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A Concise and Stereoselective Synthesis of Squalamine

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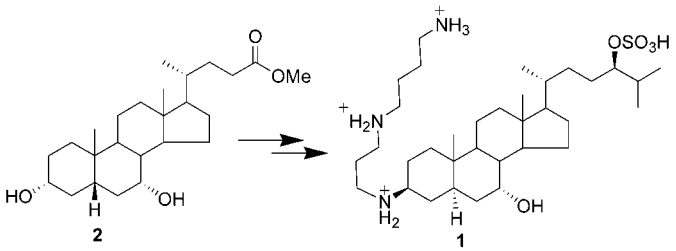
ABSTRACT



A short and highly stereoselective synthesis of the novel steroid squalamine (1) was accomplished in nine steps from easily available methyl chenodeoxylcholanate 2. Our synthesis featured improved dehydrogenation of 4 followed by conjugate reduction to construct the *trans* AB-ring system and efficient asymmetric isopropylation of aldehyde 6 to introduce the C-24*R*-hydroxyl group.

Squalamine (Figure 1) is the first member of a class of natural aminosterols isolated by Zasloff and co-workers from the stomach of the dogfish shark *squalus acanthias* in 1993.[1] This important compound has been shown to possess antiangiogenic and antitumor activity[2] and was developed as a new chemotherapeutic approach in the treatment of late stage lung cancer and ovarian cancer.[3] The novel structural features and remarkable antitumor activity have provided the impetus for several synthesis studies. Two lengthy syntheses (17 steps) of an equal mixture of C24-stereoisomers were reported, starting from 3β-acetoxy-5-cholenic acid[4] and 3β-hydroxy-5-cholenic acid, respectively.[5] Stereoselective syntheses of squalamine were also achieved from stigmasterol[6] or methyl 3-keto-5α-chenodeoxy cholanate.[7] All these syntheses required many steps and were impractical for the

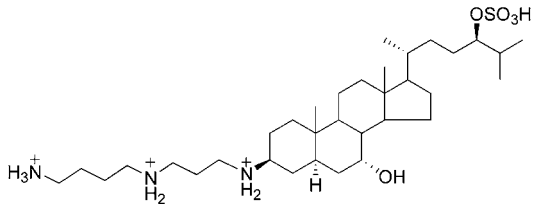


Figure 1. Squalamine **1**.

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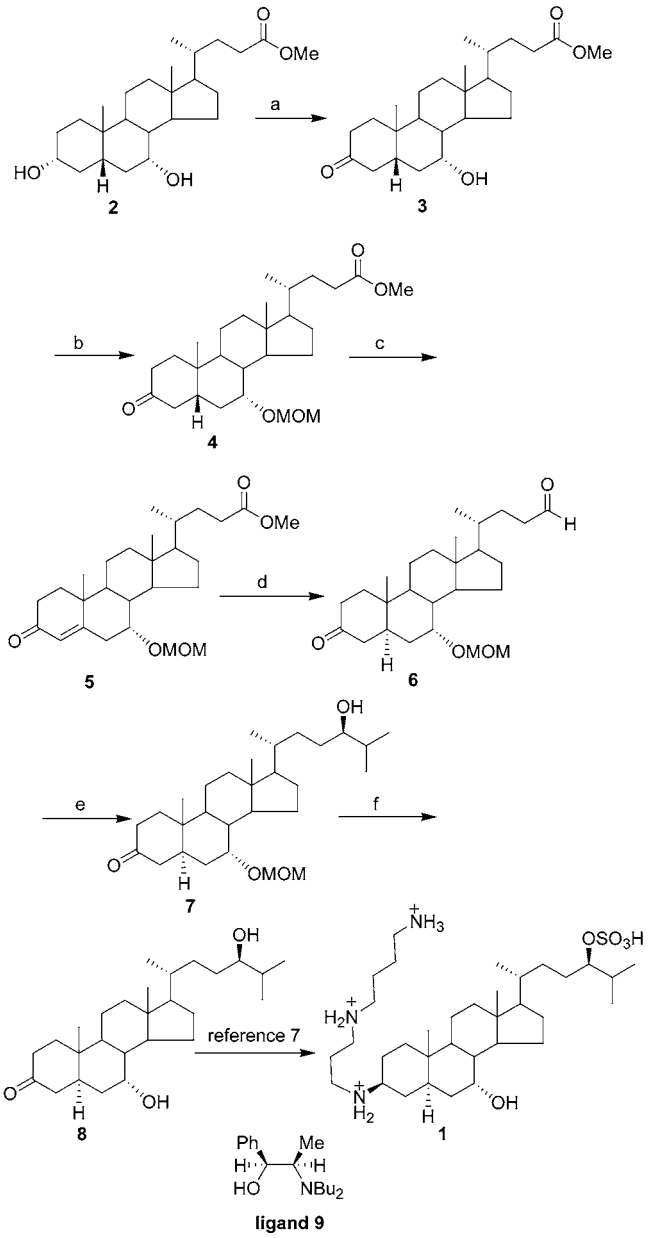
large-scale synthesis of squalamine. To provide adequate supplies for clinical trials, the pursuit of a more efficient synthesis of squalamine became necessary. Recently, great advance on the synthesis of squalamine has been achieved, which reduced the number of steps from 16 to 11 by utilizing biotransformation methodology to introduce the 7α-hydroxyl group.[8] In connection with our previous work, herein, we wish to describe a new concise route to squalamine starting from easily available material, methyl chenodeoxylcholanate **2**, with efficient construction of the *trans* AB-ring system and highly setereoselective introduction of the C-24*R*-hydroxyl group. This concise synthesis shortened the route to nine steps and, to our best knowledge, is the shortest synthetic route to squalamine so far described.

