Pergamon

Tetrahedron Letters 42 (2001) 2537–2539

TETRAHEDRON LETTERS

A new highly stereoselective construction of the sidechain of squalamine through improved Sharpless catalytic asymmetric dihydroxylation

Xiang-Dong Zhou,† Feng Cai and Wei-Shan Zhou*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Fenglin Lu 354, Shanghai 200032, China

Received 22 November 2000; revised 15 January 2001; accepted 1 February 2001

Abstract—A new highly stereoselective construction of the sidechain of squalamine has been achieved by using methyl-3-keto-5α-chenodeoxycholanate (**2**) as the starting material and an improved Sharpless catalytic asymmetric dihydroxylation as the key step.

The discovery of the novel aminosterol squalamine resulted from a search for new small molecule antibiotics.[1] In 1993, Zasloff and co-workers discovered squalamine (Fig. 1) in minute quantities from the stomach of the dogfish shark *Squalus acanthias* as a broad-spectrum antibiotic displaying potent bactericidal activities against both Gram-negative and Gram-positive bacteria.[2] The structure of squalamine was determined as 3β-*N*-1-{*N*-[3-(4-aminobutyl)]-1,3-diaminopropane}-7α,24*R*-dihydroxy-5α-cholestane-24-sulfate by ^{1}H, ^{13}C NMR and FAB mass spectrometry.[2–4b] It is a water soluble cationic steroid and consists of an unusual adduct of spermidine with an anionic bile–salt intermediate. Thereafter, many efforts were made to synthesize squalamine[4] and its analogues[5] and explore their biological activities.[6] Among them, antiviral activity of squalamine was also found.[6a] However, the most significant event was the presentation of its anti-angiogenic activity,[6b] which first directly led to the development of squalamine into an anti-cancer chemotherapeutic.[7] Furthermore, the applicable range of squalamine has been highly expanded into age-related macular degeneration, malaria, obesity and asthma.[8] All these facts, along with the most recent discovery of several analogues of squalamine from the stomach of the dogfish shark *Squalus acanthias*,[9] may bring research of squalamine into a new era. Therefore, the design and syntheses of squalamine and its analogues would be a highlight of future research work.

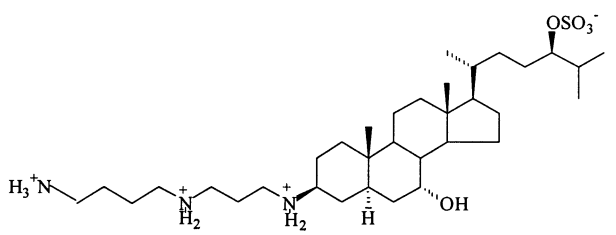


Figure 1. Squalamine.

Herein, we address a new highly stereoselective construction of the sidechain of squalamine using an improved Sharpless catalytic asymmetric dihydroxylation[10] as a key step from methyl 3-keto-5α-chenodeoxycholanate **2** as the starting material.

