ORGANIC LETTERS

2006
Vol. 8, No. 7
1435−1438

A Versatile Approach for the Asymmetric Syntheses of (1*R*,9a*R*)-Epiquinamide and (1*R*,9a*R*)-Homopumiliotoxin 223G

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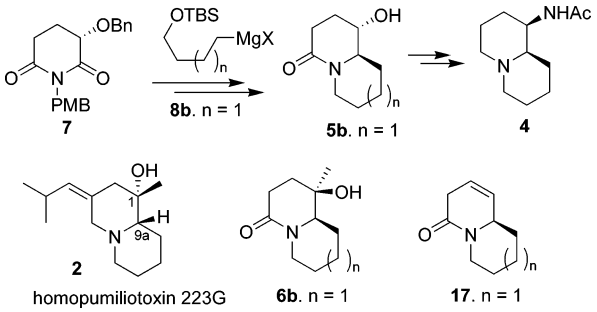
Received January 25, 2006

ABSTRACT



Using 5b as a common intermediate, the first asymmetric synthesis of (−)-epiquinamide (4) and a formal asymmetric synthesis of (−)-homopumiliotoxin 223G (2) is described. A key feature of our approach is the flexible introduction of a functionalized C_4 side chain to (*S*)-3-benzyloxyglutarimide 7 in a regio- and diastereoselective manner. Utilization of a tandem Swern oxidation–Grignard addition strategy efficiently prevented racemization. An unexpected NaN_3-promoted methanesulfonic acid elimination yielded 17, a reaction which could be useful for the syntheses of 8-dehydrodesmethylpumiliotoxins such as alkaloid 235C (3).

Amphibian skin has been proven a rich source of bioactive alkaloids, from which more than 800 alkaloids have been detected.[1] While pumiliotoxins **1** have been known since 1967,[2] homopumiliotoxins such as (+)-homopumiliotoxin 223G (**2**) (Figure 1) were isolated 20 years later from the Panamanian poison frog *Dendrobates pumilio*.[3] The absolute configuration of homopumiliotoxin 223G was determined by asymmetric synthesis in 2000.[4] Alkaloid 235C (**3**)[1,5a] and three other indolizidine alkaloids were isolated from mantellid frogs.[5b] Their structures were revised recently to 8-dehydrodesmethylpumiliotoxins.[1,5a,c] In 2003, epiquinamide (**4**), another unprecedented quinolizidine alkaloid, was isolated in minute amounts (240 μg from 183 frogs) from

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(2) Daly, J. W.; Myers, C. W. *Science* **1967**, *156*, 970−973.

(3) (a) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643−652. (b) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, Tf.; Andriamaharavo, Nr.; Andriantsiferana, M. *J. Nat. Prod.* **1993**, *56*, 1016−1038. (c) Garraffo, H. M.; Spande, T. F.; Daly, J. W.; Baldessari, A.; Gros, E. G. *J. Nat. Prod.* **1993**, *56*, 357−373.

(4) (a) Kibayashi, C.; Aoyagi, S.; Wang, T. C.; Saito, K.; Daly, J. W.; Spande, T. F. *J. Nat. Prod.* **2000**, *63*, 1157−1159. For an earlier asymmetric synthesis of (+)-homopumiliotoxin 223G, see: (b) Aoyagi, S.; Hasegawa, Y.; Hirashima, S.; Kibayashi, C. *Tetrahedron Lett.* **1998**, *39*, 2149−2152.

(5) (a) Andriamaharavo, N. R.; Andriantsiferana, M.; Stevenson, P. A.; O′Mahony, G.; Yeh, H. J. C.; Kaneko, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *J. Nat. Prod.* **2005**, *68*, 1743−1748. For original isolation and initial structural determination, see: (b) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1993**, *56*, 1016−1038. For a racemic synthesis of the initially proposed structure of alkaloid 235C, see: (c) Armstrong, P.; Feutren, S.; McAlonan, H.; O′Mahony, G.; Stevenson, P. J. *Tetrahedron Lett.* **2004**, *45*, 1627−1630.

10.1021/ol0602203 CCC: $33.50
Published on Web 03/07/2006

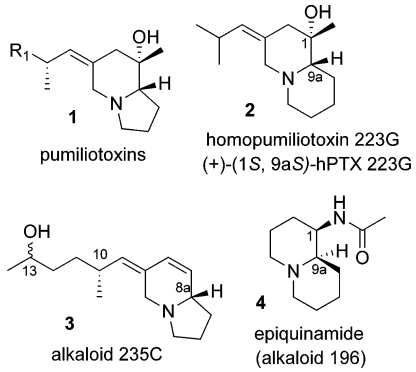


Figure 1. Structures of some poison frog alkaloids.

