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Article

Synthesis of an Analogue of Squalamine: 6*β*-Hydroxyl-3-aminosterol†

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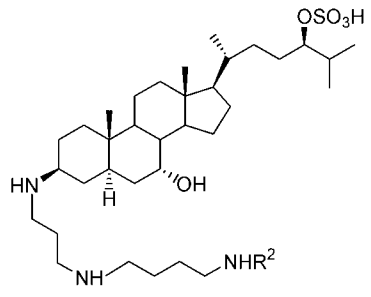
6*β*-Hydroxylsqualamine was synthesized stereoselectively in 13 steps and 19% overall yield from methyl hyodeoxycholanate by using stereospecific epoxidation and asymmetric isopropylation as key steps.

Keywords squalamine, analogue, 6*β*-hydroxyl

Squalamine (**1**, Figure 1) is a very especial steroid molecule isolated from the stomach of dogfish shark in 1993.[1] It has distinct antiangiogenic and antitumor activity[2] and was developed into a new chemotherapeutic approach in the treatment of late stage lung cancer and ovarian cancer.[3] For these reasons, many methods have been developed to synthesize this compound[4] and its analogues.[5] Among them, some 6*β*-hydroxyl analogues of squalamine have been reported[5a] to exhibit potent antimicrobial activity. Having developed two practical routes to squalamine,[6] we are now working on its analogues (**2**, Figure 1) and designed six compounds that are quite similar to their parent. All these compounds could be prepared from one starting material, methyl hyodeoxycholanate (Me-HDCA, **3**), which is very readily available in China. Here, we report our work on the synthesis of 6*β*-hydroxylsqualamine (**2a**).

As described in literature,[7] compound **4** was easily prepared from Me-HDCA in 3 steps in 80% yield. For stereospecific formation of 6*β*-hydroxyl group, we applied an elegant method.[8] Thus, oxidation of **4** with $KMnO_4$ and $CuSO_4$ gave 5,6-*β*-epoxyl compound **5** in 92% yield after removing its diastereoisomer by silica gel chromatography. From the crucial compound **5**, three leading compounds **6a—6c** could be developed into all of six new analogues **2a—2f**. In the presence of BF_3•Et_2O, reduction of **5** with $NaBH_3CN$[9] in ice-water bath could afford **6a** in 85% yield with a minute amount of the 5*α*-hydroxyl compound. Treating **5** only with BF_3•Et_2O in THF, we obtained **6b** in 83% yield. Then, by acidification of **5** with HIO_4[10] in acetone, **6c** was formed in 76% yield as the sole product. Reduced by $LiBH_4$ in the presence of BF_3•Et_2O, compound **5** gave 3,6,24-triol **7** as the major product. Selective protection of 3,24-dihydroxyl of **7** led to compound **8**, which is another precursor that could also proceed to target molecule **2a** (Scheme 1).

To protect the 6*β*-hydroxy group of **6a**, it was stirred with MOMCl, $^iPr_2NEt$, and NaI, in refluxing CH_2Cl_2 to afford 6*β*-methoxymethyl ether **9** in 92% yield. Afterwards, compound **9** was reduced with $LiAlH_4$ to afford 3,24-diol compound **10** in 95% yield. Collins oxidation of **10** gave 3-oxo-24-aldehyde **11** in 75% yield. In the presence of 20 mol% of ligand **12** (1,2-*O*-isopropylidene-5-deoxy-5-morpholino-*α*-*L*-xylofutanose), aldehyde **11** was isopropylated with diisopropylzinc to give **13** in 78% yield. Although 24*R*-hydroxyl **13** cannot be separated through HPLC from its 24*S*-diastereoisomer,



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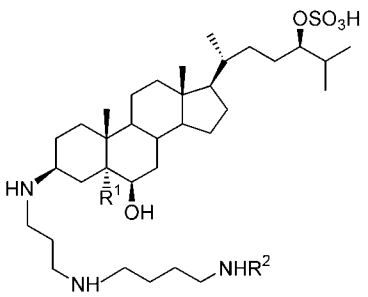

2

2a: R^1= H, R^2= H
2b: R^1= H, R^2= $CH_2CH_2CH_2NH_2$
2c: R^1= F, R^2= H
2d; R^1= F, R^2= $CH_2CH_2CH_2NH_2$
2e: R^1= OH, R^2= H
2f : R^1= OH, R^2= $CH_2CH_2CH_2NH_2$

Figure 1 Squalamine and its analogues.

