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A New Synthesis of Cerebrosterol and Its 24-Epimer from Lithocholic Acid

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Abstract—A new method for the synthesis of both isomers of 24-hydroxycholesterol starting from lithocholic acid is proposed.

Key words: asymmetric hydroxylation, cerebrosterol, oxysterols, steroids

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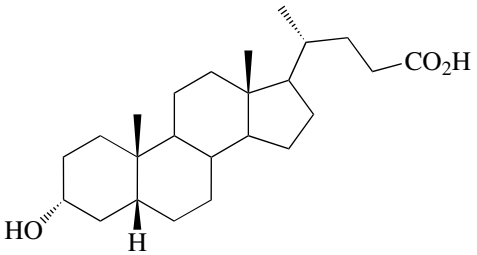
INTRODUCTION

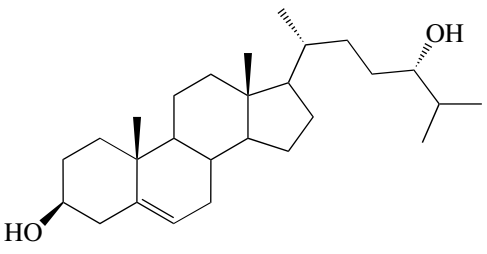
Oxidation of cholesterol at position C24 in human and mammalian organisms is the major pathway of the removal of its excess and maintenance of a proper level of this sterol in brain [1–3]. The resulting (24*S*)-24-hydroxycholesterol (cerebrosterol) readily penetrates through blood–brain barrier and further transforms in liver into bile acids or is removed from organism as the corresponding sulfates or glucuronides [4]. Brain produces up to 80% of total amount of cerebrosterol in human organism, which allows the use of this compound as a marker of cholesterol metabolism in brain. Changes in cerebrosterol content can be used for monitoring neurodegenerative diseases related to disturbances in cholesterol metabolism, such as multiple sclerosis [5] and Alzheimer's disease [6]. An additional impulse to the study of this compound was its identification as one of the ligands of receptors LXR_α and LXR_β [7–9] participating in the control of cholesterol metabolism beyond brain [10–12].

The study of biological properties of cerebrosterol implies the availability of this compound and its analogues as standards. Up to now, 24-functionalized oxysterols have remain rather inaccessible despite a large number of publications on their synthesis [13–16]. The preparative chromatographic separation of C24-isomers at the stage of final products is difficult [17], and, hence, the synthetic method to be developed should be originally targeted at the synthesis of desired isomer.

Previously, we have synthesized some analogues of cerebrosterol and (24*S*)-24,25-epoxycholesterol [18], as along with cerebrosterol itself from 3β-hydroxychol-5-enoic acid [19]. In this paper, we propose a new method of the cerebrosterol (**II**) and its 24-epimer synthesis using acid (**I**) as an available starting material.



Lithocholic acid (**I**)



(24*S*)-24-Hydroxycholesterol (Cerebrosterol) (**II**)

