Tetrahedron Letters 51 (2010) 157–159

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Asymmetric and diastereodivergent approach to key intermediates for the synthesis of homopumiliotoxin 223G and epiquinamide isomer

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ARTICLE INFO

Article history:
Received 23 September 2009
Revised 21 October 2009
Accepted 22 October 2009
Available online 29 October 2009

ABSTRACT

A stereoselective reaction followed by a sequential cyclization route has been used in the divergent synthesis of 1-hydroxyquinolizidione isomers. Sharpless asymmetric dihydroxylation afforded hydroxyl lactone and the following mesylation provided the required precursor for cyclization.

The skin of amphibians provides more than 800 biologically attractive alkaloids.[1] Especially, indolizidine alkaloids, pumiliotoxins (**1**) and allopumiliotoxins (**2**), and quinolizidine alkaloids. homopumiliotoxins (**3**) have been shown to exhibit myotonic and cardiotonic activities (Fig. 1).[2] Since the synthesis of these compounds highlights their structural diversity and bioactivity, numerous synthetic methods have been published. However, there are just a few publications on the synthesis of homopumilotoxin 223G (**3a**), isolated in 1987 from the Panamanian poisonous frog, *Dendrobates pumilio*.[3] Epiquinamide (**4**) is another quinolizidine alkaloid isolated from extracts of the skin of the Ecuadorian poisonous frog, *Epipedobates tricolor,* in 2003. Epiquinamide is a potential lead compound for the development of pharmaceutical drugs in a new class of niconitic agonists selective for the niconitic receptor containing the β2-subunit.[4] Hence, pharmacologists and researchers in synthetic chemistry have given epiquinamide much attention.[5] As we were preparing this Letter, however, Fitch et al. predicated after re-studying the activity and purification of the natural (+)-epiquinamide that the synthetic (+)-epiquinamide is inactive at niconitic receptors and attributed the observed activity to contaminants, like epibatidine.[6] Even though epiquinamide has been shown to lack biological activity, the synthetic development of its structure would be worthwhile and the process is applicable to the synthesis of the related quinolizidine alkaloids.

Herein, we report a new divergent synthetic strategy, applying Sharpless asymmetric dihydroxylation (ADH), and the manipulation of the subsequent reductive cyclization to the synthesis of 1-hydroxyquinolizidinone isomers, the potential common intermediates to the synthesis of homopumiliotoxin 223G and epiquinamide derivatives.

With intermediates **5a** and **5b** used for the synthesis of homopumiliotoxin 223G (**3a**) enantiomers and (−)-epiquinamide,[5a] we envisioned that the selective formation of these compounds from a single intermediate would provide a general and divergent way to all isomers in an asymmetric manner. We chose compound **6** as a proper precursor to the intermediates and expected to obtain it readily from the ester **7** through Sharpless asymmetric dihydroxylation and continuous lactonization of the corresponding diol-ester. Compound **7** would be prepared from **8** (Scheme 1).

We expected the precursor **6** to be selectively manipulated to give **5a** or **5b** by changing the conditions for the Staudinger reaction. During the conversion of the azide to amine **10** in the presence of enough H_2O in solvent, nucleophilic solvents would induce steps c, d, e, and b to form amino-epoxy ester **11**, and the following cyclizations would result in the formation of **5a**.

With less nucleophilic solvents, the amine group of **10** would lead the intramolecular S_N2 process (steps a and b) to form intermediate **13** and then the addition of the nucleophilic solvent would force the lactone opening for the subsequent consecutive cyclization through **14**, yielding **5b** (Scheme 2).[7]

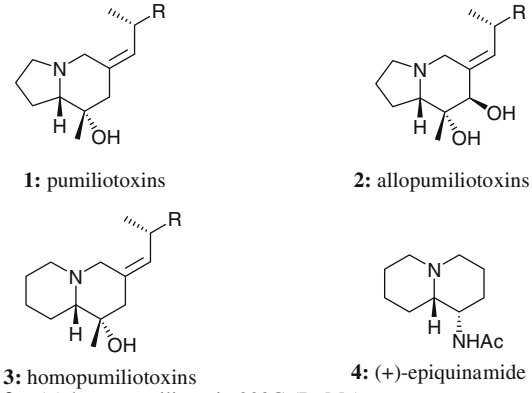

Figure 1. Structures of some poison frog alkaloids.

