STEREOCHEMICAL COURSE OF THE HYDROBORATION OF HIGHLY HINDERED STEROIDAL OLEFINS. A READY SYNTHESIS OF 14β- AND 8α,14β-STEROIDS

M. ANASTASIA, P. ALLEVI, A. FIECCHI, A. OLEOTTI and A. SCALA

Dipartimento di Chimica e Biochimica Medica, Facoltà di Medicina e Chirurgia, Università di Milano, Via Saldini 50, I-20133 Milano, Italy

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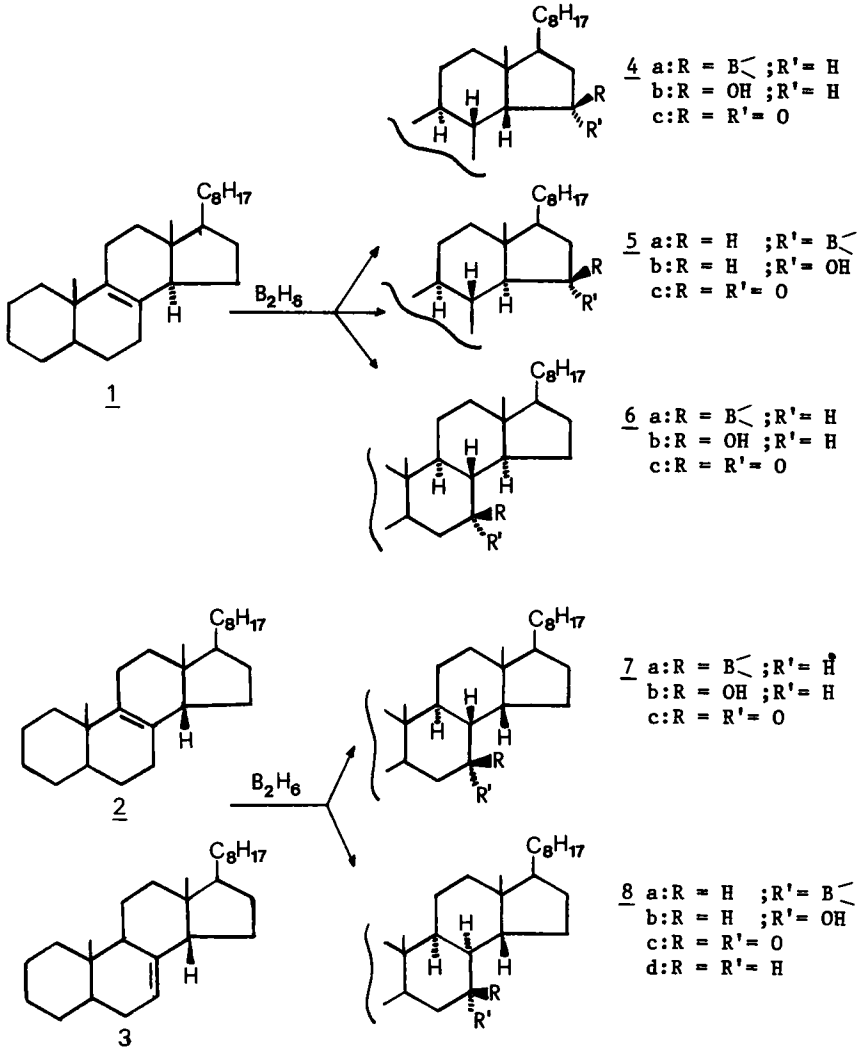
ABSTRACT

Hydroboration of 5α-cholest-8-ene, 5α,14β-cholest-8-ene and 5α,14β-cholest-7-ene provides a simple route to oxygenated steroids with 14β- and 8α,14β- unnatural stereochemistry.

