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α-Hydroxylation at C-15 and C-16 in Cholesterol: Synthesis of (25*R*)-5α-Cholesta-3*β*,15α,26-triol and (25*R*)-5α-Cholesta-3*β*,16α,26-triol from Diosgenin

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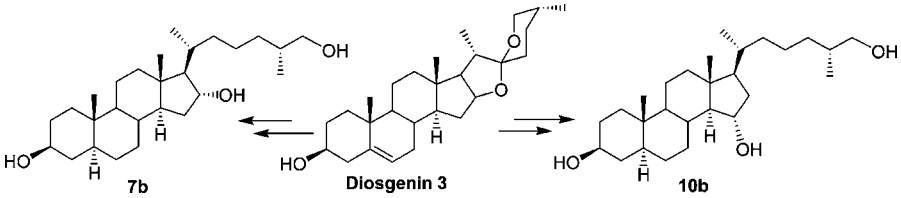
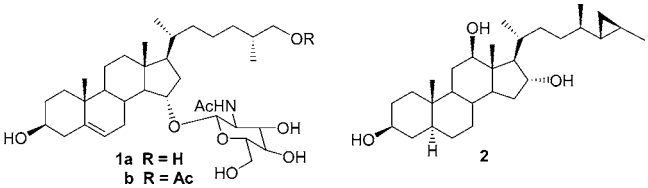
ABSTRACT



(25*R*)-5α-Cholesta-3*β*,16α,26-triol 7b and (25*R*)-5α-cholesta-3*β*,15α,26-triol 10b were synthesized, via (25*R*)-5α-cholesta-3*β*,16*β*,26-triol 5a, from diosgenin 3 in 52% yield over six steps and 47% yield over eight steps, respectively. An efficient method for inversion of a C-16*β* hydroxyl to the C-16α position and a short method for transposition of a C-16*β* hydroxyl to the C-15α position via the unexpected *β*-reduction of a C-15 ketone in a steroid are reported.

Oxysterols constitute a class of oxygenated derivatives of cholesterol with remarkably diverse, important biological actions.[1] Steroids oxygenated at C-15α lower 3-hydroxy-3-methylglutaryl-CoA reductase activity and affect sphingolipid metabolism, platelet aggregation, and protein prenylation.[1] A large number of oxysterols also occur as marine natural products.[2] Among those with 15α-hydroxylation is the shark-repelling pavoninin-5 (**1b**).[3] 16α-Hydroxylation is found in aragusterol H (**2**),[4] which shows antiproliferative activity toward KB cells with an IC_{50} of 6.48 μg/mL.



Few synthetic efforts have been devoted to C-15 and C-16 D-ring hydroxylation. Remote functionalization has afforded C-15 keto[5] and C-15α-hydroxy steroids.[6] Hydroboration−oxidation of cholesta-7,14-dien-3*β*-ol afforded the C-15α hydroxyl.[7] Marino functionalized D rings of steroids with a C-15*β* hydroxyl by alkyl cyanocuprate addition to a 1,3-diene mono-*β*-epoxide system.[8] De Riccardis found that reduction of the C-15 carbonyl is stereoselective, affording the C-15α hydroxyl group when C-16 and C-17 are sp^2

