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A Stereoselective Synthesis of 7β-Phenyl and 7β-Methylcholesterol

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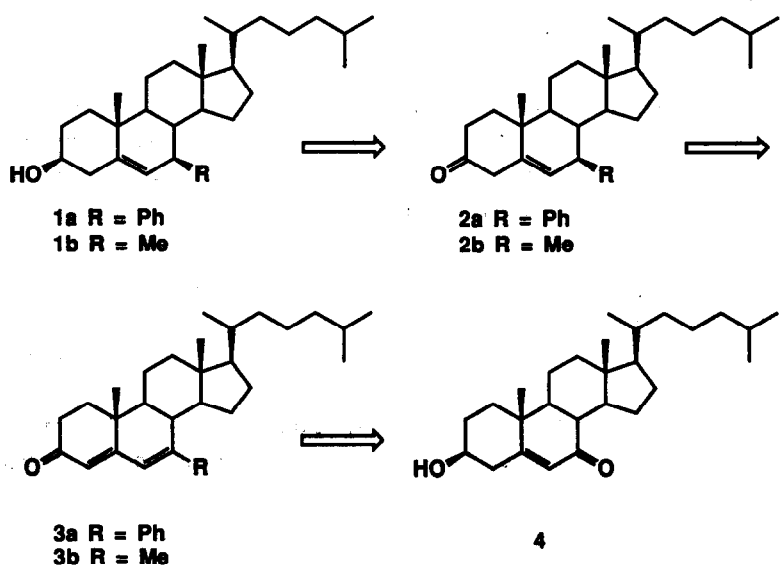
Abstract: A stereoselective synthesis of 7β-phenylcholesterol and 7β-methylcholesterol is described.

Cholesterol is an immensely important biological molecule. Its biosynthesis,[1] conversion to steroid hormones[2,3] and even its intracellular esterification[4] (cholesterol acyltransferase, ACAT) form important areas of research. Cholesterol is metabolized in the body to bile acids in which the rate limiting step is the conversion of cholesterol to 7α-hydroxycholesterol by the enzyme 7α-hydroxylase.[5] Substituents of cholesterol at the 7 position should metabolically stabilize the molecule. 7α-Substituted steroids are conveniently prepared and have shown interesting antiprogestational,[6] antiestrogen,[7] antiandrogen,[8] aldosterone antagonist[9] and aromatase[8] inhibitory activities. Chemistry for the stereoselective synthesis of 7β-substituted steroids is relatively less developed.[10] In this paper, we report a new stereoselective synthesis of 7β-phenyl and 7β-methylcholesterol. Chemistry described here should be applicable to the preparation of other 7β-substituted steroids.

Retrosynthetic analysis of the synthesis is shown in Scheme 1. We envisaged that **1a** and



1a R = Ph
1b R = Me

2a R = Ph
2b R = Me

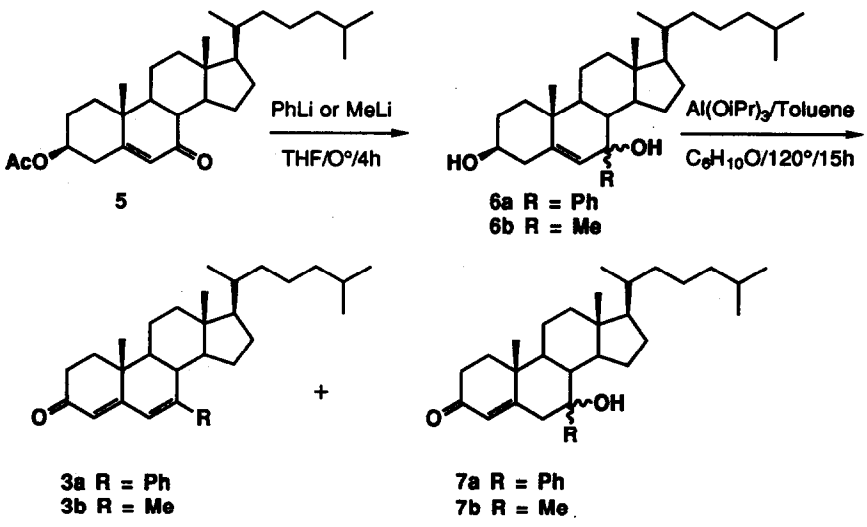
3a R = Ph
3b R = Me

4

Scheme 1

1b could be synthesized from **3a** and **3b** by stereoselective 1,6-reduction with Li/NH_3 followed by reduction of **2a** and **2b** with $LiAlH_4$. Compounds **3a** and **3b** should be easily accessible from 7-ketocholesterol **4** by corresponding organometallic reagent addition followed by oxidation.

The synthesis starts with 7-ketocholesteryl acetate **5** which was prepared from cholesteryl acetate by oxidation following a literature procedure.[11] Addition of phenyl lithium to **5** at 0°C gave a diastereoisomeric mixture (1:1 mixture, nmr) of **6a** in 89% yield. Methyl lithium addition to **5** under similar conditions also gave a diasteroisomeric mixture (1:1 mixture) of **6b** in 95% yield. Conversion of **6a** and **6b** to **3a** and **3b** were done in 77% and 80% yields, respectively, by stirring at 120° in presence of $Al(OiPr)_3$/ cyclohexanone/toluene for 15hrs. Under these conditions **7a** and **7b** were obtained as by-products in ~10% yields. No attempt was made to convert them to **3a** and **3b** by dehydration.