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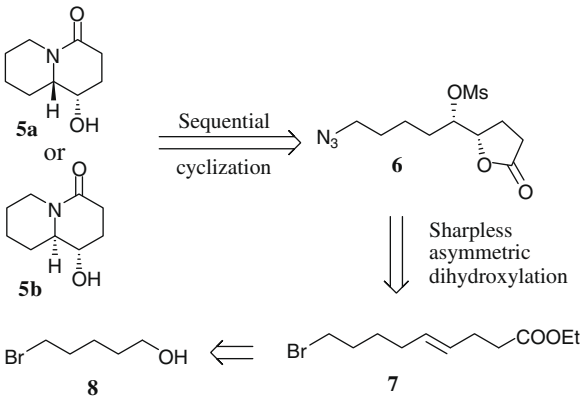
doi:10.1016/j.tetlet.2009.10.098

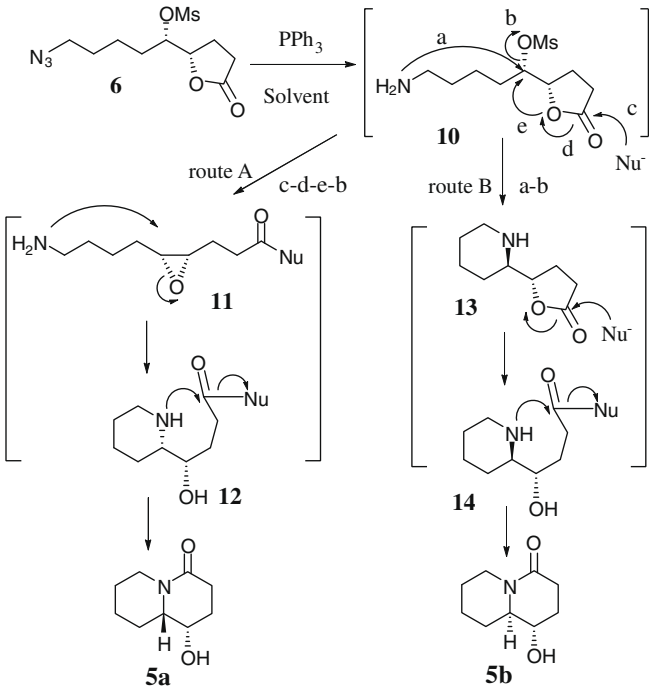


Scheme 1. Retrosynthetic analysis.

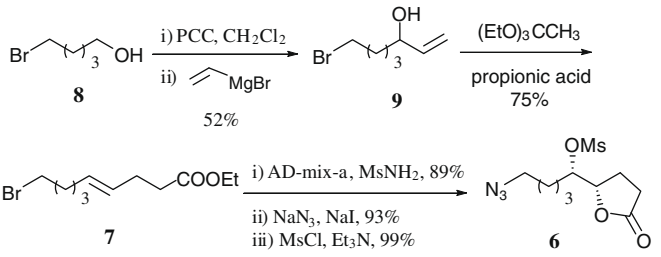
For the preparation of **6**, the commercially available alcohol **8** was oxidized by pyridinium chlorochromate to give the corresponding aldehyde, and then the addition of vinylmagnesium bromide provided allylic alcohol **9** in 52% yield. Claisen rearrangement of **9** with triethylorthoacetate provided (*E*)-alkene **7**, which was dihydroxylated by AD-mix-α,[8] to form hydroxyl lactone in 89% yield.[9] Subsequent heating of the resulting lactone with sodium azide (93%) followed by mesylation (99%) gave compound **6**[10] (Scheme 3).