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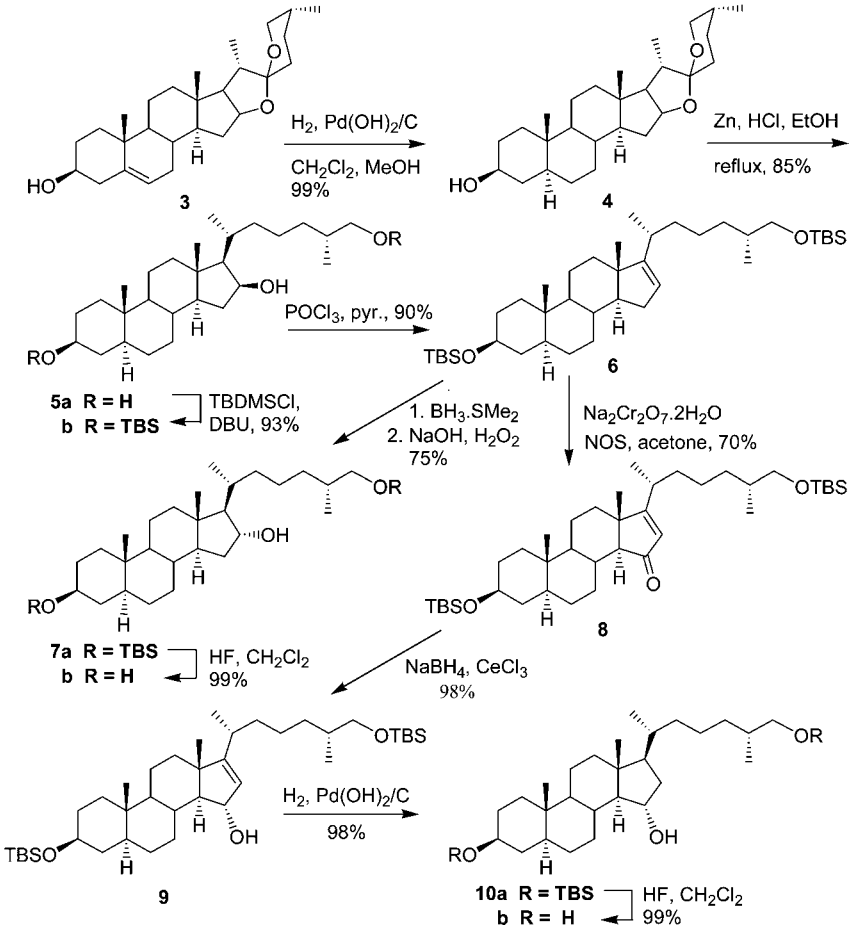
Scheme 1. Synthesis of (25*R*)-5α-Cholesta-3*β*,16α,26-triol, **7b**, and (25*R*)-5α-Cholesta-3*β*,15α,26-triol, **10b**.



hybridized.[9] Recently, we reported two methods for the transposition of C-16*β* hydroxyl to the 15α position, as well as a successful synthesis of the aglycone of 26-*O*-deacetyl pavoninin-5 (**1a**) via the 15α-hydroxy-16-ketone, using the Barton deoxygenation reaction on the 16-alcohol.[10] In this paper, we report a more efficient method for executing this transposition via allylic oxidation and subsequent stereospecific reduction. A good method for epimerization of steroidal C-16*β* hydroxyl to the C-16α position is also reported.

Tigogenin, [(25*R*)-5α-spirostan-3*β*-ol] **4**, obtained in quantitative yield by catalytic reduction of diosgenin **3**, was reacted with zinc and hydrochloric acid using our improved conditions to yield (25*R*)-5α-cholesta-3*β*,16*β*,26-triol **5a** in 85% yield.[10,11] Selective protection of the triol **5a** with *tert*-butyldimethylsilyl chloride (TBDMSCl) and DBU gave the 3*β*,26-bissilyloxy ether, 5**b**, in 93% yield. Kim et al.[12] reported the synthesis of a C-16 ene in good yield from a 16-mesylate using NaI in DMF at 120 °C. However, when we treated the 16-mesylate of **5b** with NaI, the 16-ene **6** was obtained in poor yield, probably because NaI removed some of the silyl protecting groups. We also tried elimination of the 16-mesylate with other reaction conditions, but the yield of alkene was still poor. Dehydration of the 16*β* alcohol with phosphorus oxychloride[13] showed good regioselectivity to give the C-16 olefin **6** in 90% yield. From **6**, we can synthesize both the C-16α and C-15α hydroxy steroids **7b** and **10b**, respectively, as shown in Scheme 1.