INTRODUCTION

Our interest in inhibitors of cholesterol biosynthesis prompted us to seek simple methods for the synthesis of oxygenated sterols of unnatural stereochemistry (1-3) as possible inhibitors of sterol biosynthesis in L-cells and in primary cultures of liver cells (4,5). Previous success in the synthesis of 14β-cholest-5-en-3β-ol *via* hydroboration of the sterically hindered double bond of 3α,5-cyclo-5α-cholest-8(14)-en-6α-ol at 50°C (3,6) prompted us to hydroborate the 5α-cholest-8-ene 1 in order to obtain 5α,8β,9β-cholestanes of unnatural 9β-configuration as reported in a literature note (7). Since we observed an unexpected regio and stereochemical course of the hydroboration of 1, we reexamined this reaction and also studied the behavior of 5α,14β-cholest-8-ene 2 and 5α,14β-cholest-7-ene 3 to the hydroboration, in order to evaluate the influence of the steroid C/D ring junction geometry in the stereochemical course of the hydroboration.

Our results show that hydration of 5α-cholest-8-ene 1, *via* hydroboration, affords a steroid with an unnatural 14β-configuration instead of a 9β-configuration (7). Similar hydration of 5α,14β-cholest-8- and 7-enes 2 and 3 affords 8β,14β- and 8α,14β-steroids.


C8H17
B2H6
R
R'
H
1
2
3
4 a:R = B< ;R'= H
b:R = OH ;R'= H
c:R = R'= O
5 a:R = H ;R'= B<
b:R = H ;R'= OH
c:R = R'= O
6 a:R = B< ;R'= H
b:R = OH ;R'= H
c:R = R'= O
7 a:R = B< ;R'= H
b:R = OH ;R'= H
c:R = R'= O
8 a:R = H ;R'= B<
b:R = H ;R'= OH
c:R = R'= O
d:R = R'= H

EXPERIMENTAL

Melting points (m.p.) are uncorrected. Ir spectra were recorded for solutions in chloroform or for Nujol mulls. ^{1}H nmr spectra were recorded on a Varian HA-100 or a Varian XL-200 instrument for solutions in ^{2}H chloroform and are reported as δ values relative to internal Me_4Si. Optical rotations were recorded for chloroform solutions. The mass spectra were determined on a Varian MAT 112 S spectrometer by direct inlet methods. The progress of all reactions and column chromatography determinations (silica 230-400 mesh) were monitored by thin-layer chromatography (tlc) on silica gel (HF_{254}) plates. Hexane-ethyl acetate mixtures were used as developing solvents, and spots were detected by spraying with 70% sulfuric acid followed by heating. The $[\alpha]_D$ values are in degrees. Diglyme is diethylene glycol dimethyl ether.

5α-Cholest-8-ene 1. A solution of 5α-cholest-8-en-3β-ol (10 g) and toluene-p-sulfonyl chloride (10 g) in dry pyridine (70 mL) was kept at 0°C for 24 h. Standard treatment afforded the toluene-p-sulfonate (11.1 g): m.p. 110-112°C (tritured in ethanol) (Found: C, 75.5; H, 9.5; S, 5.8. $C_{34}H_{52}O_3S$ requires C, 75.3; H, 9.4; S, 6.3%); ir 1183 and 1170 cm^{-1}. The toluene-p-sulfonate (10 g) was refluxed in diglyme with sodium iodide (20 g) and zinc dust (16.8 g) for 10 h. The product was chromatographed on 10% deactivated alumina (150 g). Light petroleum eluted 5α-cholest-8-ene 1 (6.5 g): m.p. 93-95°C from methanol; $[\alpha]_D^{20}$ 56° (lit (8) 93°C; $[\alpha]_D^{20}$ 56°); δ 0.61 (3 H, s, 18-CH_3), 0.88 (3 H, s, 19-CH_3) [Calc.(9) δ 0.559 and 0.900]; M (mass spectrum) 370 (M^+), 355, 257, 201 (Found : C, 87.6; H, 14.5. $C_{27}H_{46}$ requires C, 87.5; H, 14,5%); the compound showed a single component on gas liquid chromatography (glc) analyses with relative retention time (rrt) 1.1 (the 8(14) isomer has rrt 1), on silica gel G plates and on silica gel PF-silver nitrate plates (hexane) with the same mobility of 8(14)-isomer.