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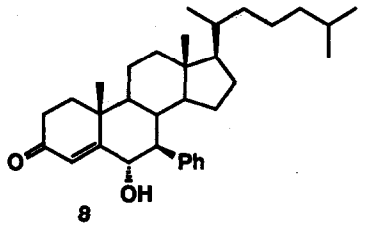
6a R = Ph
6b R = Me

3a R = Ph
3b R = Me

7a R = Ph
7b R = Me

The metal ammonia reduction of conjugated dienones of type **3a** and **3b** to β,γ-ketones **2a** and **2b** has not been extensively studied.[12] Campbell[13] et al and Marshall[14] et al have reported metal-ammonia reduction of similar conjugated dienones to α,β-unsaturated ketones in poor yields. In our case, critical stereoselective 1,6-reduction of **3a** and **3b** was carried out by reaction with Li (15eq.) in NH_3/THF/toluene (5:1:1) solution for 2hrs at dry ice/CH_3CN bath temperature. The excess Li was decomposed by stirring the solution with 1,2-dibromoethane and the enolate was kinetically quenched with NH_4Cl.[15] Surprisingly **2a** and **2b** had limited stability in solution. Compound **2a** reacted in ene fashion with oxygen[16] to give after work-up the alcohol **8**[17] and other unidentified polar products related to it. Careful workup in the absence of oxygen and use of degassed solvent circumvented the problem. The crude products contained only the 7β-substituted material (**2a**; **2b**) with no 7α-substituted steroid being detected by nmr. The exclusive formation of 7β–phenyl or -methyl product (**2a** and **2b**) can be explained by invoking the Stork

axial protonation rule,[18] the axial protonation of **9** should give 7β-product only. For practical purposes the crude reduction product was not purified and was used as such in the next reaction.



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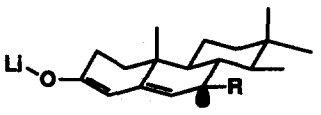
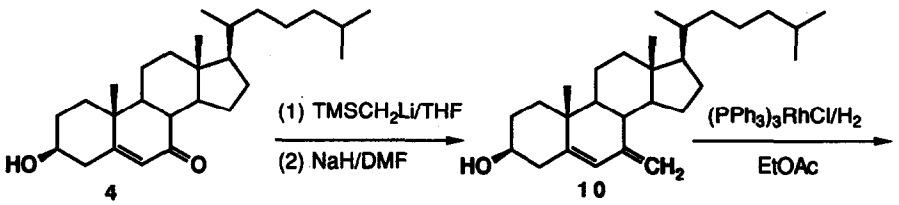


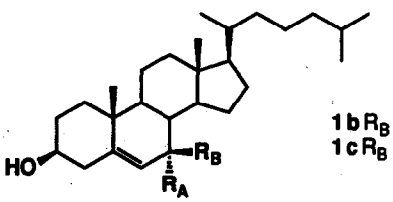
9

Addition of **2a** and **2b** to $LiAlH_4$/THF at -78° gave the corresponding **1a** and **1b**. NMR of the crude products indicated **1a**[19] and **1b**[20] to be stereochemically pure at C-3 with no detectable 3α isomer of **1a** and **1b** being present. The yield of **1a** and **1b** from **3a** and **3b** in 2 steps was 77% and 70% respectively.

The 7β-methyl compound **1b** was also synthesized from **4** by another route. Reaction of **4** with trimethylsilylmethyllithium in THF at -45° for 3 hrs followed by treatment of crude product with NaH/DMF for 15 hrs gave diene **10** in ~ 50% yield. Unfortunately the reduction of **10** with Wilkinson's catalyst/H_2 in ethyl acetate was less selective. It gave **1b** and **1c** in the ratio of 4:1.



4 **10**



1b $R_B = CH_3$, $R_A = H$
1c $R_B = H$, $R_A = CH_3$

In summary, the synthesis presented here for stereoselective synthesis of 7β-phenyl and 7β-methylcholesterol should be applicable for the synthesis of other 7β-substituted steroids and should help in developing new biologically active steroids.

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17. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30 (m, 1H), 0.65 (s, 3H, C-18), 0.79-0.83, 6H, C-26 and C-27), 0.87 (d, J = 6.5 Hz, C-21), 1.33 (s, 3H, C-19), 0.90-2.57 (m, 24H), 4.64 (dd, J = 1.8 Hz, J = 11.44 Hz, 1H, C-6), 6.23 (d, J = 1.8 Hz, 1H, C-4), 7.20-7.40 (m, 5H, Aromatic).

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19. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.35 (m, 1H), 0.61 (s, 3H, C-18), 0.82-0.84 (6H, C-26 and C-27), 0.88 (d, 3H, J = 6.6 Hz, C-21), 0.93-0.1.15 (m, 6H), 1.16 (s, 3H, C-19), 1.17-2.2 (m, 23H), 2.99 (d, 1H, J = 8.79, C-7H), 3.54 (m, 1H, C-3), 5.05 (bs, 1H, C-6), 7.1-7.3 (m, 5H, Aromatic).

20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (s, 3H, C-18), 0.84-0.87 (6H, C-26 and C-27), 0.91 (d, 3H, J = 6.5 Hz), 0.95 (d, 3H, J = 7.2 Hz, C-7 CH_3), 0.96 (s, 3H, C-19), 0.97-2.35 (m, 26H), 3.51 (m, 1H, C-3), 5.09 (t, J = 3Hz, C-6H).

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