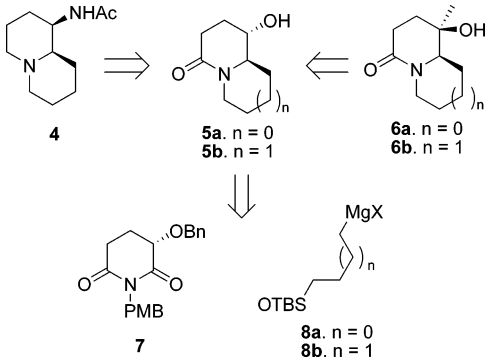


Figure 2. Retrosynthetic analysis.

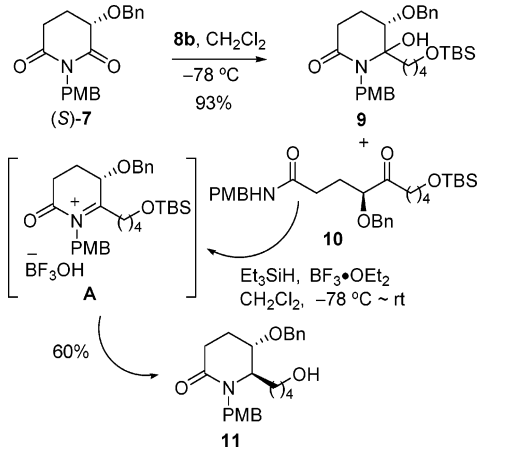
the Ecuadorian poison frog *Epipedobates tricolor*.[6] Epiquinamide represents a new structural class of nicotinic agonists and potential lead compounds for the development of new therapeutics and pharmacological probes for nicotinic receptors. Although the relative stereochemistry of (+)-epiquinamide (**4**) has been confirmed by the first asymmetric synthesis,[7] its absolute configuration and further bioactivities remain unknown due to the scarcity of epiquinamide from natural sources.

The structural diversity and remarkable bioactivities exhibited by these alkaloids have attracted much attention, and a number of synthetic approaches have been reported.[8] However, unlike pumiliotoxins, only two asymmetric syntheses of homopumiliotoxin 223G (**2**)[4,9] and one asymmetric synthesis of (+)-epiquinamide (**4**)[7] have been disclosed. In continuation of our studies on the use of protected 3-hydroxyglutarimide as a versatile building block for the asymmetric syntheses of 3-piperidinols,[10] we wished to develop a unified strategy for the asymmetric syntheses of (−)-epiquinamide and (−)-homopumiliotoxin 223G starting from easily available (*S*)-3-benzyloxyglutarimide **7**.

In view of the successful use of **6a**[11] and **6b**[9] as key intermediates in the syntheses of pumiliotoxins **1** and homopumiliotoxin 223G (**2**), respectively, **6b** was selected as our target en route to homopumiliotoxin 223G. It was envisioned that **5a**/**5b**[9c,12] could serve as the common intermediates for **4** and **6a**/**6b** (Figure 2). Lactams **5a**/**5b** were considered best synthesized by the stepwise reductive alkylation of 3-benzyloxyglutarimide **7**[10] using either a C_3 or C_4 bifunctional chain **8a** or **8b**.

With these considerations in mind, our syntheses commenced with the reaction of (*S*)-3-benzyloxy-1-(4-methoxybenzyl) glutarimide[10] **7** with Grignard reagent **8b**, easily prepared from 1,4-butanediol. The Grignard reaction (CH_2Cl_2, −78 °C) proceeded smoothly to give a separable diastereomeric mixture of **9** and the ring-opening keto-amide tautomer **10** in a combined yield of 93% (Scheme 1). Since

Scheme 1. Synthesis of 2-Piperidinone Alcohol **11**



only the C-2 regioisomers could be isolated, the C-2 regioselectivity was higher than 95%. Being interconvertible via the intermediacy of an *N*-acyliminium ion,[10,13] the diastereomeric and tautomeric mixture (**9**/**10**) was used in the subsequent step without further separation. Thus, treatment of the mixture of **9**/**10** with $Et_3SiH/BF_3{\cdot}OEt_2$ (CH_2Cl_2,

(6) Fitch, R. W.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2003**, *66*, 1345−1350.

(7) Wijdeven, M. A.; Botman, P. M. M.; Wijtmans, R.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org. Lett.* **2005**, *7*, 4005−4007.

(8) For a review on the syntheses of pumiliotoxins, see: Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505−522.