As depicted in Scheme 1, our synthesis commenced with methyl chenodeoxycholanate **2**, which is easily available in China. Ester **2** was a very appealing starting material for the synthesis of squalamine because it contained the requisite 7α-hydroxyl groups. Thus, **2** was selectively oxidized to the 7α-hydroxy-3-one **3** in 92% yield, using freshly prepared silver carbonate on Celite according to the literature.[9] Compound **3** was stirred with chloromethyl methyl ether and *N*,*N*-diisopropylethylamine in methylene chloride to afford 7α-methoxy-methyl ether **4** in 91% yield.

The next step is the dehydrogenation of **4**. Recently, Nicoloau et al.[10] have reported a new method for the synthesis of α,β-unsaturated carbonyl compounds utilizing the cheap and nontoxic IBX (*o*-iodoxybenzoic acid) as the oxidizing reagent. This IBX-based method is superior to the conventional protocols relying on highly toxic selenium reagents. Unfortunately, complex products were formed when **4** was exposed to 4.0 equiv of IBX at 85 °C in DMSO according to the standard conditions[10] (Table 1, entry 1). Careful analysis of the NMR spectrum of these products showed that the acid sensitive protecting group of methoxyl methyl in substrate **4** could not survive these conditions. When the reaction temperature was decreased to room temperature, none of the desired product was obtained accompanied by complete recovering of substrate **4**. Surprisingly, the methoxyl methyl ether of **4** was stable under this condition. Thus, we tried to effect this reaction at room temperature.[11] Because it has been reported[10] that addition of a catalytic amount of *p*-TsOH tended to significantly accelerate the reaction at 85 °C, we surmised the reaction might be triggered at room temperature by addition of *p*-TsOH. Indeed, in the presence of 0.3 equiv of *p*-TsOH, substrate **4** was smoothly oxidized to the desired α,β-unsaturated carbonyl compound **5** in 72% isolated yield by using 2.0 equiv of IBX at room temperature (entry 3). Furthermore, it was found that by using TFA (trifluoroacetic acid) instead of *p*-TsOH, the isolated yield of the product was increased to 87% (entry 4).

Scheme 1. Short Synthesis of Squalamine **1** from Methyl Chenodeoxylcholanate **2**[a]



[a] Reagents and conditions: (a) Ag_2CO_3 on Celite, toluene, reflux, 92%; (b) MOMCl, *i*Pr_2NEt, cat. NaI, CH_2Cl_2, reflux, 91%; (c) 2.0 equiv of IBX, 30 mol % of TFA, DMSO, rt, 24 h, 87%; (d) Li, ammonia, THF, −78 °C for 1 h then quenching with anhydrous NH_4Cl, 73%; (e) 20 mol % of ligand **9**, 2.2 equiv of *i*Pr_2Zn, toluene, 0 °C, 4 h, 84% yield, 99% de; (f) PPTS, *t*BuOH, reflux, 96%.

