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Achiral auxiliary-assisted chiral transfer via microwave-accelerated aza-Claisen rearrangement: a short synthesis of (+)-1-hydroxyquinolizidinone

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ABSTRACT

A short and efficient synthesis of (+)-1-hydroxyquinolizidinone as an advanced core intermediate for the syntheses of (+)-epiquinamide, (+)-homopumiliotoxin, and (+)-lupinine is described. The key feature of our strategy includes a sequential chiral transfer using an achiral phenylsulfide auxiliary via microwave-accelerated aza-Claisen rearrangement of the unexplored *N*-thiophenoxyacetyl-α-vinyl piperidine substrate and the oxone-induced transannulation.

The quinolizidine alkaloids are considered attractive synthetic targets by both organic and medicinal chemists because of their structural and biological diversity.[1] Epiquinamide was isolated in 2003 from the Ecuadoran poison frog *Epipedobates tricolor*,[2] but further studies on the biological activities were limited due to its paucity from natural sources (240 μg from 183 frogs). Homopumiliotoxin 223G was first discovered in 1987 in the Panamanian poison frog *Dendrobates pumilio*,[3] and asymmetric total syntheses of this alkaloid were completed by only two research groups[4] in spite of its unique structure. Lupin alkaloids, a large family of quinolizidine alkaloids, are known to have a wide range of biological activities including anticholinesterase activity, activation of nicotinic receptor, and antimicrobial activity.[5] Lupinine is considered a representative of the Lupin alkaloids and is of interest to synthetic chemists due to its structural simplicity.[6] Thus, we have recently worked toward development of efficient synthetic routes for the quinolizidine alkaloids.

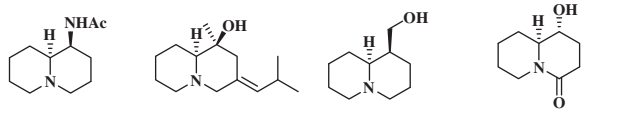
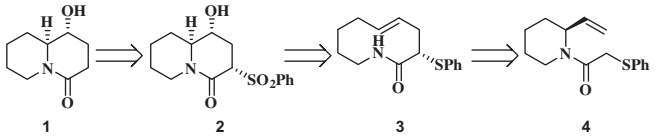


Figure 1. Representative quinolizidine alkaloids.

We previously reported asymmetric total syntheses of natural alkaloids employing azacycle ring-expansion induced by aza-Claisen rearrangement (ACR).[7] In addition, we have recently explored an extension of our ring-expansion strategy, which involved chiral transfer through the thiophenyl-substituted *N*-acyl moiety of the ACR precursor. Especially, the thiophenyl group served as an achiral auxiliary, which realized a sequential chiral transfer strategy. The thiophenyl group initially provided a 1,4-chiral transfer via ACR and then induced a tandem epoxidation-transannulation in a remarkably stereoselective manner. We were able to apply this unprecedented procedure to the asymmetric synthesis of quinolizidine alkaloid. Herein, we report an achiral auxiliary-assisted chiral transfer via ACR and its application to a concise synthesis of (+)-1-hydroxyquinolizidinone **1**, a core and advanced intermediate for the syntheses of (+)-epiquinamide, (+)-homopumiliotoxin 223G, and (+)-lupinine (Fig. 1).[8]

Our retrosynthetic approach to (+)-1-hydroxyquinolizidinone **1** is illustrated in Scheme 1. The key part of our unique synthesis includes the ACR-induced stereoselective ring expansion of *N*-thiophenoxyacetyl-α-vinyl piperidine (**4**) and the substrate-controlled



Scheme 1. Retrosynthetic analysis.

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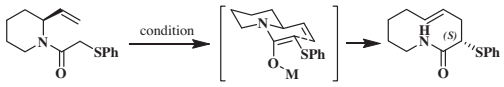
stereoselective transannulation of the resulting 10-membered lactam intermediate **3.** Through this sequence, the steroselective formations of the new stereocenters would be achieved by the sequential chiral transfers, which are assisted by the phenyl sulfide auxiliary. The final quinolizidinone **1** could be obtained from **2** by the reductive removal of the benzenesulfonyl group. The vinylpiperidine **4** was expected to be readily accessible from the commercially available carboxylic acid **5**.

The synthesis of (+)-1-hydroxyquinolizidinone **1** was commenced with the intensive examination of the ACR-induced ring-expansion of **4** as summarized in Table 1. Our initial attempt to perform the ACR-induced ring-expansion of **4** under our standard reaction conditions[7] was unfortunately not successful (entry 1). Poor stereoselectivity and unsatisfactory yield were observed. The low stereoselectivity was likely due to the epimerization of the initially established chiral center of the ring-expansion products **3** under the harsh reaction conditions, which included excess base and a long reaction time.[9] Reductions in the amount of base and in the reaction time (entries 2–3) slightly improved the stereoselectivity, as we had anticipated. Replacing LHMDS with *i*-PrMgCl slightly increased the conversion yield up to 22% (entry 4).[7b] Finally, we were able to obtain a satisfactory stereoselectivity and chemical yield by accelerating the ACR utilizing a microwave.[10] Microwave irradiation enhanced the reaction rate of ACR and consequently decreased reaction time, which resulted in the excellent stereoselectivity (1:37) and chemical yield (83%) (entry 6). The short reaction time provided the high stereoselectivity but decreased the conversion yield (entry 7). To the best of our knowledge, ACR of the α-thio-substituted amide has not been reported previously.