(9) For a racemic synthesis of homopumiliotoxin 223G, see: (a) Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6999−7001. For a formal asymmetric synthesis, see: (b) Wang, B.; Fang, K.; Lin, G. Q. *Tetrahedron Lett.* **2003**, *44*, 7981−7984. For a formal racemic synthesis, see: (c) Chen, B. F.; Tasi, M. R.; Yang, C. Y.; Chang, J. K.; Chang, N. C. *Tetrahedron* **2004**, *60*, 10223−10231.

(10) (a) Huang, P.-Q.; Liu, L.-X.; Wei, B.-G.; Ruan, Y.-P. *Org. Lett.* **2003**, *5*, 1927−1929. (b) Huang, P.-Q.; Wei, B.-G.; Ruan, Y.-P. *Synlett* **2003**, 1663−1667. (c) Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem.* **2004**, *69*, 6001−6009. (d) Ruan, Y.-P.; Wei, B.-G.; Xu, X.-Q.; Liu, G.; Yu, D.-S.; Liu, L.-X.; Huang, P.-Q. *Chirality* **2005**, *17*, 595−599. (e) Wei, B.-G.; Chen, J.; Huang, P.-Q. *Tetrahedron* **2006**, *62*, 190−198.

(11) Fox, D. N. A.; Lathburay, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652−2656.

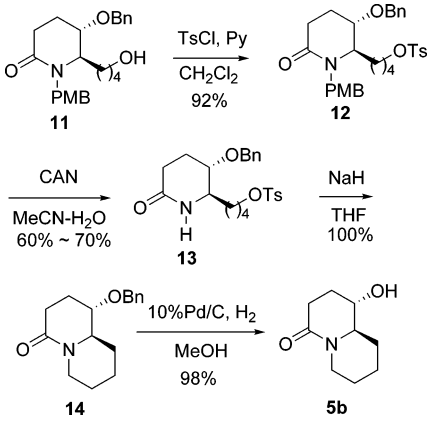
(12) D'Oca, M. G. M.; Pilli, R. A.; Vencato, I. *Tetrahedron Lett.* **2000**, *41*, 9709−9712.

(13) For recent reviews on the chemistry of *N*-acyliminium ion, see: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856.

−78 °C to rt) provided, in one pot, the desilylated[14] 6-(4-hydroxybutyl)-5-benzyloxy-2-piperidinone **11** in 60% yields. The *trans*/*cis* diastereoselectivity was 96:4 as determined by 500 MHz ^{1}H NMR spectroscopy. The stereochemistry of the major diastereomer **11** was assumed to be *trans* in the light of our previous results[10] but was confirmed by its conversion into (−)-epiquinamide (**4**)[6,7] and the known lactam **6b**.[9]

Tosylation of **11** led to **12** (92% yield), which after oxidative *N*-deprotection using ceric ammonium nitrate in a mixed MeCN−H_2O (9: 1, v/v) solvent system provided **13** in 60−70% yields (Scheme 2). Treatment of **13** with sodium

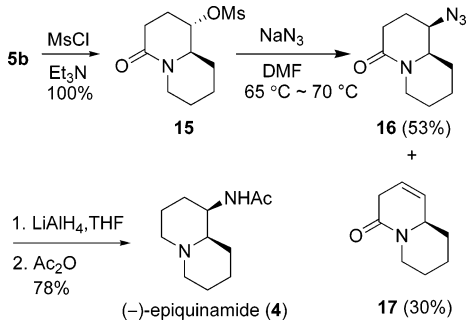
Scheme 2. Synthesis of the Common Intermediate **5b**



hydride afforded **14** in quantitative yield. Catalytic hydrogenation (10% Pd/C, H_2, 1 atm) of **14** gave the key intermediate **5b** in a yield of 98%.

For the synthesis of (1*R*,10*R*)-epiquinamide (**4**), **5b** was mesylated to give **15** (100% yield). The subsequent S_N2 reaction with sodium azide yielded, besides the desired azide **16** (yield: 53%), an elimination product **17**[15] in 30% yield (Scheme 3). Lithium aluminum hydride reductions of both

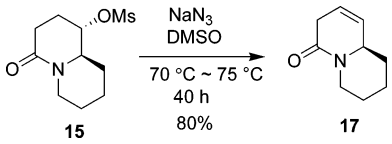
Scheme 3. Synthesis of (−)-Epiquinamide



the azide and the amide functional groups followed by *N*-acetylation then provided the desired (1*R*,10*R*)-(−)-epiquinamide (**4**) in 78% yield [mp 122−123 °C (lit.[7] mp 124 °C); $[\alpha]^{20}_D$ −25.0 (*c* 0.26, $CHCl_3$) [lit.[7] $[\alpha]^{20}_D$ +28.0 (*c* 0.23, $CHCl_3$) for the antipode]]. The physical data of the synthetic molecule were identical with those reported.[6,7]