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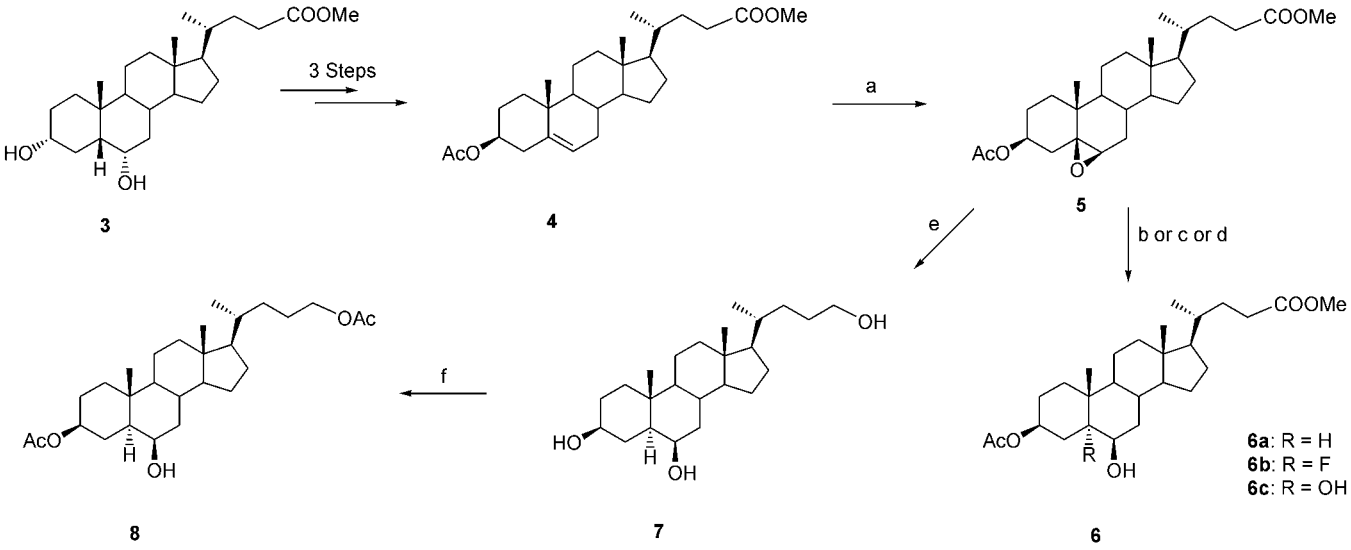