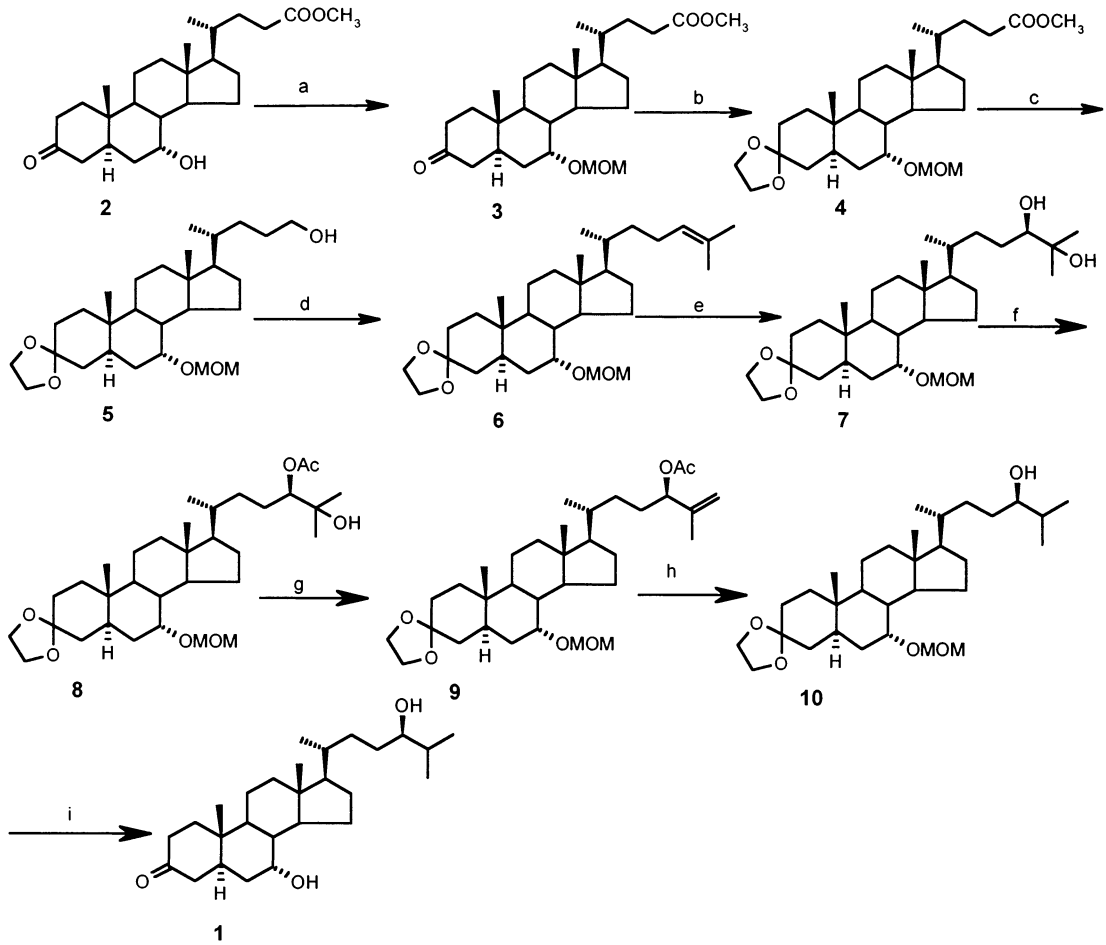
As depicted in Scheme 1, 3-keto-5α-chenodeoxycholanate **2** was prepared from methyl chenodeoxycholanate according to the literature.[11] To protect the 7α-hydroxy group of **2**, it was stirred at rt with dimethoxymethane, catalyzed by P_2O_5, in chloroform to afford 7α-methoxy methyl ether **3** in 94% yield. Afterwards, the 3-keto group was protected with ethylene glycol to afford 3-dioxolane compound **4** in 96% yield, which was then reduced with $LiAlH_4$ to afford 24-alcohol **5** in 96% yield. Swern oxidation of **5**, followed by Wittig olefination with BuLi and isopropyltriphenylphosphonium iodide in THF at rt gave Δ^{24} compound **6** in two steps with 93% overall yield. This

Keywords: methyl-5α-chenodeoxycholanate; desmosterol derivative; improved Sharpless AD; squalamine.

* Corresponding author. Tel.: 86-21-64163300; fax: 86-21-64166128; e-mail: zhws@pub.sioc.ac.cn

† Present address: Department of Chemistry, The Third Military Medical University, Chongqing 400038, China.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00191-5



Scheme 1. (a) $CH_3OCH_2OCH_3$, P_2O_5, $CHCl_3$, rt, 94%; (b) ethylene glycol, PTSA, benzene, Δ, 96%; (c) $LiAlH_4$, THF, rt, 96%; (d) (1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, (2) BuLi, $Ph_3P^+CH(CH_3)_2I^-$, THF, rt, two steps, 93%; (e) $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, *t*-butanol–methyl *t*-butyl ether–H_2O (2.5:3:2.5), rt, 83%, 100% d.e.; (f) Ac_2O, Py, rt, 92%; (g) CH_3SO_2Cl, DMAP, Et_3N, CH_2Cl_2, 0–20°C, 64%, (h) NH_2OH, EtOAc, DMF, 95°C, then KOH, MeOH, Δ, 86%; (i) PPTS, *t*-BuOH, Δ, 92%, 99% d.e.

desmosteroid derivative **6** could be used as a key intermediate for the syntheses of squalamine and its analogues. In the course of our synthesis of squalamine, the key step is the stereoselective introduction of the 24*R*,25-dihydroxy group into the sidechain of **6** via an improved Sharpless catalytic asymmetric dihydroxylation.[10]

Thus, dihydroxylation of **6** with $(DHQD)_2PHAL$ and $K_2OsO_2(OH)_4$ in *t*-BuOH–methyl *t*-butyl ether–H_2O (2.5:3:2.5) solvent system gave 24*R*,25-dihydroxy compound **7** in 15 h in 83% yield and with 100% d.e. Obviously, this solvent system has an advantage over the usual solvent system (1:1 *t*-BuOH–H_2O[12] or 1.5:1 *t*-BuOH–H_2O[13]) in the AD reaction in that it can greatly reduce the reaction time and increase the diastereoselectivity, due to the larger solubility of steroids therein. Acetylation of **7** with acetic anhydride and pyridine gave the acetate **8** in 92% yield. Dehydration of **8** with methanesulfonyl chloride and triethylamine in the presence of a catalytic amount of DMAP gave 24*R*-acetoxyl group-Δ^{25}-compound **9** in 64% yield.[14] Diimide reduction[15] of **9** followed by hydrolysis with potassium hydroxide in methanol afforded compound **10** in 86% yield. Finally, deprotection of **10** with PPTS in *t*-BuOH gave the target molecule **1**[16] with high stereoselectivity (99% d.e.) in 92% yield. Compound **1** was easily converted into squalamine by a known method.[4d]