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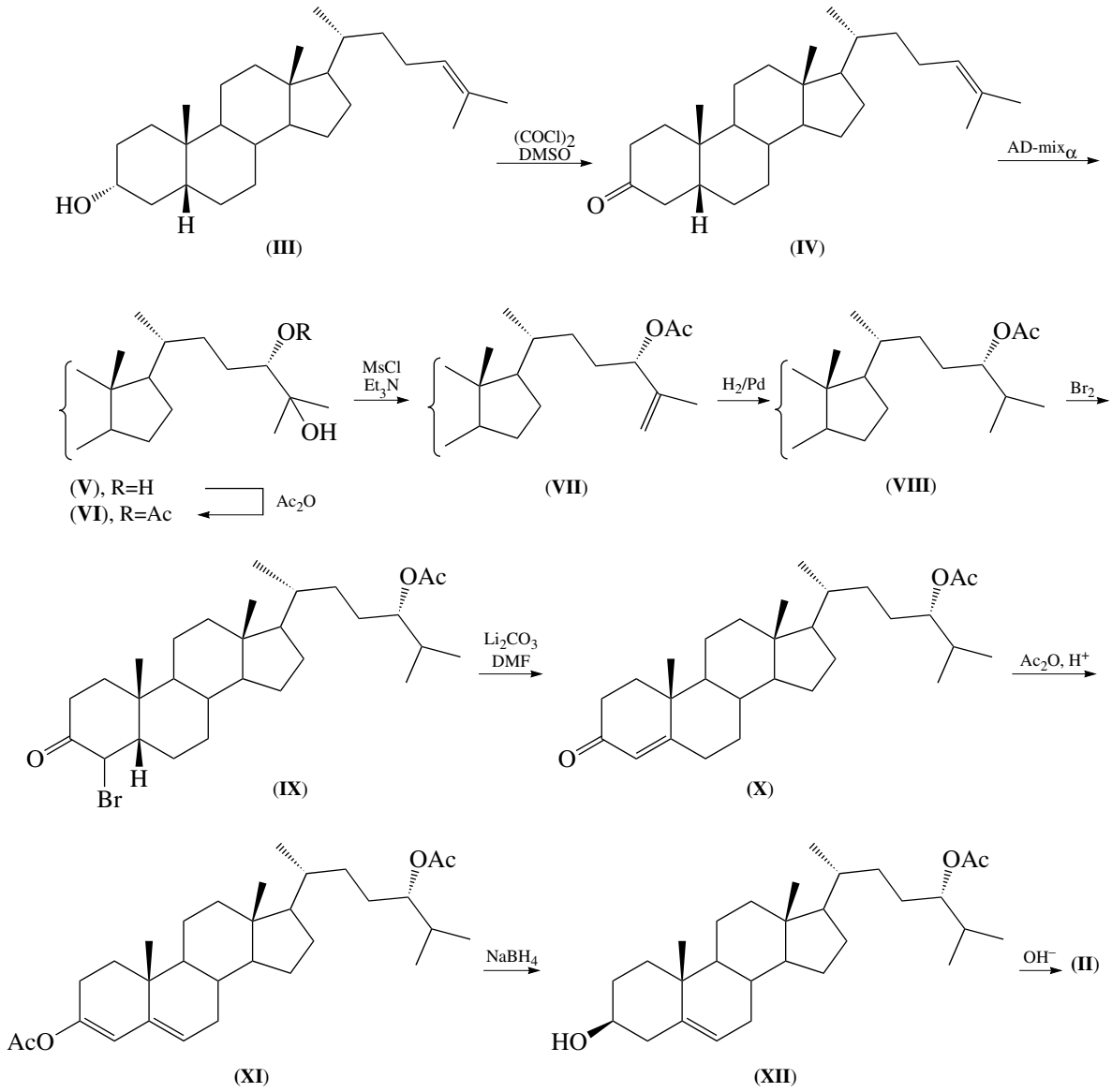


Scheme 1.