5α,14β -Cholest-8-ene 2. This hydrocarbon was prepared, as an oil, from 5α,14β-cholest-8-en-3β-ol (10) by reduction of its toluene-p-sulfonate in the same way described above for the isomer 1. It showed: δ 0.87 (3 H, s, 18-CH_3), 0.93 (3 H, s, 19-CH_3); M (mass spectrum) 370 (M^+), 355, 257, 201 (Found: C, 87.4; H, 14.7. $C_{27}H_{46}$ requires C, 87.5; H, 14.5%); the compound showed a single component on glc and tlc analyses.

5α,14β-cholest-7-ene 3. This hydrocarbon, an oil, was prepared by reduction of the hydroxy group of 5α,14β-cholest-8-en-3β-ol (2) as described above. It showed: δ 5.35 (1 H, m, 7-H); 0.72 (3 H, s, 19-CH_3), 0.81 (3 H, s, 18-CH_3) [Calc. (9) 0.742, and 0.825] (Found: C, 87.4; H, 14.6. $C_{27}H_{46}$ requires C, 87.5; H, 14.5%); single component on glc and tlc analyses.

Hydroboration Procedures: Method a. Diborane was generated by adding a solution of sodium borohydride (6 g, 15,9 mmoles) in diglyme (300 mL) to a solution of boron trifluoride etherate (50 g, 35.2 mmoles) in diglyme (200 mL), in the type of apparatus described by Brown and Subba Rao (11). The gas was passed into a solution of the steroidal olefin (1 g in 400 mL of dry diglyme) at 50-60°C during ca. 3 h by means of a slow stream of nitrogen. Water was added to destroy excess

diborane and the mixture was oxidized directly.
Method b. Diborane was generated by adding to a solution of sodium borohydride (6 g) in diglyme (300 mL) a solution of iodine (20 g) in diglyme (200 mL) (12). This procedure was used in order to avoid contamination by BF_3.

Oxidation of Organoboranes. All oxidations were carried out by the following procedure. Aqueous sodium hydroxide (20 mL of a 10% solution) was added to a solution of the organoboranes (derived from 1 g of olefin) in tetrahydrofuran (40 mL). The solution was cooled in ice-water, and aqueous hydrogen peroxide (15 mL of a 30% solution) was added dropwise with stirring and continued cooling. The mixture was stirred for 1 h at 0°C and diluted with water and diethyl ether; the organic layer was washed with sodium bisulfite solution and water. The extract was then dried over sodium sulfate and evaporated.

Hydration of 5α-cholest-8-ene 1. Hydroboration (methods a and b) of this olefin (1 g) affords, after oxidation, a mixture of alcohols which were chromatographed to give three different substances: the first eluted (500 mg) proved to be 5α,14β-cholestan-15β-ol 4b : m.p. 46-48°C (from methanol); $[\alpha]_D^{20}$ 30° ; ir 3460 cm^{-1}; δ 0.75 (3 H, s, 19-CH_3), 0.90 (3 H, s, 18-CH_3), 3.43 (1 H, m, 15α-H; $W_{\frac{1}{2}}$ = 12 Hz) [Calc. (9,10,13) δ 0.750, 0.902]; M (mass spectrum): 370 (M^+-15), 355, 257, 219 (Found: C, 83.4; H, 12.3. $C_{27}H_{48}O$ requires C, 83.6; H, 12.4%).