The advantage of this construction of the sidechain of squalamine is its highly stereoselective introduction of the 24*R*-hydroxy group to the key intermediate, desmosterol derivative **6** via an improved Sharpless asymmetric dihydroxylation. The short route to the precursor **1** of squalamine was achieved in nine steps in an overall yield of 31.2% and with 99% d.e. The syntheses of squalamine and its analogues are in progress.

Acknowledgements

We thank the Shanghai-Hongkong Joint Laboratory of Synthetic Chemistry for financial support. We also thank Professor Li-Jun Xia and Jin-Hua Wang for performing the HPLC analysis. We thank Mr. Ji-Ming Sheng and Ms. Qun-Yan Pan for preparation of the starting material.

References

1. Stone, R. *Science* **1993**, *259*, 1125.
2. Moore, K. S.; Wehrli, S.; Roder, H.; Rogers, M.; Forrest, J. N.; McCrimmon, J. D.; Zasloff, M. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 1354–1358.
3. Wehrli, S. L.; Moore, K. S.; Roder, H.; Durell, S.; Zasloff, M. *Steroids* **1993**, *58*, 370–378.
4. (a) Moriarty, R. M.; Tuladhar, S. M.; Guo, L.; Wehrli, S. *Tetrahedron Lett*. **1994**, *35*, 8103–8106; (b) Moriarty, R. M.; Enache, L. A.; Kiney, W. A.; Allen, C. S.; Canary, J. W.; Tuladhar, S. M.; Guo, L. *Tetrahedron Lett*. **1995**, *36*, 5139–5142; (c) Pechulis, A. D.; Bellevuell, C. L. C.; Trapp, S. G.; Fojtik, J. P.; McKitty, A. A.; Frye, L. L. *J. Org. Chem*. **1995**, *60*, 5121–5126; (d) Rao, M. N.; McGuigan, M. A.; Zhang, X.; Shaked, Z.; Kinney, W. A.; Bulliard, M.; Laboue, B.; Lee, N. E. *J. Org. Chem*. **1997**, *62*, 4541–4545; (e) Jones, S. R.; Selinsky, B. S.; Rao, M. N.; Zhang, X. H.; Kinney, W. A.; Tham, F. S. *J. Org. Chem*. **1998**, *63*, 3786–3789; (f) Zhang, X. H.; Rao, M. N.; Jones, S. R.; Shao, B.; Feibush, P.; McGuigan, M.; Tzodikov, N.; Feibush, B.; Sharkansky, I.; Snyder, B.; Mallis, L. M.; Sarkahian, A.; Wilder, S.; Turse, J. E.; Kinney, W. A. *J. Org. Chem*. **1998**, *63*, 8599–8603; (g) Weis, A. L.; Bakos, T.; Alferiev, I.; Zhang, X. H.; Shao, B.; Kinney, W. A.; Williams, A. *Tetrahedron Lett*. **1999**, *40*, 4863–4864; (h) Kinney, W. A.; Zhang, X. H.; Williams, J. I.; Johnston, S.; Michalak, R. S.; DeshPande, M.; Dostal, L.; Rosazza, J. P. N. *Org. Lett*. **2000**, *2*, 2921–2922.
5. (a) Zasloff, M. PCT Int. Appl. WO 9,640,151; Chem. Abstr. **1997** *126*, 15799; (b) Sadownik, A.; Deng, G.; Janout, V.; Regen, S. L.; Bernard, E. M.; Kikuchi, K.; Armstrong, D. *J. Am. Chem. Soc*. **1995**, *117*, 6138–6139; (c) Jones, S. R.; Kinney, W. A.; Zhang, X. H.; Jones, L. M.; Selinsky, B. S. *Steroids* **1996**, *61*, 565–571; (d) Zasloff, M.; Shinnar, A.; Kinney, W. A.; Anderson, M. PCT Int. Appl. WO 9744044; Chem. Abstr. **1998** *128*, 43837; (e) Kim, H. S.; Choi, B. S.; Kwon, K. C.; Lee, S. O.; Kwak, H. J.; Lee, C. H. *Bioorg. Med. Chem*. **2000**, *8*, 2059–2065; (f) Khabnadideh, S.; Tan, C. L.; Croft, S. L.; Kendrick, H.; Yardley, V.; Gilbert, I. H. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 1237–1239.