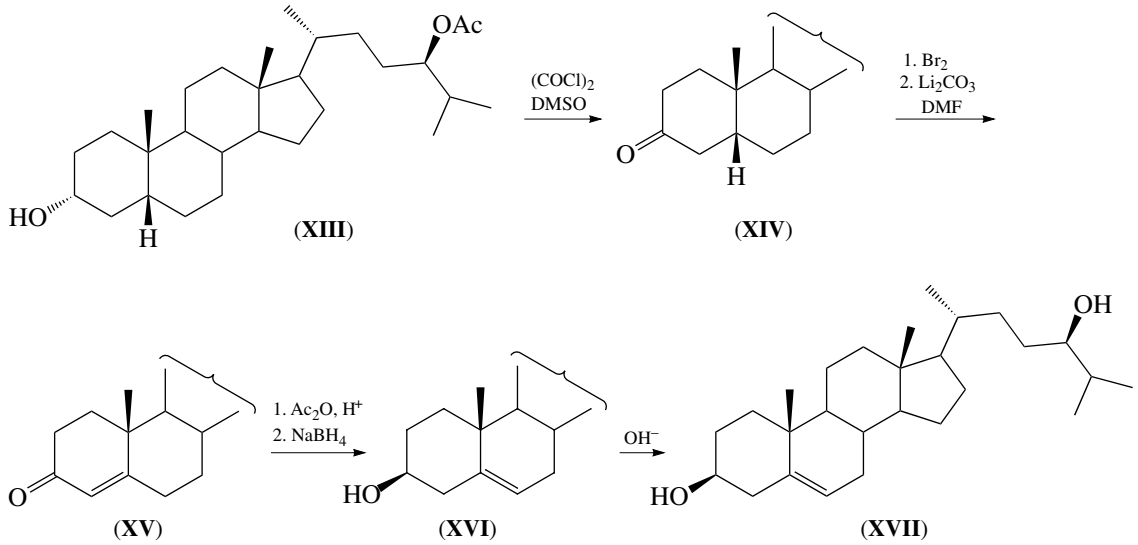
RESULTS AND DISCUSSION

Alcohol (**III**), the obtaining of which from lithocholic acid (**I**) we had previously described [18], was used for the synthesis of cerebrosterol (**II**). The Swern oxidation of alcohol (**III**) yielded ketone (**IV**), the oxidation of which with AD-mix$_\alpha$ under conditions of the Sharpless reaction led to diol (**V**) (Scheme 1). Hydroxyacetate (**VI**) obtained from this diol was treated with methanesulfonyl chloride in the presence of Et_3N and the elimination product (**VII**) was hydrogenated over Pd catalyst with the formation of (**VIII**).

The introduction of double bond into the cyclic moiety was achieved by bromination of ketone (**VIII**) at position 4 [20] and subsequent dehydrobromination of bromoderivative (**IX**) in the presence of DMF–Li_2CO_3 to enone (**X**). Its treatment with acetic anhydride in the presence of trace amounts of $HClO_4$ at room temperature resulted in the formation of enol acetate (**XI**) [21]. The reduction of this product with $NaBH_4$ yielded cerebrosterol 24-acetate (**XII**), the subsequent saponification of which with KOH in methanol resulted in the target cerebrosterol (**II**).

24-Epicerebrosterol (**XVII**) was synthesized according to a modified scheme (Scheme 2) using acetate (**XIII**) [18] as a key intermediate; this has a side chain with the required configuration of substituent at C24. The application to it of the reaction sequence described above, which involves the formation of intermediate ketone (**XIV**), enone (**XV**), and 3β-hydroxy-Δ^5-steroid (**XVI**), led to the target product (**XVII**).

Thus, we propose a method of synthesis of cerebrosterol (**II**) from lithocholic acid (**I**) that allowed the prep-



Scheme 2.

aration of the target product in 7.7% total yield and excludes the use of inaccessible synthetic 3β-hydroxychol-5-enoic acid [19]. By the example of synthesis of 24-epicerebrosterol, we studied an alternative sequence of reactions that led to the target product in 5.8% total yield from lithocholic acid.

EXPERIMENTAL

The following chemicals were used in this work: oxalyl chloride, AD-mix$_\alpha$, methanesulfonyl chloride, and sodium borohydride from Aldrich (United States). NMR spectra were measured in $CDCl_3$ on a Bruker Avance 500 spectrometer (Germany) at 500 MHz for ^{1}H and 125 MHz for ^{13}C nuclei. Tetramethylsilane was used as an internal standard. Mps were measured using a Koeffler block. The reactions were monitored by TLC on Kieselgel 60 F_{254} precoated aluminum sheets (VWR Art. 5715, Merck, Germany). Column chromatography was carried out on Kieselgel 60 (VWR, Art. 7734).