With the key precursor **6** in hand, we tried to study selective cyclization under reductive conditions (Table 1).

The Staudinger reaction of **6** in methanol in the presence of 10 equiv H_2O yielded **5a** exclusively in 32% yield (entry 1). Addition of a base, such as K_2CO_3 and Hünig , raised the yields to 65% and 90% (entries 2 and 3). Optical rotation of **5a** {$[\alpha]_D^{30}$ 11.7 (*c* 1, CH_2Cl_2)} was in agreement with the reported outcome {$[\alpha]_D^{20}$ 11.9 (*c* 1, CH_2Cl_2)}.[5c] For the formation of the desired (−)-1-hydroxyquinolizidinone **5b**, we substituted tetrahydrofuran for methanol. The mixture of **6a** and triphenylphosphine was heated at 60 °C for 24 h and then evaporated and the crude mixture was treated with K_2CO_3 in methanol (step 2). The process provided a mixture of **5a** and **5b** in a ratio of 42:58 (entry 4), suggesting route A competed with route B in Scheme 2. Better selectivity was achieved using triethylamine as a base in step 1 (29:71) (entry 5) and by using Hünig base (4:96) (entry 6). With acetonitrile and Hünig base only **5b** was obtained in a good yield of 95% (entry 7). Optical rotation of **5b** {$[\alpha]_D^{25}$ −8.0 (*c* 1.2, $CHCl_3$)} was identical with that in the literature {$[\alpha]_D^{20}$ −8.5 (*c* 0.7, $CHCl_3$)}.[5a] Thus, we could develop selective conditions for the synthesis of intermediates **5a** and **5b** in good yields.[11]

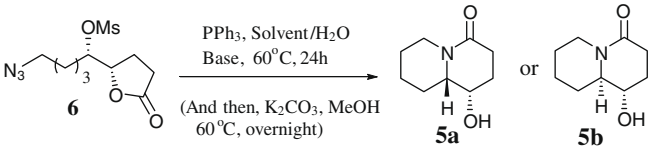


Scheme 2. Stereoselective way to intermediate **5a** or **5b**.



Scheme 3. Synthesis of compound **6**.

Table 1
Sequential cyclization reaction of **6**



Entry	Solvent[a]	Base	**5a**/**5b**[b]	Yield[d] (%)
1[c]	MeOH	No	**5a** only	32
2[c]	MeOH	K_2CO_3	**5a** only	65
3[c]	MeOH	Hünig base	**5a** only	90
4	THF	No	42/58	69
5	THF	Et_3N	29/71	66
6	THF	Hünig base	4/96	65
7	MeCN	Hünig base	**5b** only	95

[a] All solvents contain ca. 10 equiv of H_2O.
[b] Ratios were detected by ^1H NMR.
[c] Reactions were finished without the next step.
[d] Isolated yields of mixtures.

We have developed an efficient and stereoselective route to the key intermediate 1-hydroxyquinolizidinone for the synthesis of homopumiliotoxin 223G and epiquinamide. Also, we have suggested a practical and divergent way to all four isomers of the intermediate, depending on the ligands of Sharpless asymmetric dihydroxylation and the reaction conditions of the subsequent reductive sequential cyclization.

Acknowledgment

This work was supported by the Korea Research Foundation Grant funded by Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2008-313-C00461).

References and notes

1. Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556.
2. Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1993; p 85.
3. (a) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643; (b) Kibayashi, C.; Aoyagi, S.; Wang, T.-C.; Saito, K.; Daly,

J. W.; Spande, T. F. *J. Nat. Prod.* **2000**, *63*, 1157; (c) Aoyagi, S.; Hirashima, S.; Kibayashi, C. *Tetrahedron Lett.* **1998**, *39*, 2149; For a total synthesis of racemic homopumiliotoxin 223G, see: (d) Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6999–7001; For a formal synthesis of racemic homopumiliotoxin 223G, see: (e) Chen, B.-F.; Tasi, M.-R.; Yang, C.-Y.; Chang, J.-K.; Chang, N.-C. *Tetrahedron* **2004**, *60*, 10223; (f) Buchanan, J. G.; Sable, H. Z.. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1972; Vol. 2, pp 1–95.