To introduce the C-16α hydroxyl group we first tried the Mitsunobu reaction,[14] to invert the C-16*β* hydroxy stereochemistry in **5b**. Unfortunately, no reaction was observed even when we used trimethylphosphine instead of triphenylphosphine to reduce steric congestion. We also tried Dodge's methodology, which varies the acid component.[15] Introduction of the C-16α hydroxyl by oxidation of the C-16*β* hydroxy to the 16-one followed by KBH_4 afforded in poor yield a mixture of C-16α and C-16*β* hydroxy compounds in a 1:9 ratio.[16] An ene reaction on a (*Z*)-16-pregnene has afforded a bisnorchol-16-en-22-ol, which upon hydroboration−oxidation gave the C-16α-hydroxy steroid.[9]

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With the C-16 olefin in hand, treatment of **6** with borane-dimethyl sulfide, followed by oxidation with alkaline hydrogen peroxide, afforded the C-16α hydroxy steroid **7a** in 75% yield. (25*R*)-5α-Cholesta-3*β*,16α,26-triol, **7b**, was obtained by desilylation of **7a** using 49% aqueous HF in 99% yield.

The 3*β*,15α,26-triol **10b** was synthesized by allylic oxidation of the olefin **6** with $Na_2Cr_2O_7 \cdot 2H_2O$ and *N*-hydroxysuccinimide to give the Δ^{16}-15-oxo compound **8** in 70% yield. This represents a considerable improvement over the CrO_3/dimethylpyrazole oxidation method, which gave **8** in a yield of 50%. Reduction of the enone **8** under Luche conditions[17] afforded the allylic alcohol **9** in 98% yield. The 500 MHz ^{1}H NMR of **9** in $CDCl_3$ showed H-15 as a doublet with coupling constant $J = 9.8$ Hz at δ 4.50 ppm. Catalytic hydrogenation of the 16-olefin in **9** afforded only the saturated C-15α alcohol **10a** in 98% yield. Desilylation of **10a**, using HF in dichloromethane, afforded (25*R*)-5α-cholesta-3*β*,15α,26-triol **10b** in excellent yield. The α-configuration of the 15-hydroxy group was confirmed by an X-ray structure (see Figure 1). This represents an efficient method for transposing the C-16*β* hydroxyl to the 15α position in 60% yield over four steps. At first glance, the reduction of enone **8** to the 15α alcohol **9** may seem unexpected. However, molecular modeling using Spartan 4 shows that when C-16 and C-17 are sp^2 hybridized, C-22 of the cholesterol side chain can move down such that the side chain can protect the C-15 carbonyl from α attack. The top face of **8** is less hindered, which results in *β* delivery of the hydride to give the 15α alcohol. Furthermore the enone system flattens ring D in **8**, decreasing the protective effect of the C-18 methyl.

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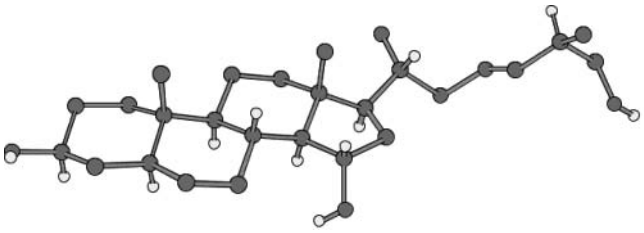

Figure 1. X-ray structure of (25*R*)-5α-cholesta-3*β*,15α,26-triol, **10b**.

In conclusion, we report short and efficient methods for α-hydroxylation at C-15 and C-16 in cholesterol. Namely, the syntheses of (25*R*)-5α-cholesta-3*β*,16α,26-triol **7b** and (25*R*)-5α-cholesta-3*β*,15α,26-triol **10b** from diosgenin **3** in 52% yield over six steps and 47% yield over eight steps, respectively.

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Supporting Information Available: Full experimental details for the synthesis of **4**, **5a**,**b**, **6**, **7a**,**b**, **8**, **9**, and **10a**,**b** and selected spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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