5β-Cholest-24-en-3-on (IV). A mixture of DMSO (2.6 ml, 36.6 mmol) and dichloromethane (5 ml) was dropwise added in argon atmosphere to a cooled to –70°C solution of oxalyl chloride (1.42 ml, 16.7 mmol) in anhydrous dichloromethane (50 ml), while maintaining temperature below –60°C. The reaction mixture was stirred for 30 min at –70°C, and a solution of (**III**) (3.98 g, 10.3 mmol) in dichloromethane (50 ml) was then added at the temperature below –60°C. The mixture was stirred for additional 30 min at –70°C, then Et_3N (9.0 ml, 66 mmol) was added, and the reaction mixture was allowed to warm up to room temperature. After addition of water (30 ml), the mixture was stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 40 ml). The combined organic layers were dried with Na_2SO_4 and evaporated in a vacuum. The residue was chromatographed on a column eluted with 40 : 1 ⟶ 10 : 1 petroleum ether–ethyl acetate gradient to get ketone (**IV**), yield 3.34 g (84%); mp 59–61°C (methanol); ^{1}H NMR (δ, ppm, *J*, Hz): 5.09 (1 H, t, *J* 7.0, H24), 1.68 (3 H, s, H27 or H26), 1.60 (3 H, s, H26 or H27), 1.01 (3 H, s, H19), 0.93 (3 H, d, *J* 6.6 Hz, H21), 0.68 (3 H, s, H18); ^{13}C NMR (δ, ppm): 213.41, 130.95, 125.19, 56.49, 56.29, 44.37, 42.78, 42.39, 40.80, 40.12, 37.23, 37.05, 36.07, 35.59, 35.58, 34.91, 28.27, 26.66, 25.81, 25.72, 24.73, 24.22, 22.68, 21.23, 18.62, 17.63, 12.08.

(24*S*)-5β-Cholestan-3-one-24,25-diol (V). AD-mix$_\alpha$ (8 g) and $MeSO_2NH_2$ (457 mg, 4.80 mmol) were added to a solution of olefin (**IV**) (3.34 g, 8.69 mmol) in 5 : 4 *tert*-BuOH–water mixture (137 ml). The reaction mixture was vigorously stirred for 64 h at room temperature, then Na_2SO_3 (5.0 g, 39 mmol) was added, and the mixture was stirred for additional 30 min. The mixture was evaporated to dryness in a vacuum; the residue was mixed with water (50 ml) and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were dried with Na_2SO_4 and evaporated in a vacuum. The residue was chromatographed on a column eluted with a 20 : 1 ⟶ 5 : 1 petroleum ether–ethyl acetate gradient to get diol (**V**); yield 3.37 g (93%); mp 73–76°C (hexane–ethyl acetate); ^{1}H NMR (δ, ppm, *J*, Hz): 3.28 (1 H, d, *J* 9.4 Hz, H24), 1.21 (3 H, s, H27 or H26), 1.16 (3 H, s, H26 or H27), 1.01 (3 H, s, H19), 0.94 (3 H, d, *J* 6.5 Hz, H21), 0.68 (3 H, s, H18); ^{13}C NMR (δ, ppm): 213.55, 79.57, 73.21, 56.46, 56.18, 44.33, 42.76, 42.36, 40.78, 40.10, 37.21, 37.01, 35.97, 35.55, 34.89, 33.25, 28.34, 28.25, 26.63, 26.53, 25.78, 24.18, 23.22, 22.66, 21.22, 18.81, 12.09.

(24*S*)-24-Acetoxy-5β-cholestan-3-on-25-ol (VI). Acetic anhydride (16 ml) was added to a mixture of diol (**V**) (3.34 g, 7.99 mmol) and pyridine (16 ml). The reaction mixture was kept at room temperature for 17 h, mixed with water (50 ml), stirred for 30 min, and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were dried with Na_2SO_4 and evaporated in a vacuum. The residue was chromatographed on a column eluted with 30 : 1 ⟶ 8 : 1 petroleum ether–ethyl acetate gradient to get diol (**VI**); yield 3.50 g (95%); mp 132–134°C (hexane–ethyl acetate); ^{1}H NMR (δ, ppm, *J*, Hz): 4.77 (1 H, dd, *J* 2.5 and 10.2 Hz, H24), 2.10 (3 H, s, OAc), 1.20 (3 H, s, H27 or H26), 1.19 (3 H, s, H26 or H27), 1.01 (3 H, s, H19), 0.93 (3 H, d, *J* 6.5 Hz, H21), 0.67 (3 H, s, H18); ^{13}C NMR (δ, ppm): 213.41, 171.26, 80.78, 72.50, 56.43, 55.94, 44.35, 42.75, 42.38, 40.76, 40.05, 37.22, 37.03, 35.83, 35.55, 34.90, 32.41, 28.16, 26.74, 26.64, 26.03, 25.79, 25.01, 24.16, 22.66, 21.20, 21.07, 18.78, 12.06.