6. (a) Williams, T. J.; Pinto, A.; Bedi, G. 4th International Conference in Chemical Synthesis of Antibiotic and Related Microbial Products, Nashville, Indiana USA, Sep 11–16, 1994; (b) Sills, Jr., A. K.; Williams, J. I.; Tyler, B. M.; Epstein, D. S.; Sipos, E. P.; Davis, J. D.; McLane, M. P.; Pitchford, S.; Cheshire, K.; Gannon, F. H.; Kinney, W. A.; Chao, T. L.; Donowitz, M.; Laterra, J.; Zasloff, M.; Brem, H. *Cancer Res*. **1998**, *58*, 2784–2792; (c) Kikuchi, K.; Bernard, E. M.; Sadownik, A.; Regen, S. L.; Armstrong, D. *Antimicrob. Agents Chemother*. **1997**, *41*, 1433–1438; (d) Schiller, J. H.; Bittner, G.; Williams, S. *Clin. Cancer Res*. **1999**, *5*, 4287–4294; (e) Alper, S. L.; Chernova, M. N.; Williams, J.; Zasloff, M.; Law, F. Y.; Knauf, P. A. *Biochem. Cell Biol*. **1998**, *76*, 799–806; (f) Akhter, S.; Nath, S. K.; Tse, C. M.; Williams, J.; Zasloff, M.; Donowitz, M. *Am. J. Physiol*. **1999**, *276*, C136–C144; (g) Teicher, B. A.; Williams, J. I.; Takeuchi, H.; Ara, G.; Herbst, R. S.; Buxton, D. *Anticancer Res*. **1998**, *18*, 2567–2673; (h) Parker, L. *Lancet* **1999**, *354*, 1100.
7. Hinde, A.; Ramster, B. *Drug Discov. Today* **2000**, *5*, 489–491.
8. Senior, K. *Drug Discov. Today* **2000**, *5*, 267–268.
9. Rao, M. N.; Shinnar, A. E.; Noecker, L. A.; Chao, T. L.; Feibush, B.; Snyder, B.; Sharkansky, I.; Sarkahian, A.; Zhang, X. H.; Jones, S. R.; Kinney, W. A.; Zasloff, M. *J. Nat. Prod*. **2000**, *63*, 631–635.
10. (a) Kolb, H. C.; van Nieumenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483–2549; (b) Zhou, X. D.; Zhou, W. S. Chinese Patent ZL99124007.3.
11. Iida, T.; Nishida, S.; Chang, F. C.; Niwa, T.; Goto, J.; Nambara, T. *Chem. Pharm. Bull*. **1993**, *41*, 763–765.
12. Sharpless dihydroxylation of (22*E*)-3α,5-cyclo-5α-ergost-22-en-6-one with DHQD–PHN in 1:1 *t*-BuOH–H_2O proceeded in 4–6 days to give a mixture of (22*R*,23*R*,24*R*)-2α,3α,22,23-tetrahydroxy and (22*S*,23*S*,24*R*)-2α,3α,22,23-tetrahydroxy compounds in 78% yield and with 93:7 diastereo-selectivity. Huang, L. F.; Zhou, W. S.; Sun, L. Q.; Pan, X. F. *J. Chem. Soc., Perkin Trans. 1* **1993**, *29*, 1683–1686.
13. Sharpless dihydroxylation of desmosterol with $(DHQD)_2PYDZ$ in 1.5:1 *t*-BuOH–H_2O proceeded in 52 h to give 24(*R*),25-dihydroxycholesterol in 83% yield and with 96:4 diastereoselectivity. Corey, E. J.; Grogan, M. J. *Tetrahedron Lett*. **1998**, *39*, 9351–9354.
14. Yadav, J. S.; Mysorekar, S. V. *Synth. Commun*. **1989**, *19*, 1057–1060.
15. Wade, P. A.; Amin, N. V. *Synth. Commun*. **1982**, *12*, 287.
16. Compound **1**: mp: 149–151°C (Lit.[4e] 151–153°C), $[\alpha]_D^{20}$ +22.6 (*c* 0.32, $CHCl_3$); IR (KBr, film): 3447 (-OH), 1707 (3-one); ^1H NMR (300 MHz, $CHCl_3$): 3.92 (7β-H), 3.32 (24-H); EI-MS (m/e): 419 (4.8%, $[M^+ + 1]$), 400 (24.2%, $[M^+ - H_2O]$), 382 (33.4%, $[M^+ - 2H_2O]$); HRMS: calcd for $C_{27}H_{46}O_3$: 418.3449. Found: 418.3419. The d.e. value was determined as 99% by HPLC analysis on Inersil ODS-3 column with CH_3CN–H_2O as an eluent. The d.e. value of **7** was determined by using the same instrument and eluent.