of $PPh_3$ to yield the (*E,E*)-diene ester **4** in 84% yield, this being the common precursor for the synthesis of both the enantiomers of the target molecule. The diene ester **4** was subjected to the enantio- and regioselective Sharpless asymmetric dihydroxylation using ADmix α and also ADmix β to yield the diols **8** and **8a** in over 80% yield and 98% enantioselectivity. One of the enantiomers, **8,** has been successfully transformed to target (−)-epiquinamide (vide infra). Thus **8** was subjected to hydrogenation using Pd-C in EtOAc at room temperature and atmospheric pressure for 6 h. This following filtration and evaporation was further refluxed in THF in the presence of $K_2CO_3$, which only yielded the butyrolactone **9** in 75% yield for two steps. The secondary hydroxyl group was transformed to the azido group via tosylate to realize azide **3** in 80% yield (two steps). As the stage is set for building the quinolizine framework, the silyl ether group in **3** was transformed to mesyl ester **11** via alcohol **10** in 76% yield (for two steps). The mesylate **11** was subjected to one-pot reduction–double cyclization involving azide reduction to amine which underwent intramolecular cyclization displacing mesylate. Another facile lactamization opened up the butyrolactone ring to furnish the hydroxyl quinolizinone **2** in 55% yield. The acetamino group in **2** was introduced following the literature procedure to realize the (−)-epiquinamide **1a** whose spectral data was in full agreement with the literature data[3c,e] (Scheme 3).[8]

In conclusion, a strategy devised to synthesize either of the enantiomers has been developed and successfully demonstrated for the synthesis of (−)-isomer in good yields amenable to analoging and derivatization.

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8. *Spectral data of selected compounds*: *(4S,5S,E)-Ethyl 9-(tert-butyldimethylsilyloxy)-4,5-dihydroxynon-2-enoate* **(8)**: $[\alpha]_D^{27}$ −15.8 (*c* 1.0, $CHCl_3$); IR (KBr): $\nu_{max}$ 3425, 2932, 2858, 1717, 1655, 1465, 1254 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz): δ 6.88 (dd, *J* = 15.6, 5.4 Hz, 1H), 6.10 (dd, *J* = 15.6, 1.5 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.12–4.02 (m, 1H), 3.68–3.57 (m, 2H), 3.56–3.47 (m, 1H), 2.55 (d, *J* = 5.4 Hz, 1H), 2.40 (d, *J* = 3.9 Hz, 1H), 1.64–1.36 (m, 6H), 1.30 (t, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 166.4, 146.9, 122.3, 74.0, 73.9, 63.0, 60.5, 32.6, 32.4, 25.9, 21.9, 18.3, 14.1, −5.3; ESIMS: *m/z* 347 $(M+H)^+$; HRMS: calcd for $C_{17}H_{34}O_5NaSi$ $(M+Na)^+$: 369.2073, found: 369.2079. *(4R,5R,E)-Ethyl 9-(tert-butyldimethylsilyloxy)-4,5-dihydroxynon-2-enoate* **(8a)**: $[\alpha]_D^{27}$ +17.0 (*c* 1.5, $CHCl_3$); IR (KBr): $\nu_{max}$ 3430, 2931, 2858, 1718, 1656, 1466, 1254 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 6.88 (dd, *J* = 15.8, 5.2 Hz, 1H), 6.10 (dd, *J* = 15.8, 1.5 Hz, 1H), 4.19 (q, *J* = 6.7 Hz, 2H), 4.12–4.02 (m, 1H), 3.68–3.57 (m, 2H), 3.56–3.47 (m, 1H), 2.46–2.38 (m, 1H), 2.30–2.21 (m, 1H), 1.64–1.36 (m, 6H), 1.30 (t, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 166.4, 146.9, 122.3, 74.0, 73.9, 63.0, 60.5, 32.6, 32.4, 25.9, 21.9, 18.3, 14.1, −5.3; ESIMS: *m/z* 347 $(M+H)^+$; HRMS: calcd for $C_{17}H_{34}O_5NaSi$ $(M+Na)^+$: 369.2073, found: 369.2077. *(S)-5-((S)-5-(tert-Butyldimethylsilyloxy)-1-hydroxypentyl)-dihydrofuran-2(3H)-one* **(9)**: $[\alpha]_D^{27}$ +15.0 (*c* 1.4, $CHCl_3$); IR (KBr): $\nu_{max}$ 3446, 2931, 2858, 1773, 1466, 1631, 1466, 1254 $cm^{-1}$; δ 4.36 (td, *J* = 10.9, 7.0 Hz, 1H), 3.63–3.56 (m, 2H), 3.55–3.45 (br m, 1H), 2.65–2.41 (m, 2H), 2.36 (br m, 1H), 2.27–2.04 (m, 2H), 1.61–1.45 (m, 6H), 0.87 (s, 9H), 0.02 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 177.3, 83.1, 73.8, 63.1, 32.8, 32.6, 28.8, 25.9, 24.2, 22.1, 18.5, −5.2; ESIMS: *m/z* 325 $(M+Na)^+$; HRMS: calcd for $C_{15}H_{30}O_4NaSi$ $(M+Na)^+$: 325.1811, found: 325.1806. *(1S,9aR)-1-Hydroxy-hexahydro-1H-quinolizin-4(6H)-one* **(2)**: $[\alpha]_D^{27}$ −8.0 (*c* 1.0, $CHCl_3$); IR (KBr): $\nu_{max}$ 3424, 2922, 2853, 1616, 1462 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz): δ 4.77–4.69 (m, 1H), 3.77–3.69 (m, 1H), 3.14 (ddd, *J* = 12.0, 4.6, 2.7 Hz, 1H), 2.57 (ddd, *J* = 17.5, 7.4, 5.5 Hz, 1H), 2.41 (dt, *J* = 12.9, 2.7 Hz, 1H), 2.34 (ddd, *J* = 17.5, 8.3, 5.5 Hz, 1H), 2.02–1.79 (m, 4H), 1.67 (br d, *J* = 12.9, 1H), 1.54–1.42 (m, 1H), 1.42–1.33 (m, 1H), 1.27–1.16 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 168.4, 69.8, 63.7, 42.9, 31.6, 28.5, 27.0, 25.2, 24.4; ESIMS: *m/z* 170 $(M+H)^+$; HRMS: calcd for $C_9H_{15}NO_2Na$ $(M+Na)^+$: 192.1000, found: 192.1002. Opposite enantiomer of compound **2**: *(1R,9a S)-1-Hydroxy-hexahydro-1H-quinolizin-4(6H)-one*: $[\alpha]_D^{27}$ +7.8 (*c* 1.0, $CHCl_3$); IR (KBr): $\nu_{max}$ 3430, 2920, 2851, 1616, 1462 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 4.77–4.69 (m, 1H), 3.77–3.69 (m, 1H), 3.16 (ddd, *J* = 11.7, 4.4, 2.9 Hz, 1H), 2.57 (ddd, *J* = 17.5, 8.0, 5.8 Hz, 1H), 2.41 (dt, *J* = 13.1, 2.9 Hz, 1H), 2.33 (ddd, *J* = 16.8, 8.0, 5.8 Hz, 1H), 2.03–1.79 (m, 4H), 1.67 (br, d, *J* = 13.0, 1H), 1.54–1.42 (m, 1H), 1.42–1.33 (m, 1H), 1.27–1.16 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz): δ 168.4, 69.6, 63.7, 42.9, 31.5, 28.4, 26.9, 25.2, 24.4; ESIMS: *m/z* 170 $(M+H)^+$; HRMS: calcd for $C_9H_{15}NO_2Na$ $(M+Na)^+$: 192.1000, found: 192.1003.