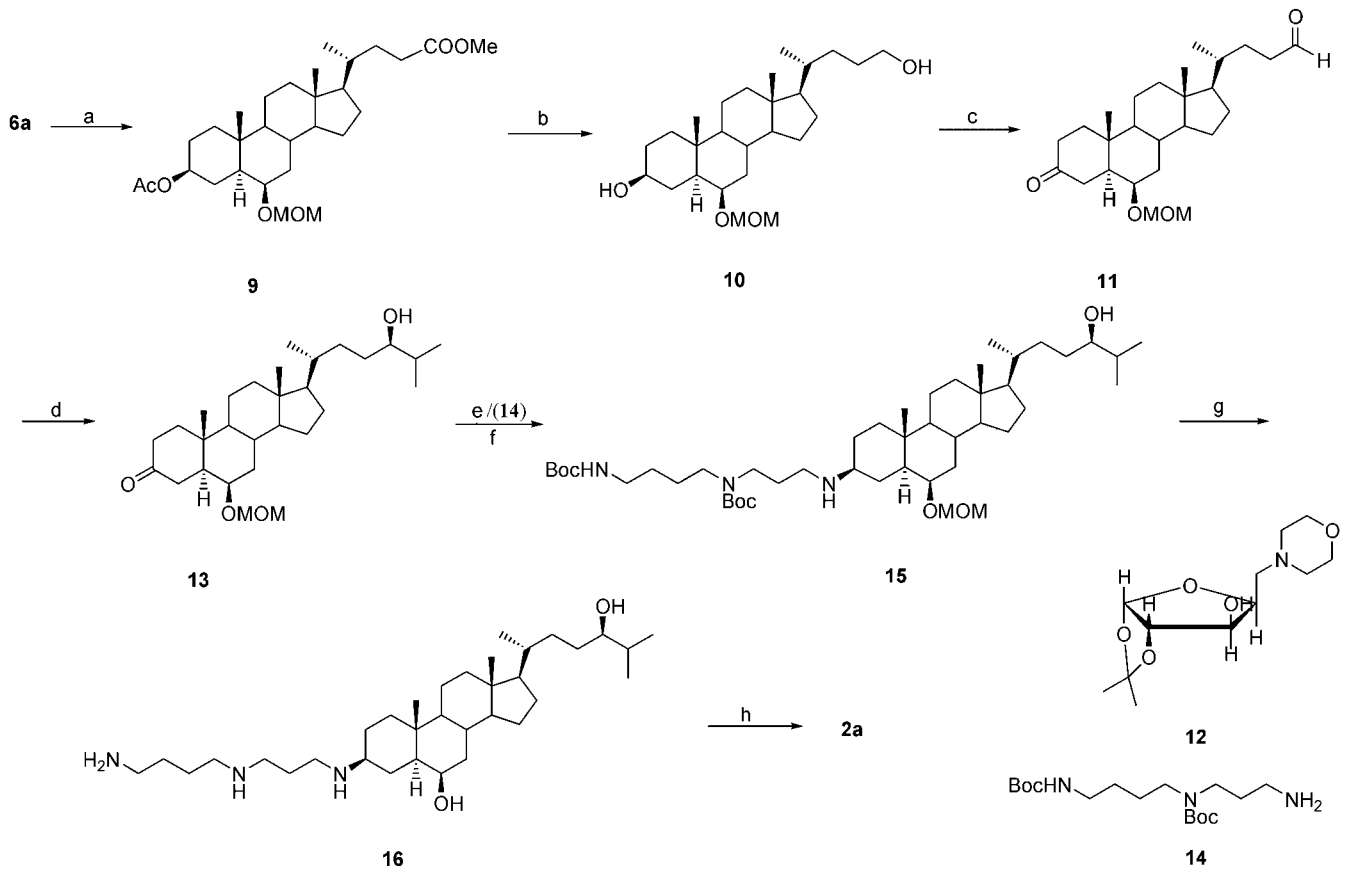
Scheme 1