The second eluted compound (218 mg) was 5α-cholestan-15α-ol 5b: m.p. 111-113°C (from methanol); $[\alpha]_D^{20}$ 48°; ir 3460 cm^{-1}; δ 0.70 (3 H, s, 18-CH_3), 0.78 (3 H, s, 19-CH_3), 3.94 (1 H, m, 15β-H, $W_{\frac{1}{2}}$ = 10 Hz) [Calc.(9) δ 0.725, and 0.800]; M (mass spectrum): 388 (M^+),370,355, 257,218 (Found: C, 83.5; H, 12.3. $C_{27}H_{48}O$ requires C, 83.6; H, 12.4%).

Last eluted compound (107 mg) was 5α-cholestan-7β-ol 6b: m.p. 113-115°C; $[\alpha]_D^{20}$ 52° (lit. (14) m.p. 113°C; $[\alpha]_D^{20}$ 52°); ir 3450 cm^{-1}; δ 0.68 (3 H, s, 18-CH_3), 0.80 (3 H, s, 19-CH_3), 3.35 (1 H, m, 7α-H; $W_{\frac{1}{2}}$ = 11 Hz); M (mass spectrum) 388 (M^+), 370, 356, 285, 257, 234, 217 (Found: C, 83.7; H, 12.5. $C_{27}H_{48}O$ requires C, 83.6; H, 12.4%). Identified by direct comparison with an authentic sample, and by oxidation to the corresponding ketone 6c.

Jones oxidation of the alcohols. Jones reagent (1.0 mL) was added dropwise to an ice-cooled solution of the alcohol (160 mg) in acetone (30 mL). After 2 min at 0°C the solution was allowed to warm to room temperature and then was diluted with water. The usual workup gave the ketones.

i. 5α,14β-cholestan-15β-ol 4b afforded 5α,14β-cholestan-15-one 4c (140 mg): m.p. 101-102°C (from methanol); ir 1740 cm^{-1}; δ 0.74 (3 H, s, 19-CH_3), 0.95 (3 H, s, 18-CH_3); M (mass spectrum) 386 (M^+), 370, 245, 218, 209 (Found: C, 84.1; H,12.2. $C_{27}H_{46}O$ requires C, 84.0; H, 12.0%).

ii. 5α-cholestan-15α-ol 5b afforded 5α-cholestan-15-one 5c (130 mg): m.p. 144-145°C (from methanol); $[\alpha]_D^{20}$ 50°; ir 1740 cm^{-1}; δ0.73 (3 H, s, 18-CH_3), 0.77 (3 H, s, 19-CH_3); M (mass spectrum) 386 (M^+), 260, 245, 218, 209 (Found: C, 83.9; H, 12.2. $C_{27}H_{46}O$ requires C, 84.0; H, 12.0%). All these properties were identical with those reported for the authentic compound (13).

iii. 5α-cholestan-7β-ol 6b afforded 5α-cholestan-7-one 6c (140 mg): m.p. 112-113°C (from methanol); this product was identified by m.p. and mixed m.p., optical rotation, and comparison of its ^{1}H nmr and mass spectrum with that of an authentic specimen prepared with the procedure outlined in ref.15.

Equilibration of 5α,14β-cholestan-15-one 4c. The ketone 4c (200 mg) was heated under reflux in 10% sodium methoxide for 24 h followed by conventional workup to give a clear glass which was a mixture consisting (glc-mass spectrometry) of 80% of the 14α-ketone 5c and 20% of the 14β-isomer 4c identified after preparative tlc and comparison with the original ketone 4c and the isomer 5c.

Hydration of 5α,14β-cholest-8-ene 2. Hydroboration (methods a and b) of 5α,14β-cholest-8-ene 2 (1 g) occurs at 25°C affording, after oxidation, a mixture of alcohols which were chromatographed to give first the less polar 5α,14β-cholestan-7β-ol 7b (150 mg); m.p. 58-61°C; ir 3460 cm^{-1}; δ 0.78 (3 H, s, 19-CH_3), 0.99 (3 H, s, 18-CH_3); M (mass spectrum) 388 (M^+) (Found: C, 83.5; H, 12.5. $C_{27}H_{48}O$ requires C, 83.6; H, 12.4%). Identical with those reported (13).

