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A concise synthesis of (±) and a total synthesis of (+)-epiquinamide

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Abstract—A total synthesis of the quinolizidine alkaloid (+)-epiquinamide **1** has been achieved starting from (−)-pipecolinic acid **3**. The key step is the highly diastereoselective addition of a TBDMS-protected propargyl alcohol to a chiral aldehyde derived from **3** to give *erythro* alkynol **19**, which is then easily transformed into the desired bicyclic skeleton.

Epiquinamide **1** is a quinolizidine alkaloid recently isolated from extracts of the skin of *Epipedobates tricolor*, an Ecuadorian poisonous frog.[1] Epiquinamide **1**, has been found to be highly selective for β2 nicotinic acetylcholine receptors (nAChRs), as such, representing a new structural class of nicotinic agonists and could be considered a lead compound for the development of nAChR therapeutic agents. The minute amount (~240 μg) of **1** isolated from the skin extracts was enough to determine the structure and the relative stereochemistry of the natural product as (1*R**,10*R**)-1-acetamidoquinolizidine. Due to **1** being a novel nicotinic agonist with unresolved absolute stereochemistry it was decided to synthesise epiquinamide **1** with the aim of developing new nicotinic agents. During the course of this work, the structure and relative stereochemistry of epiquinamide **1** were confirmed by two independent asymmetric syntheses.[2,3] We herein report a simple synthesis of (±)-epiquinamide **1** and its (1*S**,10*R**) diastereoisomer **2** as well as the synthesis of (+)-**1**, both syntheses utilising commercially available pipecolinic acid **3** as the starting material.

For confirming the relative stereochemistry of **1** we decided to prepare both diastereoisomers of 1-aminoquinolizidine **4**, which have been previously reported only as a mixture of diastereoisomers,[4–6] from the reduction of the known oxime **5**.[6,7] During our synthesis of oxime **5**, we found many of the previously reported steps to be low yielding and irreproducible, and hence it was decided to optimise this synthesis (Scheme 1). Racemic pipecolinic acid **3** was converted into ethyl pipecolinate hydrochloride[8] using thionyl chloride in ethanol and then alkylated with ethyl 4-bromobutyrate to give diester **6**[9,10] in 85% overall yield. Dieckmann cyclisation of diester **6** was achieved using potassium *tert*-butoxide in THF at room temperature to give keto-ester **7**[7,10] in high yield, the NMR spectra of which showed that it existed exclusively in the enol form. Hydrolysis and decarboxylation of **7** was achieved by heating in 4 M HCl overnight[11] to give ketone **8**[6] in 89% yield; it was found that this method was higher yielding and more reliable than refluxing in sulfuric acid.[6,9] Ketone **8** was found to be particularly unstable (~50% decomposition occurred if left standing overnight at room temperature) and was used immediately. Conversion of ketone **8** to oxime **5** was achieved in 82% yield, using the previously reported method.[6] Reduction of oxime **5** using $LiAlH_4$ in THF gave a 1.1:1 ratio of (1*S**,10*S**)-**4** to (1*R**,10*S**)-**4**, in 84% yield, which were separated using repeated column chromatography (98:2 MeOH/aq NH_3). Both amines **4** were acetylated using acetyl chloride in DMF to give (±)-epiquinamides **1** and **2** in reasonable yields. The ^1H NMR spectrum of **1** was identical to that reported for the isolated natural product.[1]

Disappointed with the ratio of products from the oxime reduction, we investigated an alternative method of introducing the 1-amino group. Reduction of ketone **8** with $NaBH_4$ gave a 5:1 ratio of the desired equatorial alcohol **9**[12–14] over the axial **10**, and that the separation of the two alcohols by column chromatography (using 100% MeOH) being far more easily achieved than separation of amines **4**. Alcohol **9** was then converted via the mesylate to azide **11** in 75% overall yield. The optimal