(24*S*)-24-Acetoxy-5β-cholest-26-en-3-on (VII). A solution of acetoxy alcohol (**VI**) (3.50 g, 7.60 mmol) in anhydrous dichloromethane (196 ml) was mixed with Et_3N (17.6 ml, 126 mmol), cooled to 0°C and mixed under vigorous stirring with mesyl chloride (4.9 ml, 63 mmol), maintaining temperature at 0°C. The mixture was stirred for 16 h at room temperature, then water (50 ml) was added, the organic and aqueous phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 60 ml). The combined organic phases were dried with Na_2SO_4 and evaporated in a vacuum. The residue was chromatographed on a column eluted with 60 : 1 ⟶ 10 : 1 petroleum ether–ethyl acetate gradient to get 2.29 g (68%) of olefin (**VII**); mp 73–75°C (hexane); ^{1}H NMR (δ, ppm, *J*, Hz): 5.11 (1 H, t, *J* 6.8 Hz, H24), 4.94 (1 H, s, H26), 4.89 (1 H, m, H26), 2.05 (3 H, s, OAc), 1.71 (3 H, s, H27), 1.01 (3 H, s, H19), 0.93 (3 H, d, *J* 6.5 Hz, H21), 0.67 (3 H, s, H18); ^{13}C NMR (δ, ppm): 213.43, 170.34, 142.95, 113.08, 77.99, 56.38, 55.94, 44.27, 42.68, 42.31, 40.67, 39.99, 37.16, 36.96, 35.47, 35.36, 34.83, 31.21, 28.77, 28.11, 26.56, 25.72, 24.10, 22.60, 21.22, 21.13, 18.55, 17.83, 12.01. In addition, 0.69 g (19%) of starting alcohol (**VI**) was isolated.

(24*S*)-24-Acetoxy-5β-cholestan-3-one (VIII). A solution of olefin (**VII**) (53 mg, 0.119 mmol) in a 4 : 1 ethanol–THF mixture (5 ml) was hydrogenated over 5% Pd/$BaSO_4$ (30 mg) for 20 h. The reaction mixture was then filtered through a layer of silica gel and filtrate was evaporated in a vacuum. The residue was chromatographed on a column eluted with 50 : 1 ⟶ 15 : 1 petroleum ether–ethyl acetate gradient; yield of ketone (**VIII**) 40 mg (75%); mp 59–61°C (methanol); ^{1}H NMR (δ, ppm, *J*, Hz): 4.68 (1 H, m, H24), 2.05 (3 H, s, OAc), 1.01 (3 H, s, H19), 0.92 (3 H, d, *J* 6.5 Hz, H21), 0.89 (3 H, d, *J* 1.6 Hz, H26 or H27), 0.88 (3 H, d, *J* 1.6 Hz, H27 or H26), 0.67 (3 H, s, H18); ^{13}C NMR (δ, ppm): 213.35, 170.99, 79.05, 56.38, 55.93, 44.30, 42.68, 42.32, 40.69, 40.00, 37.17, 36.98, 35.70, 35.49, 34.84, 31.44, 30.98, 28.13, 27.54, 26.58, 25.73, 24.11, 22.61, 21.14, 18.68, 18.64, 17.29, 12.01.