In the course of our investigation on the azidation of **15**, DMSO was selected as a solvent due to its improved ability to dissolve sodium azide. Although treatment of **15** with sodium azide in DMSO at 50−60 °C for 48 h gave **16** in only 20% yield along with a large amount of the recovered starting material, the reaction at higher temperature (70−75 °C) for 40 h led to eliminated product **17**[15] in 80% yield as a single product (Scheme 4). Since the ring size of the fused

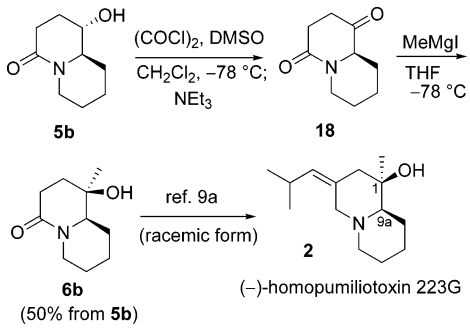
Scheme 4. Preparation of the Eliminated Product **17**



piperidine ring in **17** can be modified by using an appropriate alkylating agent (e.g., **8a**), this method could be useful for the preparation of 8-dehydrodesmethylpumiliotoxins such as alkaloid 235C (**3**).[5]

In pursuit of the synthesis of **6b**, **5b** was subjected to Swern oxidation[16] [$(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; −40 °C, *i*-Pr_2NEt] (Scheme 5). To prevent possible racemization,

Scheme 5. A Formal Asymmetric Synthesis of (−)-Homopumiliotoxin 223G (**2**)



Hünig base[17] was used, and the reaction was quenched with a NaOAc−HOAc buffer solution. In such a way, the desired ketone **18** was isolated in 87% yield. Treatment of **18** with methylmagnesium iodide afforded the known **6b**[9] as the sole diastereomer (yield: 65%). The ^{1}H and ^{13}C NMR spectral data of **6b** were identical with those reported.[9c] The stereoselectivity of the reaction can be attributed to the addition of methylmagnesium iodide from the less hindered face opposite to the piperidine ring. Unfortunately, the ee of **6b** was only 6% as indicated by HPLC analysis on a chiral

(14) For a review on Et_3SiH-mediated ionic hydrogenation, see: Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633−651.

(15) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056−9062.

(16) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.

(17) Calvez, O.; Langlois, N. *Tetrahedron Lett.* **1999**, *40*, 7099−7100.

column. To overcome the problem of racemization, we tried to perform the Grignard reagent addition with crude ketone **18**; the ee of **6b** was also disappointing (9%). On the other hand, using $MeTiCl_3$[18] as the methylating agent led to **6b** in only 33% yield. Finally, we elected to explore a one-pot tandem Swern oxidation−methylmagnesium iodide addition reaction.[19] Gratifyingly, a 50% yield of **6b** with 90% ee was obtained from **5b**. Since racemic **6b** has been converted to racemic homopumiliotoxin 223G (**2**),[9a] our synthesis of **6b**, together with that of Pilli,[9a] thus constitutes a formal asymmetric synthesis of (−)-homopumiliotoxin 223G (**2**). It is noteworthy that the present synthesis of **6b** also confirmed the *trans*-stereoselection in both the reductive 4-benzyloxybutylation of **7** and the nucleophilic addition to **18**.

In summary, starting from easily available glutarimide **7**, a concise, 10-step synthesis of (−)-epiquinamide (**4**) has been achieved in a total yield of 14.6%. The versatility of our method was demonstrated by the synthesis of **6b**, which constituted a formal synthesis of homopumiliotoxin 223G (−)-**2**. The easy accessibility to compound **17**, by an unexpected finding, in combination with the flexibility in the reductive alkylation of **7** also formed the basis of asymmetric syntheses of 8-dehydrodesmethylpumiliotoxins such as alkaloid 235C. Application of the present strategy to the asymmetric syntheses of other members of homopumiliotoxins and pumiliotoxins is in progress.

Acknowledgment. We are grateful to the NSF of China (20390050, 20572088), the Ministry of Education (Key Project 104201), and the NSF of Fujian Province (China) (C0510001) for financial support.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. ^1H NMR spectra of **4**, **5b**, **6b**, **16**, and **17**; ^{13}C NMR spectrum of **5b** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0602203

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