Communications to the Editor

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A NEW METHOD FOR INTRODUCING THE 14-HYDROXYMETHYL GROUP INTO THE STEROIDAL NUCLEUS

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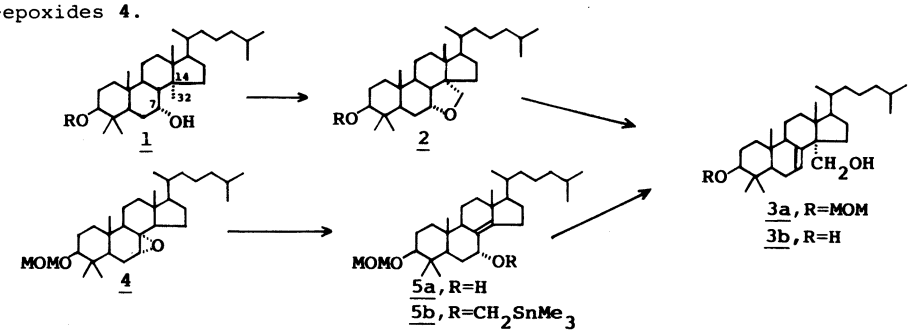
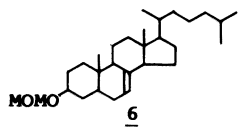
A [2,3] sigmatropic Wittig rearrangement of the stanylmethyl ether of steroidal 8(14)-en-7α-ol systems induced angular hydroxymethylation at the C-14 position.

KEYWORDS —— [2,3] sigmatropic rearrangement; Wittig rearrangement; cholesterol biosynthesis; 32-hydroxylanost-7-en-3β-ol; 14-hydroxymethylcholest-7-en-3β-ol; 7α-hydroxycholest-8(14)-en-3β-ol

In the pathway of cholesterol biosynthesis, the 32-oxygenated lanostane compounds, e.g. **3b**, are of crucial importance.[1] However, standard samples of them have been available only by chemical synthesis, in which the key step is the Barton-Kalvoda reaction[2] of the appropriate 7α-hydroxylanostane derivative **1**, followed by acidic cleavage of the resultant 7,32-oxide **2**, to afford a mixture of the 6-, 7- and 8-en-32-alcohols.[3] As a promising alternative to obtain the 32-alcohol derivative, we envisioned a [2,3] sigmatropic Wittig rearrangement[4] of the trialkylstannylmethyl ether of the 7α-hydroxy-8(14)-ene system **5**, which in turn should be prepared efficiently, in a way described recently,[5] from the 7α,8α-epoxides **4**.



The methoxymethyl (MOM) ether **6**, mp 63-64°C of cholest-7-en-3β-ol was oxidized with m-chloroperbenzoic acid to give the 7α,8α-epoxide **7**, which was then treated with boron trifluoride-etherate in tetrahydrofuran (THF),[5] yielding the allylic alcohol **8a** (65% yield), δ 0.67 (13- Me), 3.55 (3-H), 4.52 (7-H), 4.67 ($MeOC\underline{H}_2O$), accompanying the 7α-hydroxy-8(9)-ene isomer (ca 15%), δ 0.59 (13-Me), 4.00 (7-H). A similar result was obtained on treatment of the epoxie **7** with p-toluenesulfonic acid in dimethoxyethane.[6] When the allylic alcohol **8a** was deprotonated (KH, THF) and alkylated with iodomethyltrimethyltin[7] at ambient temperature, the stanylmethyl ether **8b**, δ 0.67(13-Me), 3.50 (ABq, J=11 Hz, $OC\underline{H}_2SnMe_3$), 3.90 (7-H) was formed in 71% yield. Treatment of the ether **8b** with excess n-butyllithium



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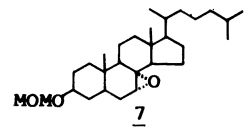

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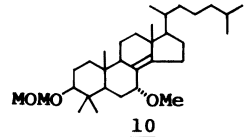
8a, R=H

8b, R=CH_2SnMe_3

8c, R=Me

9a, R=MOM

9b, R=H



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in THF at -78°C to ambient temperature induced a smooth [2,3] sigmatropic rearrangement to give the 14-hydroxymethyl derivative **9a** (79%), mp 108-109°C, δ 0.73 (13-Me), 3.43 (ABq, J=9.5 Hz, CH_2OH), 5.32 (7-H), together with the allylic methyl ether **8c** (5%), δ 3.19 (OMe), 4.02 (7-H), m/z 460 (M^+). Removal of the MOM group of **9a** with 2.5% HCl/THF-MeOH-H_2O, gave the diol **9b** (98%), mp 166-168°C, δ 0.74 (13-Me), 3.45 (ABq, J=10 Hz, CH_2OH), 3.57 (3-H), 5.32 (7-H), m/z 416 (M^+).

With the angular hydroxymethylation at the C-14 position completed, we next applied this method to the preparation of the 32-hydroxylanostane derivative. To this end, 4,4-dimethylcholest-7-en-3β-ol[8] was transformed in a manner similar to that described above, into the 7α,8α-epoxide **4**, mp 195-196°C, m/z 474(M^+), and then into the allylic alcohol **5a**, δ 0.74 (13-Me), 3.17 (3-H), 4.60 (ABq, J=6.9 Hz, $MeOCH_2O$), 4.58 (7-H), m/z 474(M^+) in 45% overall yield. Deprotonation and alkylation of this intermediate with iodomethyltin afforded the allyl stanylmethylether **5b** (75%), δ 0.74(13-Me), 3.48 (ABq, J=10 Hz), 3.97(7-H). The [2,3] sigmatropic rearrangement of this ether **5b** with excess n-butyl lithium gave the expected homoallylic alcohol **3a** (83%), mp 144-146°C, δ 0.72 (13-Me), 3.42 (ABq, J=9.4 Hz, CH_2OH), 5.37(7-H), and the methyl ether **10** (7%), mp 87-88°C. Removal of the MOM group, afforded 32-hydroxylanost-7-en-3β-ol **3b** (87%), mp 207-209°C (lit.[2] mp 207.0-208.5°C). Transformation of **3b** into the biologically more important 8-ene isomer has already been established.[1] Thus, the present procedures pave a convenient way leading to various 32-oxygenated sterols.

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