(24*S*)-24-Acetoxycholest-4-en-3-one (X). A 8.48% solution of Br_2 in AcOH (3.6 ml) was dropwise added for 30 min to a solution of (**VIII**) (950 mg, 2.14 mmol) in AcOH (40 ml). The reaction mixture was stirred for 1 h, diluted with water (80 ml), and extracted with $CHCl_3$ (3 × 50 ml). The combined organic extracts were dried with $MgSO_4$ and evaporated in a vacuum. The residue containing bromide (**IX**) was mixed with DMF (30 ml) and Li_2CO_3 (600 mg, 8.10 mmol), and the mixture was stirred for 2 h at 165°C, cooled to room temperature, diluted with ethyl acetate (80 ml), and filtered. The filtrate was evaporated, and the residue was chromatographed on a column eluted with 50 : 1 ⟶ 20 : 1 petroleum ether–ethyl acetate gradient to give 440 mg (46%) of ketone (**X**); mp 99–100°C (hexane); ^{1}H NMR (δ, ppm, *J*, Hz): 5.72 (1 H, s, H4), 4.68 (1 H, m, H24), 2.05 (3 H, s, OAc), 1.17 (3 H, s, H19), 0.92 (3 H, d, *J* 6.5 Hz, H21), 0.89 (3 H, d, *J* 1.6 Hz, H26 or H27), 0.88 (3 H, d, *J* 1.6 Hz, H27 or H26), 0.70 (3 H, s, H18). ^{13}C NMR (δ, ppm): 199.66, 171.66, 171.06, 123.75, 79.08, 55.82, 55.74, 53.76, 42.38, 39.58, 38.59, 35.70, 35.68, 35.60, 33.97, 32.93, 32.01, 31.45, 31.02, 28.05, 27.55, 24.14, 21.16, 21.01, 18.73, 18.64, 17.37, 17.32, 11.94.

(24*S*)-24-Acetoxycholest-5-en-3β-ol (XII). A solution of ketone (**X**) (262 mg, 0.592 mmol) in ethyl acetate (21 ml) was mixed with acetic anhydride (2.0 ml, 21 mmol) and then with a 10% $HClO_4$ solution in ethyl acetate (0.07 ml). The reaction mixture was stirred for 5 min, diluted with saturated $NaHCO_3$ solution, and extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried with $MgSO_4$ and evaporated in a vacuum. Ethanol (50 ml) and $NaBH_4$ (200 mg, 5.26 mmol) were added to the residue containing enol acetate (**XI**). The reaction mixture was stirred for 16 h and formic acid was then dropwise added until cessation of gas liberation. The mixture was evaporated in a vacuum, mixed with water (30 ml), and extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried with $MgSO_4$ and evaporated in a vacuum. The residue was applied onto a silica gel column and eluted with a 9 : 1 ⟶ 3 : 1 petroleum ether–ethyl acetate gradient to give 155 mg (59%) of alcohol (**XII**); mp 108–111°C (methanol); ^{1}H NMR (δ, ppm, *J*, Hz): 5.34 (1 H, m, H6), 4.68 (1 H, m, H24), 3.52 (1 H, m, H3), 2.05 (3 H, s, OAc), 1.00 (3 H, s, H19), 0.93 (3 H, d, *J* 6.5 Hz, H21), 0.89 (6 H, d, *J* 1.6 Hz, H26 and H27), 0.67 (3 H, s, H18); ^{13}C NMR (δ, ppm): 171.09, 140.78, 121.65, 79.15, 71.76, 56.72, 55.80, 50.10, 42.29, 39.74, 37.26, 36.50, 35.75, 31.89, 31.64, 31.51, 31.03, 28.12, 27.57, 24.26, 21.16, 21.07, 19.39, 18.73, 17.34, 11.85.

24*S*-Cholest-5-ene-3β,24-diol (II) / (24*S*)-24-hydroxycholesterol (cerebrosterol)]. A mixture of alcohol (**XII**) (165 mg, 0.371 mmol), methanol (20 ml), and

KOH (0.60 g, 10.7 mmol) was stirred for 24 h, silica gel (2 ml) was then added, and the mixture was evaporated in a vacuum. The residue was chromatographed on a column eluted with 9 : 1 ⟶ 3 : 1 petroleum ether–ethyl acetate gradient to give 134 mg (89%) of (**II**); mp 173–176°C (methanol) (lit. [16] mp 181–182°C); ^{1}H NMR (δ, ppm, *J*, Hz): 5.34 (1 H, m, H6), 3.52 (1 H, m, H3), 3.30 (1 H, m, H24), 1.00 (3 H, s, H19), 0.95–0.88 (9 H, m, H21, H26 and H27), 0.68 (3 H, s, H18); ^{13}C NMR (δ, ppm): 140.90, 121.78, 77.55, 71.88, 56.86, 56.07, 50.24, 42.45, 42.37, 39.89, 37.37, 36.62, 36.05, 33.23, 32.32, 32.03, 32.01, 31.72, 30.81, 28.31, 24.39, 21.99, 19.50, 19.16, 18.93, 16.82, 11.98.