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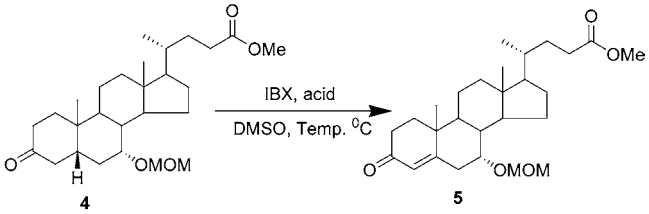
(11) It was reported that addition of *N*-methylmorpholine tended to decrease the reaction temperature. (See: Nicoloau, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993−996.) However, we found this condition had no effect on the substrate **4**.

Table 1. Dehydrogenation of **4** with IBX in DMSO



4 **5**

entry[a]	acid	mol %	temp (°C)	yield[b] (%)
1	none	0	85	–[c]
2	none	0	25	0
3	*p*-TsOH	30	25	72
4	TFA[d]	30	25	87

[a] Reactions 1 and 2 were performed with 4.0 equiv of IBX in DMSO, reactions 3 and 4 were performed with 2.0 equiv of IBX in DMSO. [b] Isolated yields were calculated after purification by silica gel chromatography. [c] Complex products. [d] TFA = trifluoroacetic acid.

The following step involved the saturation of the 4,5-double bond of **5** with lithium in liquid ammonia. This method was commonly used to afford the *trans* AB-ring junction.[12] Exposure of **5** to lithium in liquid ammonia at −78 °C for 1 h followed by quenching with anhydrous NH_4Cl smoothly delivered **6** in 73% isolated yield. Surprisingly, at some point during the course of the reduction event, the C-24 methyl ester was simultaneously reduced to the aldehyde group. Thus, two functional groups were successfully transformed in only one step. The next crucial step was the introduction of the required C-24*R*-hydroxyl group, by asymmetric isopropylation of aldehyde **6**.[13] Although **6** contained two carbonyl groups, the C-24 aldehyde carbonyl group is more active toward nucleophilic attack than the C-3 ketone carbonyl group. Consequently, the prospects for effecting a chemical selective and stereoselective isopropylation of **6** seemed very favorable. Indeed, the asymmetric addition reaction of this aldehyde **6** with diisopropylzinc[14] smoothly afforded the isopropylated adduct **7** in 82% isolated yield, in the presence of 20 mol % of ligand **9**, (−)-(*N*,*N*)-di-*n*-butylamino-1-pheneylpropane-1-ol ((−)-DBNE). The diastereomeric ratio of the product **7** was determined to be 99.5:0.5 by HPLC analysis and the absolute configuration was established at the level of **8** by comparing with the authentic sample from our previous work.[7] After removal of the methoxyl methyl group in **7**, the advanced intermediate **8** was obtained in 96% isolated yield. This key intermediate, which contained two hydroxyl groups at C-7 and C-24 in the proper orientation, was used to conveniently produce the natural product squalamine (**1**) in 33% overall yield in three steps according to our previous published work.[7]

In summary, a short and highly stereoselective synthesis of squalamine has been accomplished in nine steps and 14% overall yield from easily available methyl chenodeoxycholanate **2**, by taking advantage of the improved mild dehydrogenation reaction as a key step to construct the *trans* AB-ring system and utilizing a highly stereoselective isopropylation to introduce the C-24*R*-hydroxyl group. Our current efforts are focused on applying this remarkably practical strategy to provide adequate supplies for clinical trials and synthesizing analogues of squalamine for exploring their biological activities.

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Supporting Information Available: Spectroscopic and analytical data for **4**, **5**, **6**, **7**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For a similar example, see: Okamoto, M.; Tabe, M.; Fujii, T.; Tanaka, T. *Tetrahedron*: *Asymmetry* **1995**, *6*, 767−778.

(14) Diisopropylzinc is now available from Aldrich Inc.