The more polar alcohol was identified as 5α,8α,14β-cholestan-7α-ol 8b (630 mg): an oil; ir 3460 cm^{-1}; δ 0.88 (6 H, 2xs, overlapping, 18- and 19-CH_3), 3.98 (1 H, m, 7β-H; $W_{\frac{1}{2}}$ = 5 Hz); M (mass spectrum) 388 (M^+), 370, 356, 285, 257, 234, 217 (Found: C, 83.7; H, 12.5. $C_{27}H_{48}O$ requires C, 83.6; H, 12.4%).

Following the hydroboration at 50-60°C and H_2O_2 oxidation, the described alcohols 7b and 8b were obtained in 1:1 ratio. When the hydroboration was effected at 120°C the oxidation afforded the alcohol 7b accompanied by only trace amounts of the isomer 8b.

Hydration of 5α,14β-cholest-7-ene 3. Hydroboration (method a and b) of 5α,14β-cholest-7-ene 3 (1 g) occurs at room temperature, affording after oxidation and chromatography the 5α,14β-cholestan-7β-ol 7b (280 mg) and the 5α,8α,14β-cholestan-7α-ol 8b, both identical (m.p., ^{1}H nmr, and mass spectrum) with those described above.

5α,8α,14β-cholestane 8d. To a stirred solution of 5α,8α,14β-cholestan-7β-ol 8b (70 mg) in pyridine (3 mL) at 0°C toluene-p-sulfonyl chloride (100 mg) was added. The mixture was kept at 4°C for 16 h. After usual workup the crude toluene-p-sulfonate (75 mg) which was obtained was stirred with aluminium hydride (100 mg) at 25°C in diethyl ether (10 mL) for 5 h. Usual workup and chromatography afforded 5α,8α,14β-cholestane (50 mg) as the exclusive hydrocarbon compound: a clear liquid; $[\alpha]_D^{20}$ 85°; all physico-chemical properties were identical with those of an authentic (10,16) compound.

5α,8α,14β-cholestan-7-one 8c. The alcohol 8b (80 mg) was oxidized with Jones reagent at -25°C as described above. Usual workup afforded 5α,8α,14β-cholestan-7-one 8c as an oil (which appeared to equilibrate slowly to a less polar compound on standing in solution or upon tlc): δ 0.90 (6 H, 2xs, overlapping, 18- and 19-CH_3); M (mass spectrum) 386 (M^+), 368, 353, 290, 255, 232.

Equilibration of 5α,8α,14β-cholestan-7-one 8c. 5α,8α,14β-Cholestan-7-one 8c (30 mg) was dissolved in 5% methanolic potassium hydroxide and heated under reflux for 3 h. After the usual workup and crystallization 5α,14β-cholestan-7-one 7c was obtained as needles (25 mg, from methanol): m.p. 90-91°C, $[\alpha]_D^{20}$ 74°; identical in all respects with that reported (13).

RESULTS AND DISCUSSION

Attempting to obtain 8β,9β-steroids we effected the hydroboration of 5α-cholest-8-ene 1 at 50-60°C in the reported conditions (7). However, in our hands, a mixture of the steroidal boranes 4a, 5a, and 6a in 48%, 21%, and 11% yields was obtained. They were characterized, after oxidation with hydrogen peroxide, as 5α,14β-cholestan-15β-ol 4b, 5α-cholestan-15α-ol 5b , and 5α-cholestan-7β-ol 6b.