(a) $KMnO_4$, $CuSO_4$, CH_2Cl_2, r.t., 92%; (b) BF_3•Et_2O, $NaBH_3CN$, 85%; (c) BF_3•Et_2O, THF, 83%; (d) HIO_4, acetone, 76%; (e) BF_3•Et_2O, $LiBH_4$, THF, 92%; (f) Ac_2O, pyridine, 82%.

Scheme 2



(a) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 92%; (b) $LiAlH_4$, THF, 95%; (c) CrO_3, C_5H_5N, CH_2Cl_2, 75%; (d) $^iPr_2Zn$, ligand **12,** $C_6H_5CH_3$, 78%; (e) 3 Å molecular sieves, absolute CH_3OH, **14**, 18 h; (f) $NaBH_4$, CH_3OH, −78 ℃, 4 h, 90% for two steps; (g) HCl, CH_3OH, 92%; (h) SO_3· C_5H_5N, C_5H_5N, 71%.

which was obtained in the reaction catalyzed by 1,2-*O*-isopropylidene-5-deoxy-5-morpholino-*α*-*D*-xylofutanose, the diastereoisomer of **12**, it can be clearly found that these two diastereoisomers display two different spots in TLC. In fact, the trace of 24*S*-hydroxyl compound can not be found in the TLC of our product system, thus the ratio of 24*R*-hydroxyl **13** to its 24*S*-diastereoisomer is probably more than 90∶10.

In the presence of 3 Å molecular sieves, compound **13** was stirred with Boc-protected spermidine **14** in absolute methanol for 18 h at r.t., then the whole system was cooled to −78 ℃ and a methanol solution of $NaBH_4$ was dropped in and stirring was continued for other 4 h. A high yield (90%) of 3β compound **15** was obtained through silica gel chromatography after separation from its 3α isomer. Removing the Boc and MOM protective groups by HCl in one step afforded compound **16**[11] in 92% yield. Dissolved in dry pyridine, **16** was stirred with sulfur trioxide pyridine complex for 2 h in 40 ℃ to give the target compound **2a**[12] in 71% yield (Scheme 2).

Thus, the 6β-hydroxyl analogue of squalamine (**2a**) was synthesized through 13 steps with 19% overall yield from the Me-HDCA. The syntheses of other analogues and the detection of their activities are in progress.

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11 Compound **16**: ^{1}H NMR (CD_3OD, 300 MHz) δ: 0.79 (s, 3H), 0.91—1.00 (m, 9H), 1.10 (s, 3H), 1.12—1.35 (m, 8H), 1.35—1.50 (m, 6H), 1.50—1.70 (m, 4H), 1.70—2.10 (m, 13H), 2.10—2.30 (m, 2H), 3.03 (t, J=6.0 Hz, 2H), 3.12 (t, J=6.0 Hz, 2H), 3.16—3.29 (m, 6H), 3.81 (br, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ: 11.2, 14.7, 16.6, 17.8, 18.0, 20.7, 23.9, 25.6, 25.7, 26.0, 27.9, 29.6, 30.0, 30.2, 31.9, 33.5, 35.3, 35.6, 38.1, 39.2, 39.4, 39.9, 42.4, 43.6, 46.6, 47.5, 48.1, 54.0, 56.2, 56.3, 57.4, 70.7, 76.3; MS (ESI) *m/z*: 548[M+1]$^+$; HRMS calcd for $C_{34}H_{66}N_3O_2$ (M+H) 548.5150, found 548.5161.

12 Compound **2a**: ^{1}H NMR (CD_3OD, 300 MHz) δ: 0.79 (s, 3H), 0.97—1.03 (m, 9H), 1.11 (s, 3H), 1.12—1.35 (m, 7H), 1.30—1.75 (m, 10H), 1.70—1.90 (m, 11H), 1.95—2.18 (m, 5H), 3.03 (t, J=6.0 Hz, 2H), 3.10 (t, 2H, J=6.0 Hz), 3.20—3.29 (m, 5H), 3.84 (br, 1H), 4.10—4.18 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ: 84.9, 70.4, 62.0, 57.9, 56.2, 54.0, 50.9, 48.5, 46.8, 44.8, 42.6, 41.7, 40.0, 39.3, 38.6, 38.0, 36.0, 35.4, 31.3, 30.7, 30.3, 28.7, 27.8, 24.6, 24.3, 23.8, 23.2, 23.1, 18.0, 17.0, 16.8, 14.6, 11.2; MS (ESI) *m/z*: 628 [M+1]$^+$; HRMS calcd for $C_{34}H_{66}N_3O_5S$ (M+H) 628.4718, found 628.4702.

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