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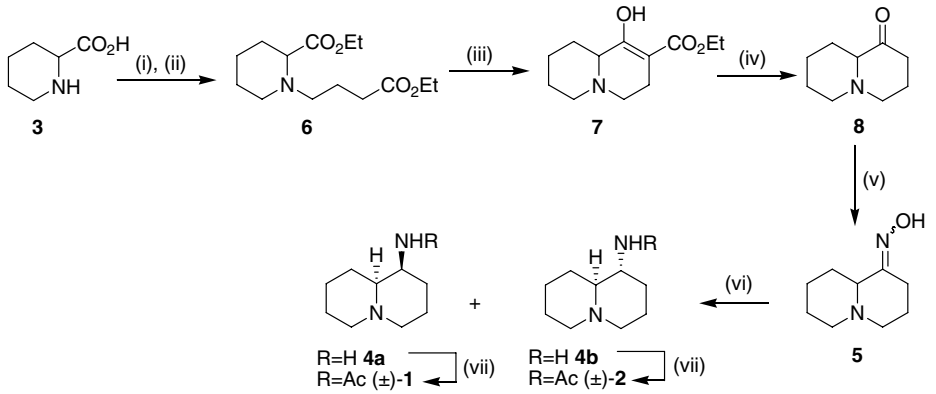
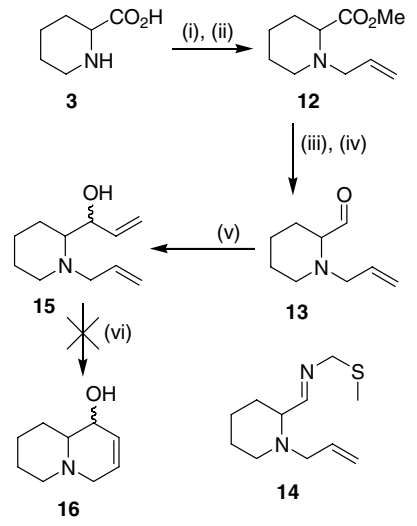


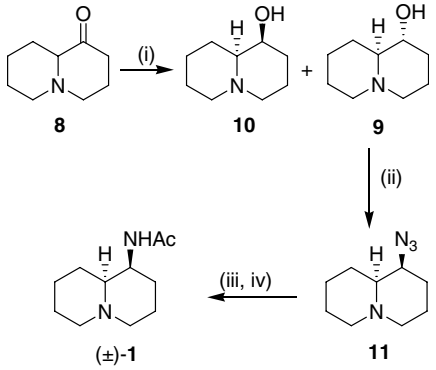
Scheme 1. Reagents, conditions and yields: (i) $SOCl_2$, EtOH, reflux, 2 h, 99%; (ii) 1.05 equiv ethyl 4-bromobutyrate, K_2CO_3, acetone, reflux, 22 h, 85%; (iii) 2 equiv KO^{t}Bu, THF, 0 °C to rt, 2 h, 95%; (iv) 4 M HCl, 90–100 °C, 12 h, 89%; (v) $NH_2OH{\cdot}HCl$, pyridine, EtOH, reflux, 1 h, 82%; (vi) $LiAlH_4$, THF, 0 °C to rt, 1 h, **4a** (45%) and **4b** (39%); (vii) AcCl, NEt_3, DMF, rt, 20 h, **1** (69%), **2** (72%).

temperature for azide addition was found to be 70–80 °C, below which only trace amounts azide **11** was formed and unreacted mesylate was returned whilst temperatures above 100 °C resulted in extensive decomposition. Reduction of azide **11** was achieved in 92% yield using $LiAlH_4$ to give amine **4**, which was acetylated as above to give (±)-**1** (Scheme 2).

With racemic **1** in hand we then wished to synthesize **1** asymmetrically, again beginning with pipecolinic acid **3**. Starting from chirally pure **3** using the schemes outlined above was, however, unfeasible as complete racemisation occurred during the Dieckmann and decarboxylation steps of the synthesis. We therefore turned to alternative methods to convert pipecolinic acid **3** to the required quinolizidine ring system and we initially envisaged using ring-closing metathesis to form the second ring and began by trialing the route on racemic **3** (Scheme 3). Pipecolinic acid **3** was converted to the methyl ester and then allylated to form **12**[15] in 65% overall yield. Reduction of ester **12** with $LiAlH_4$ gave the primary alcohol which was then oxidized using Swern conditions[16,17] to give the unstable aldehyde **13**[18] in a modest 50% yield. It was discovered that the use of a workup procedure with ammonium chloride[17] resulted