Table 1
ACR of *N*-thiophenoxyacetyl-α-vinyl piperidine 4

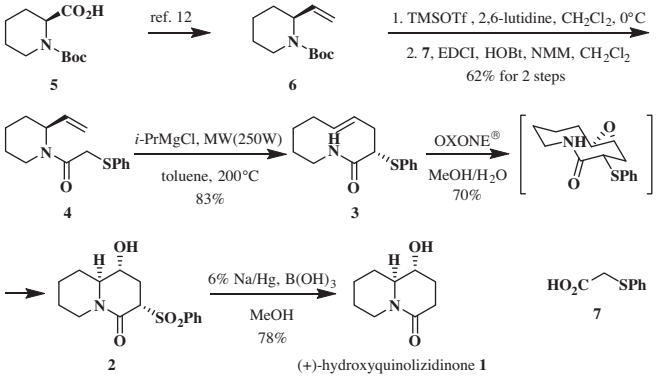


4 3

Entry	Condition[a]	Ratio[b] (R:S)	Yield[c] (%)
1	LHMDS(4.0 equiv), 140 °C, 48 h	1:1.5	64
2	LHMDS(2.0 equiv), 140 °C, 24 h	1:2.0	19
3	LHMDS(1.0 equiv), 140 °C, 24 h	1:4.2	10
4	*i*-PrMgCl(2.0 equiv), 140 °C, 24 h	1:2.8	22
5	LHMDS(1.0 equiv), MW(250 W), 200 °C, 10 min	1:35	10
6	*i*-PrMgcl(1.0 equiv), MW(250 W), 200 °C, 10 min	1:37	83
7	*i*-PrMgcl(1.0 equiv), MW(250 W), 200 °C, 5 min	1:46	65

[a] All reaction proceeded in toluene (0.05 M).
[b] Ratios were detected by HPLC.
[c] Isolated yield of mixtures.

The ACR precursor **4** was prepared from the known (*S*)-2-vinyl-*N*-Boc-piperidine **6**, which was readily derived from commercially available (*S*)-*N*-Boc-pipecolinic acid **5** (Scheme 2[11]).[12] Boc deprotection of **6** with TMSOTf in the presence of 2,6-lutidine and subsequent acylation of the resulting amine with **7** afforded amide **4** in 62% yield in 2 steps. The microwave-assisted ACR of amide **4** with *i*-PrMgCl provided the ring-expanded lactam **3** in a yield of 83%. During the ACR, the C-2 chirality of **6** was transferred to the thiophenyl-substituted stereocenter of **3**. Lactam **3** was stereoselectively transformed into the key quinolizidinone intermediate **2** by oxone-induced transannulation.[13] Quinolizidinone **2** was effectively obtained in a high yield and with a high stereoselectivity (> 12:1). The sulfide auxiliary was oxidized to the readily removable sulfonyl group.[14] Finally, (+)-1-hydroxyquinolizidinone **1** could be obtained by desulfonylation of **2** with 6% Na/Hg in the presence of boric acid.[15] The structure of synthetic **1** was confirmed by comparison of the spectral data with the reported data (^{1}H NMR, ^{13}C NMR, IR, HR-MS and optical rotation).[7a,10]



Scheme 2. Synthesis of (+)-1-hydroxyquinolizidinone 1.

In conclusion, the synthesis of (+)-1-hydroxyquinolizidinone, a core and advanced intermediate for the synthesis of (+)-epiquinamide, (+)-homopumiliotoxin 223G, and (+)-lupinine, was accomplished in five steps and with an overall yield of 28% from the known 2-vinylpiperidine **6**. The key part of the synthesis involves the microwave-accelerated ACR of *N*-thiophenoxyacetyl-α-vinyl piperidine and the oxone-induced transannulation of the 10-membered lactam intermediate. In particular, an unprecedented chiral transfer during the ACR utilizing the achiral phenyl sulfide auxiliary is reported. Our unique synthetic approach is expected to be utilized in the syntheses of quinolizidine alkaloids.