4. Fitch, R. W.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2003**, *66*, 1345.
5. (a) Huang, P. Q.; Guo, Z. Q.; Ruan, Y. P. *Org. Lett.* **2006**, *8*, 1435; (b) Voituriez, A.; Ferreira, F.; Perez-Luna, A.; Chemla, F. *Org. Lett.* **2007**, *9*, 4705; (c) Wijdeven, M. A.; Wijtmans, R.; van den Berg, R. J. F.; Noorduin, W.; Schoemaker, H. E.; Sonke, T.; van Delft, F. L.; Blaauw, H. R.; Fitch, R. W.; Spande, T. F.; Daly, J. W.; Rutjes, F. P. J. T. *Org. Lett.* **2008**, *10*, 4001; (d) Tong, S. T.; Barker, D. *Tetrahedron Lett.* **2006**, *47*, 5017; (e) Wijdeven, M. A.; Botman, P. N. M.; Wijtmans, R.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org. Lett.* **2005**, *7*, 4005; (f) Suyama, T. L.; Gerwick, W. H. *Org. Lett.* **2006**, *8*, 4541; (i) Kanakubo, A.; Gray, D.; Innocent, N.; Wonnacott, S.; Gallagher, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4648.
6. Fitch, R. W.; Sturgeon, G. D.; Patel, S. R.; Spande, T. F.; Garraffo, M.; Daly, J. W.; Blaauw, R. H. *J. Nat. Prod.* **2009**, *72*, 243.
7. D'Oca, M. G. M.; Pilli, R. A.; Vencato, I. *Tetrahedron Lett.* **2000**, *41*, 9709.
8. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1969.
9. The enantiomeric purity was determined to be >95% via ^{1}H NMR of Mosher ester of the hydroxyl lactone.
10. $[\alpha]_D^{30}$ 14.64 (*c* 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (1H, q, *J* = 6.4 Hz), 4.62 (1H, dt, *J* = 5.6, 7.2 Hz), 3.32 (2H, t, *J* = 6.4 Hz), 3.14 (3H, s), 2.70–2.52 (2H, m), 2.42–2.32 (1H, m), 1.83–1.75 (2H, m), 1.73–1.50 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 82.7, 79.4, 51.0, 39.0, 30.3, 28.4, 28.0, 24.2, 22.1; IR (neat, cm^{-1}) 2941, 2099, 1779, 1350, 1171, 922, 526; EI-MS *m*/*z* 258 ($[M-N_2]^+$). EI-HRMS calcd for $C_{10}H_{17}N_3O_5S$ 291.0889, found: 291.0883.
11. *Synthesis of compound* **5a**: PPh_3 (72 mg, 0.274 mmol), 0.2 mL H_2O, and 3 equiv of Hünig base were added to the solution of lactone **6** (40 mg, 0.137 mmol) in 7 mL MeOH. After heated overnight at 60 °C, the reaction mixture was evaporated in vacuo and purified by silica gel column chromatography (CH_2Cl_2/MeOH 30:1 to 10:1) to afford **5a** as a white solid in 90% yield.*Synthesis of compound* **5b**: PPh_3 (41 mg, 0.158 mmol), 0.2 mL H_2O, and 0.2 mL of Hünig base were added to the solution of lactone **6** (23 mg, 0.08 mmol) in 5 mL of MeCN. After heating at 60 °C for 24 h, the reaction mixture was evaporated in vacuo and dissolved in MeOH. K_2CO_3 (32 mg, 0.232 mmol) was added and the mixture was heated at 60 °C for 12 h. After treatment with H_2O, the reaction mixture was extracted with CH_2Cl_2 (3×20 mL), dried over $MgSO_4$, and evaporated in vacuo. The resultant residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH 30:1 to 10:1) to give **5b** as a white solid in 95% yield.