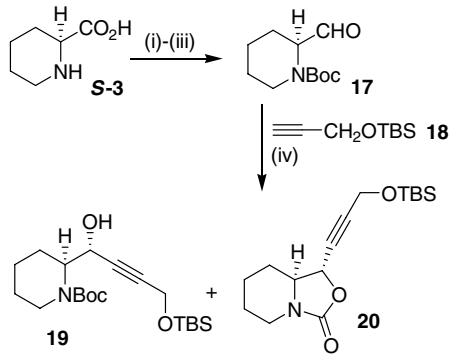
Scheme 3. Reagents, conditions and yields: (i) $SOCl_2$, MeOH, reflux, 2 h, 97%; (ii) 1 equiv allyl bromide, K_2CO_3, acetone, reflux, 17 h, 68%; (iii) $LiAlH_4$, THF, 0 °C to rt, 50 min, 92%; (iv) $(COCl)_2$, DMSO, DCM, −78 °C to rt, 1 h, 50%; (v) 4 equiv vinyl magnesium bromide, 0 °C to rt, 2 h, 66% (1:1 mixture of inseparable diastereoisomers); (vi) Grubb's first and second generation RCM catalysts (5 and 10 mol %) DCM, **16** (0%).



Scheme 2. Reagents, conditions and yields: (i) $NaBH_4$, MeOH, 0 °C to rt, 6 h, **10** (16%) and **9** (82%); (ii) (a) 1.2 equiv MsCl, NEt_3, DCM, 0 °C, 30 min; (b) 5 equiv NaN_3, DMF, 70–80 °C, 18 h, 75% from **9**; (iii) $LiAlH_4$, THF, rt, 3 h, 92%; (iv) AcCl, NEt_3, DMF, rt, 21 h, 73%.

in significant amounts of methylthiomethyl imine **14** being generated, which was alleviated by the use of brine rather than the ammonium chloride. Addition of vinyl magnesium bromide to aldehyde **13** gave alcohol **15** as a 1:1 inseparable mixture of diastereoisomers in 66% yield. Unfortunately ring-closing metathesis of diene **15**, using either Grubb's first or second generation catalysts under a variety of conditions, did not result in the desired allylic alcohol **16**. Decomposition of the starting material occurred under all the conditions tested and this route was abandoned.

We then turned to an approach involving addition of a nucleophile with all the required carbons to form the second ring to the known aldehyde **17**.[19,20] Aldehyde **17** was synthesized from *S*-**3**, which in turn was obtained by resolution of the tartrate salts of racemic **3**.[21] Addi-



Scheme 4. Reagents, conditions and yields: (i) Boc_2O, NEt_3, dioxane, H_2O, rt, 18 h, 84%; (ii) (a) ^tBuCOCl, NEt_3, DCM, −10 to 0 °C, 90 min; (b) (MeO)MeNH·HCl, NEt_3, DCM, 18 h, 72% over two steps; (iii) $LiAlH_4$, Et_2O, 0 °C to rt, 30 min, 99%; (iv) see Ref./note 26, **19** (69%) and **20** (5%).

tion of the lithium anion of TBDMS-protected propargyl alcohol **18**[22–24] to aldehyde **17** gave predominantly (14:1, overall 79% yield) the desired *erythro* alkynol **19** and also the *threo* isomer **20**, which was isolated in its cyclised form (Scheme 4).[25,26]

With alkyne **19** now having the carbons to make up the quinolizidine ring system and the correct stereochemistry for transformation into **1** all that was required was to close the second ring and convert the 1-hydroxyl group into the required 1-acetamide. We initially investigated the idea of exchanging the hydroxyl group for an azide at an earlier stage, thereby allowing us to hopefully reduce the azide and alkyne functionalities in **21** in a single synthetic step (Scheme 5). However, when using our previously successful conditions, activation of the hydroxyl group as a mesylate prior to azide addition resulted in an intramolecular attack of the Boc group displacing the mesylate with resultant inversion of stereochemistry to give the previously isolated oxazolidinone **20**.[27] Alcohol **19** was protected as the acetyl ester and the alkyne reduced to give silyl ether **22** in 77% yield over two steps. Formation of the quinolizidine was achieved by firstly deprotecting the silyl ether, using TBAF, conversion of the free alcohol to the mesylate and then Boc deprotection with TFA, neutralizing the reaction mixture with added NEt_3 to give (1*R*,10*S*)-1-acetoxyquinolizidine **23** in 86% over three steps. Hydrolysis of the acetyl ester with NaOH gave (1*R*,10*S*)-**9** in 80% yield, which was converted to (+)-(1*S*,10*S*)-epiquinamide **1**[28] using the same procedure as outlined for racemic **9**, the only alteration in the synthesis being the use of a higher yielding N-acetylation procedure.[2]