Acknowledgment

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9. To confirm the epimerization, intermediate 3 (a mixture of R and S in a 1:4.2 ratio) was retreated under the condition 3 of Table 1 (entry 3). As a result, we could obtain the racemized product of 3 as a 1:1.3 mixture.
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11. *Spectral data*: (*S*)-2-(phenylthio)-1-(2-vinylpiperidin-1-yl)ethanone (**4**): $[\alpha]_D^{20}$ −93.6 (*c* 0.411, $CHCl_3$); FT-IR (thin film, neat) υ_{max} 2938, 2860, 1644, 1583, 1481, 1439, 1324 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 7.42 (d, 2H, *J* = 7.5 Hz), 7.27 (t, 2H, *J* = 7.6 Hz), 7.19 (t, 1H, *J* = 7.3 Hz), 5.72 (m, 1H), 5.29 (s), 5.21 (dd, 1H, *J* = 21.6, 10.5 Hz), 5.06 (d, 1H, *J* = 17.4 Hz), 4.56–4.41 (m, 1H), 3.77 (s, 2H), 3.66 (m, 2H), 3.18 (t, 0.5H, *J* = 12.16 Hz), 2.68 (t, 0.5H, *J* = 12.46 Hz), 1.81–1.58 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, mixture of rotamers) δ 167.9, 167.3, 136.2, 136.0, 135.3, 130.1, 129.0, 126.8, 116.6, 116.4, 55.4, 50.2, 42.9, 42.8, 38.0, 37.0, 36.9, 29.8, 28.4, 26.2, 25.2, 19.4; LR-MS (FAB+) m/z 262 ($M+H^+$); HR-MS (FAB+) calcd for $C_{15}H_{20}NOS$ ($M+H^+$) 262.1266; found 262.1263. *(S,E)-3-(phenylthio)-3,4,7,8,9,10-hexahydroazecin-2(1H)-one* (**3**): $[\alpha]_D^{20}$ −42.3 (*c* 0.625, $CHCl_3$); FT-IR (thin film, neat) υ_{max} 3295, 2919, 1739, 1653, 1552, 1481, 1438, 1365 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 7.37 (m, 1H), 7.23 (m, 2H), 7.15 (m, 2H), 6.62 (m, 1H), 5.61–5.35 (m, 2H), 4.05 (m, 1H), 3.59 (m, 1H), 3.34 (m), 3.06 (m), 2.88–2.75 (m, 2H), 2.64 (m), 2.54 (d, 1H, *J* = 13.0 Hz), 2.23 (m, 1H), 1.89 (m, 2H), 1.50 (m, 1H), 1.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 137.1, 134.6, 129.2, 129.2, 128.2, 128.2, 126.5, 124.6, 54.6, 40.5, 36.5, 32.7, 29.5, 28.9; LR-MS (FAB+) *m*/*z* 262 ($M+H^+$); HR-MS (FAB+) calcd for $C_{15}H_{20}NOS$ ($M+H^+$) 262.1266; found 262.1271. *(1R,3S,9aS)-1-hydroxy-3-(phenylsulfonyl)hexahydro-1H-quinolizin-4(6H)-one* (**2**): $[\alpha]_D^{20}$ +23.4 (*c* 0.150, $CHCl_3$); FT-IR (thin film, neat) υ_{max} 3419, 2940, 2860, 1634, 1469, 1446, 1308 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (t, 2H, *J* = 7.8 Hz), 7.60 (t, 1H, *J* = 7.4 Hz), 7.51 (t, 2H, *J* = 7.6 Hz), 4.54 (d, 1H, *J* = 12.8 Hz), 4.19 (t, 1H, *J* = 6.9 Hz), 4.05 (m, 1H), 3.23 (s, 1H), 3.12 (d, 1H, *J* = 11.2 Hz), 2.48 (m, 1H), 2.43–2.25 (m, 2H), 1.84 (m, 2H), 1.62 (d, 1H, *J* = 12.7 Hz), 1.46–1.17 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2, 139.4, 133.6, 128.9, 128.9, 128.7, 128.7, 66.4, 63.7, 63.5, 43.6, 31.0, 27.0, 25.1, 24.1; LR-MS (FAB+) *m*/*z* 310 ($M+H^+$); HR-MS (FAB+) calcd for $C_{15}H_{20}NO_4S$ ($M+H^+$) 310.1113; found 310.1114. *(+)-Hydroxyquinolizidi none* (**1**): $[\alpha]_D^{20}$ +8.4 (*c* 0.0947, $CHCl_3$); FT-IR (thin film, neat) υ_{max} 3390, 2936, 2860, 1602, 1485, 1446, 1421, 1363, 1339 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.64 (d, 1H, *J* = 13.1 Hz), 3.76 (s, 1H), 3.65 (m, 1H), 3.10 (m, 1H), 2.50 (m, 1H), 2.35 (td, 1H, *J* = 13.0, 2.0 Hz), 2.24 (m,1H), 1.95–1.72 (m, 4H), 1.61 (d, 1H, *J* = 12.9 Hz), 1.49–1.25 (m,2H), 1.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.5, 69.2, 63.7, 42.9, 31.5, 28.4, 26.7, 25.2, 24.3; LR-MS (FAB+) *m*/*z* 170 ($M+H^+$); HR-MS (FAB+) calcd for $C_{15}H_{20}NO_4S$ ($M+H^+$) 170.1181; found 170.1176.
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