The ratio of 15-α and 15β-boranes varied when the hydroboration was effected at higher temperature, and at 120°C the 15α-borane 5a was the major component. The amount of 7β-borane 6a was independent of the temperature. The same result was obtained when the diborane saturated hydroboration mixture was heated at 120°C for 1 h before being oxidized. The cholestanols were isolated by rapid chromatography, and each alcohol showed spectral and chemical findings compatible with the assigned structure. In particular, the location at C-15 and the β-configuration of the hydroxy group in the molecule of the less polar alcohol 4b was deduced from the ^{1}H nmr spectrum and from successive Jones oxidation of 4b to the 5α,14β-cholestan-15-one 4c without epimerization at C-14. This method has been used previously for oxidation of alcohols to enolizable ketones without epimerization of a chiral center α to the ketone function (16). Subsequent basic equilibration of ketone 4c gave a mixture consisting of 80% of the known 5c and 20% of 4c. After separation, the ketone 5c showed the expected physicochemical properties and the highly characteristic mass spectrum (13).

The ketone 4c showed appropriate physico-chemical properties.

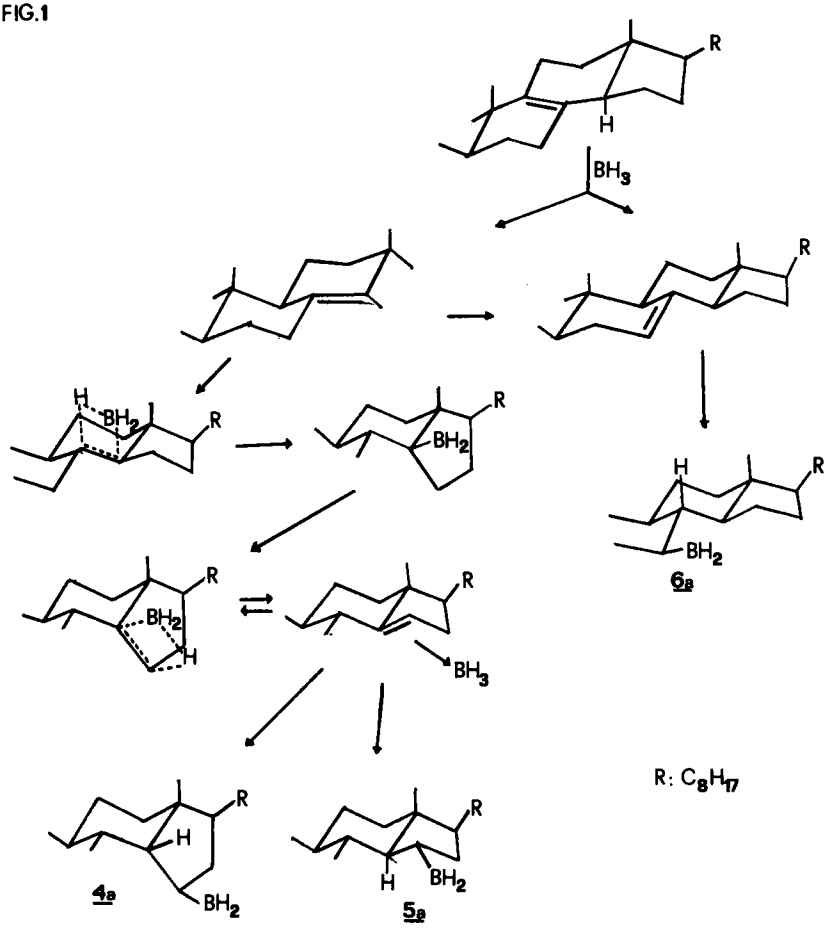
By Jones oxidation the second polar alcohol 5b afforded the ketone 5c identical with that described above.

The third eluted alcohol was identical (m.p., mixed m.p., optical rotation, ^{1}H nmr etc.) with an authentic sample (14). Moreover by Jones oxidation it afforded the known (14) 5α-cholestan-7-one 6c.