In summary, starting from commercially available pipecolinic acid **3**, (±)-epiquinamide **1** was synthesized in eight steps in 29% overall yield, whilst (+)-**1** was synthesized from *S*-**3** in 12 steps in 13% overall yield. The key step in the synthesis is the addition of acetylene **18** to aldehyde **17** giving the desired *erythro* alkynol **19** in good yield with high diastereoselectivity, with added benefit that the undesired *threo* isomer cyclises to form the easily separable oxazolidinone **20**. The synthesis of *N*-acyl analogues of epiquinamide is currently being pursued, and their preparation and biological evaluation will be reported in due course.

Acknowledgements

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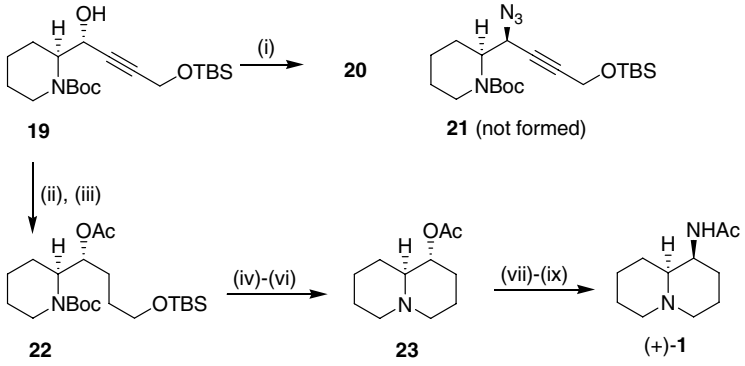

Scheme 5. Reagents, conditions and yields: (i) (a) MsCl, NEt_3, DCM, 0 °C, 30 min; (b) NaN_3, 80 °C, 18 h, **20** (64%); (ii) Ac_2O, NEt_3, DCM, rt, 4 h, 81%; (iii) H_2, 10% Pd/C, MeOH, 2 h, 95%; (iv) TBAF, THF, rt, 3 h, 99%; (v) MsCl, NEt_3, DCM, 0 °C, 40 min, 92%; (vi) (a) TFA, DCM, 0 °C, 90 min; (b) NEt_3, DCM, 20 h, 95%; (vii) NaOH, EtOH, rt, 2 h, 80%; (viii) (a) 1.1 equiv MsCl, NEt_3, DCM, 0 °C, 30 min; (b) 5 equiv NaN_3, 70–75 °C, 18 h, 75% over two steps; (ix) (a) $LiAlH_4$, THF, rt, 3 h; (b) Ac_2O, 1 M NaOH, dioxane, rt, 3 h, 80% over two steps.