(24*R*)-24-Acetoxy-5β-cholestan-3-one (XIV) was obtained from alcohol (**XIII**) in 85% yield according to the procedure described above for (**IV**); ^{1}H NMR (δ, ppm, *J*, Hz): 4.69 (1 H, m, H24), 2.05 (3 H, s OAc), 1.01 (3 H, s, H19), 0.91–0.85 (9 H, m, H21, H26, and H27), 0.67 (3 H, s, H18); ^{13}C NMR (δ, ppm): 214.40, 170.98, 78.65, 56.41, 55.98, 44.30, 42.69, 42.33, 40.70, 40.03, 37.18, 36.98, 35.49, 35.33, 34.85, 31.41, 31.32, 28.09, 27.34, 26.58, 25.74, 24.12, 22.62, 21.15, 21.14, 18.50, 17.70, 12.02.

(24*R*)-24-Acetoxycholest-4-en-3-one (XV) was obtained from ketone (**XIV**) in 43% yield as described for the synthesis of (**X**) from (**VIII**); ^{1}H NMR (δ, ppm, *J*, Hz): 5.72 (1 H, s, H4), 4.69 (1 H, m, H24), 2.05 (3 H, s, OAc), 1.18 (3 H, s, H19), 0.92–0.87 (9 H, m, H21, H26, and H27), 0.70 (3 H, s, H18); ^{13}C NMR (δ, ppm): 199.65, 171.66, 171.02, 123.75, 78.66, 55.85, 55.80, 53.78, 42.39, 39.61, 38.59, 35.69, 35.60, 35.32, 33.98, 32.93, 32.02, 31.47, 31.34, 28.02, 27.36, 24.14, 21.17, 21.01, 18.54, 18.48, 17.74, 17.38, 11.95.

(24*R*)-24-Acetoxycholest-5-en-3β-ol (XVI) was obtained from enone (**XV**) in 48% yield as described for the synthesis of (**XII**) from (**X**); mp 94–96°C (methanol); ^{1}H NMR (δ, ppm, *J*, Hz): 5.35 (1 H, m, H6), 4.69 (1 H, m, H24), 3.52 (1 H, m, H3), 2.05 (3 H, s, OAc), 1.00 (3 H, s, H19), 0.91 (3 H, d, *J* 6.6 Hz, H21), 0.89 (3 H, d, *J* 2.4 Hz, H26 or H27), 0.88 (3 H, d, *J* 2.4 Hz, H27 or H26), 0.67 (3 H, s, H18); ^{13}C NMR (δ, ppm): 171.06, 140.77, 121.66, 78.75, 71.75, 56.74, 55.83, 50.10, 42.31, 42.29, 39.76, 37.25, 36.49, 35.38, 31.88, 31.63, 31.44, 31.41, 28.08, 27.38, 24.25, 21.17, 21.07, 19.39, 18.56, 17.73, 11.85.

24*R*-Cholest-5-en-3β,24-diol (XVII) (24-epicerebrosterol) was obtained from acetate (**XVI**) in 90% yield according to the procedure of synthesis of (**II**) described above: mp 177–180°C (methanol); ^{1}H NMR (δ, ppm, *J*, Hz): 5.34 (1 H, m, H6), 3.52 (1 H, m, H3), 3.31 (1 H, m, H24), 1.00 (3 H, s, H19), 0.95–0.90 (9 H, m, H21, H26, and H27), 0.68 (3 H, s, H18); ^{13}C NMR (δ, ppm): 140.77, 121.68, 77.08, 71.77, 56.75, 56.02, 50.11, 42.34, 42.29, 39.77, 37.26, 36.49, 35.70, 33.55, 32.06, 31.90, 31.89, 31.64, 30.57, 28.28, 24.28, 21.08, 19.40, 18.91, 18.66, 17.24, 11.88.

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