The products obtained in the hydration, via hydroboration of 5α-cholest-8-ene 1 are similar (apart from the formation of the 7β-alcohol 6b) to those reported in the hydroboration of 5α-ergost-8(14)-en-3β-ol (6). This was rationalized following the reaction by glc-mass spectrometry. The formation of 5α-cholest-8(14)-ene catalyzed by borane was observed during the hydroboration. The formation of 5α-cholest-7-ene was not observed by glc; however the formation of the alcohol 6b could be explained as the product of transiently formed 5α-cholest-7-ene, which is known to suffer a β-hydroboration in these conditions (17). Moreover in our hands the hydroboration of 5α-cholest-8(14)-ene at 50-60°C resulted in the formation of a 7β-borane in about 14% yield in addition to the expected 14α and 14β,15-boranes (6). Thus, the formation of boranes 4a, 5a, and 6a is well explained by an initial α-attack of the borane which causes the observed isomerization of the double bond from the 8(9) to the 8(14) and in minor extent to the 7(8) position (Fig.1).

The 8(14) and 7(8) steroid olefins, which cannot suffer an α-hydroboration to yield highly unstable 8α,9α,14α-steroids, are hydroborated from the β-face of the molecule with the formation of a boroderivative with the boron at the 14β-position and the 7β-position respectively.

FIG.1



The isomerization of the 14β-borane through a π complex affords boranes with the boron at 15α- and 15β-position, while the 7β-borane does not isomerize to the 7α-position, since the resulting steroid with an 8α,9α,14α-junction should be less stable in respect to a 7β-isomer possessing a natural 8β,9α,14α-geometry; indeed the hydroboration of 5α-ergost-7-ene at 50°C affords only a 8β,9α,14α-borane with the boron at 7β-position (17).

Indirect support for this explanation of the behavior of 5α-cholest-7-ene derives from the results obtained in the hydroboration of 5α,14β-cholest-8-ene 2. In this case the diborane adds to the double bond from the α-face of the molecule and, in absence of a 14α-hydrogen, does not cause the isomerization of the Δ^8 double bond to the $\Delta^{8(14)}$ position as observed monitoring the reaction by glc.

The formation of a borane with the boron at 8α-position in equilibrium with a π complex may be assumed, which, at 25°C, is transformed into a mixture (1:4) of boranes 7a and 8a, identified, after oxidation with hydrogen peroxide, as the known (13) 5α,14β-cholestan-7β-ol 7b and its isomer 5α,8α,14β-cholestan-7α-ol 8b.

The structure of the alcohol 8b derives from its physico-chemical characteristics and from the chemical transformation into 5α,8α,14β-cholestan-7-one 8c and 5α,8α,14β-cholestane 8d (8, 13). The ratio of the hydration compounds 7b and 8b was 1:1 when the hydroboration was performed at 50-60°C, while at 120°C the isomer 7b was obtained accompanied only by trace amounts of the diastereomer 8b. The same result was obtained refluxing the hydroboration mixture at 120°C before oxidizing the boroderivative. So the isomer 7b clearly represents the thermodynamically more stable compound, while the isomer 8b is the product of kinetic control.

Similar results were obtained in the hydroboration followed by oxidation of 5α,14β -cholest-7-ene 3. The reaction occurs at room temperature affording hydration mixture containing the alcohols 7b and 8b in about 1:3 ratio. Heating the mixture of boranes before the oxidation resulted in the formation of compound 7b accompanied by trace amounts of the isomer 8b. This behavior parallels that of the Δ^8-14β-

isomer and supports the mechanism of an initial α-attack on the mole by borane.

In conclusion our results show that oxygenated cholestanes with unnatural 8α- and 14β-configuration can be obtained via hydroboration highly hindered 5α-cholest-8-ene, 5α,14β-cholest-8-ene, and 5α, cholest-7-ene. The steric course of the reaction depends on stability of the final boroderivative(s) rather than the stereochemi of the starting sterol as observed for the first time on other stero olefins by Mincione and Sirna (17).

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