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26. To a stirred solution of alkyne **18** (300 mg, 1.76 mmol) in THF (5 mL) at −78 °C under N_2 was slowly added *n*-BuLi (1.6 M, 1.05 mL, 1.68 mmol). The mixture was stirred at 0 °C for 75 min and then cooled to −78 °C. A solution of aldehyde **17** (190 mg, 0.88 mmol) in THF (3 mL) was added dropwise to the mixture and stirred at 0 °C for 4 h. After that, the mixture was left stirring at room temperature overnight. The mixture was then diluted with 1 M NaH_2PO_4 (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo to afford the crude product, which was purified by flash chromatography (3:1 hexane–EtOAc) to provide **19** (234 mg, 69%) as a pale yellow oil: $[\alpha]_D^{20}$ −18.9 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 3414 (O–H), 2930 (C–H), 2175 (C≡C), 1693 (C=O); δ_H (400 MHz, $CDCl_3$; Me_4Si) 0.10 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiMe_2C(CH_3)_3$), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.56–1.75 (5H, m, 3b-H, 4-H × 2, 5-H × 2), 1.97 (1H, br d, $J = 13.2$ Hz, 3a-H), 3.10–2.90 (1H, br s, 6a-H), 3.95 (1H, br d, $J = 10.8$ Hz, 6b-H), 4.18 (1H, dd, $J_1 = 10.1$ Hz, $J_2 = 6.2$ Hz, 2-H), 4.32 (2H, d, $J = 1.7$ Hz, 4′-H), 4.65 (1H, dd, $J_1 = 6.3$ Hz, $J_2 = 6.3$ Hz, 1′-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) −5.30 ($Si(CH_3)_2$), 18.11 ($SiMe_2C(CH_3)_3$), 19.08 (C-4), 24.12 (C-3 or C-5), 24.57 (C-3 or C-5), 25.67 ($SiMe_2C(CH_3)_3$), 28.28 ($CO_2C(CH_3)_3$), 40.38 (C-6), 51.65 (C-4′), 55.11 (C-2), 62.60 (C-1′), 79.52 ($CO_2C(CH_3)_3$), 83.86 (C-2′ or C-3′), 83.94 (C-2′ or C-3′), 155.39 (quat. C=O); *m*/*z* (FAB, NBA) 384 (0.14, $M+H^+$), 328 (0.29), 310 (0.24), 284 (0.29), 184 (0.25, M−CH(OH)C≡CCH_2OTBS), 128 (1.00, M−[CH-(OH)C≡$CCH_2OTBS+C(CH_3)_3^+$]), 84 (0.62, $N(CH_2)_5$); HRMS calculated for $C_{20}H_{38}NO_4Si$ ($M+H^+$) 384.25701, found 384.25768; and **20** (14 mg, 5%) as a pale yellow oil: $[\alpha]_D^{20}$ −18.9 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 2929 (C–H), 2266 (C≡C), 1758 (C=O), 1415, 1260; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.12 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $C(CH_3)_3$), 1.35–1.44 (2H, m, 6a-H, 7a-H), 1.55–1.75 (2H, m, 8a-H, 6b-H), 1.74–1.84 (1H, m, 8b-H), 1.90–2.03 (1H, m, 7b-H), 2.83 (1H, td, $J_1 = 12.7$ Hz, $J_2 = 3.4$ Hz, 5a-H), 3.66 (1H, ddd, $J_1 = 11.5$ Hz, $J_2 = 8.0$ Hz, $J_3 = 3.7$ Hz, 8a-H), 3.88 (1H, dd, $J_1 = 13.2$ Hz, $J_2 = 4.4$ Hz, 5b-H), 4.37 (2H, d, $J = 1.7$ Hz, CH_2O), 5.22 (1H, dt, $J_1 = 8.0$ Hz, $J_2 = 1.6$ Hz, 1-H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si) −5.22 ($Si(CH_3)_2$), 18.21 ($C(CH_3)_3$), 22.68 (C-4), 23.88 (C-3), 25.71 ($C(CH_3)_3$), 27.21 (C-5), 41.98 (C-2), 51.52 (CH_2O), 56.93 (C-6), 67.42 (C-7), 88.77 (C≡C), 156.0 (quat. C=O); *m*/*z* (FAB, NBA) 310 (1.00, $M+H^+$), 154 (0.28), 134 (0.40), 73 (0.40); HRMS calculated for $C_{16}H_{28}NO_3Si$ ($M+H^+$) 310.18385, found 310.18412.
27. We later were to discover that if at any time before the Boc group is removed and quinolizidine ring formation is complete that this hydroxyl group was converted to a mesylate then oxazolidinone formation is the predominant reaction, thus necessitating the protection of the hydroxyl group until that stage.
28. $[\alpha]_D^{22}$ +26.2 (*c* 0.25, $CHCl_3$) [lit.[2] $[\alpha]_D^{20}$ 28.0] (*c* 0.23, $CHCl_3$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.22–1.72 (m, 9H), 1.79–2.01 (m, 4H), 2.02 (s, 3H), 2.74–2.81 (m, 2H), 3.90–3.92 (m, 1H), 6.18 (br s, 1H); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 169.5, 64.2, 56.6, 56.5, 48.0, 29.6, 29.0, 25.5, 23.9, 23.5, 20.6; HRMS calculated for $C_{11}H_{21}N_2O$ ($M+H^+$), 197.1654, found 197.1660. These values are consistent with the literature values.[1,2]