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Venkata Suryanarayana CH
Research & Development, KLIO Pharma Private Limited, Plot No-75, ALEAP Industrial Area, Pragati Nagar, Kukatpally, Hyderabad, Telangana, India

Mutyala Veera Venkata Vara Prasad
Department of Chemistry, T. John Institute of Technology, Bengaluru, Karnataka

Talasila Srinivasarao
Dr. Reddy's Laboratories Limited, Process Research and Development, API Plant, Plot No's 116, 126C, Survey No.157, S.V. Co-operative Industrial Estate, IDA Bollaram, , Telangana, India

Satish Rasa
Research & Development, KLIO Pharma Private Limited, Plot No-75, ALEAP Industrial Area, Pragati Nagar, Kukatpally, Hyderabad, Telangana, India

Correspondence
Venkata Suryanarayana CH
Research & Development, KLIO Pharma Private Limited, Plot No-75, ALEAP Industrial Area, Pragati Nagar, Kukatpally, Hyderabad, Telangana, India

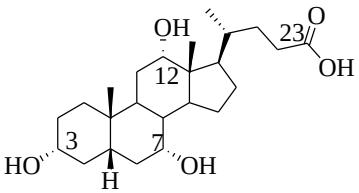
Design and syntheses of new hydroxy derivatives derived from cholic acid

Venkata Suryanarayana CH, Mutyala Veera Venkata Vara Prasad, Talasila Srinivasarao and Satish Rasa

Abstract
First syntheses of four new hydroxy functionalized derivatives of cholic acid have been reported. We have applied first time well known Saegusa oxidation, Luche reduction and α-hydroxylation (i.e., Vedejs reagent) for the syntheses of subjected cholic acid analogues.

Keywords: syntheses, new hydroxy derivatives derived, cholic acid

Introduction
Steroids and their partial synthetic analogues well studied in medicinal chemistry [1]. Bile acids (BAs) widely available natural products, have been extensively used for the preparation of receptors for various molecules and functionalized macrocylic host molecules [2]. Also, have been used for the syntheses of antimicrobial agents [3]. The biochemistry and physiology with the elegant supramolecular systems desired from bile acids well documented in the literature [4]. A series of synthetic derivatives of 6-α-alkylated chenodeoxycholic acid (CDCA) exhibits various biological properties such as potential farnesoid-X receptor (FXR) ligands [5] and potent and selective agonists of TGR5 [6].
Among the bile acids (BAs), cholic acid (ChA) has attracted significant attention primarily due to wide availability, relatively inexpensive, and the orientation of its three hydroxyl groups (i.e., C-3α, C-7 α, and C-12 α) on one face of the steroid nuclei [4]. Synthetic analogues of cholic acid have been widely explored in different scientific areas such as combinatorial and supramolecular chemistry [2], various receptors syntheses [2], as well as antimalarials and antiproliferatives [7]. In addition, it has been used for the first synthesis of 3-oxa-5β-steroid [8]. The literature reveals that, the biological activities of cholic acid derivatives depends on orientation of three hydroxyl groups. The all the synthetic analogues have been developed by performing fundamental organic reactions (i.e., reductions, oxidations, alkylation's) at three hydroxyl groups as well as C-24 carboxylic acid group. In 2009, Pellicciari and co-workers [6] identified the C-6- and C-23-alkylated cholic acid derivative as a novel and selective TGR5 agonist with remarkable *in vivo* activity.



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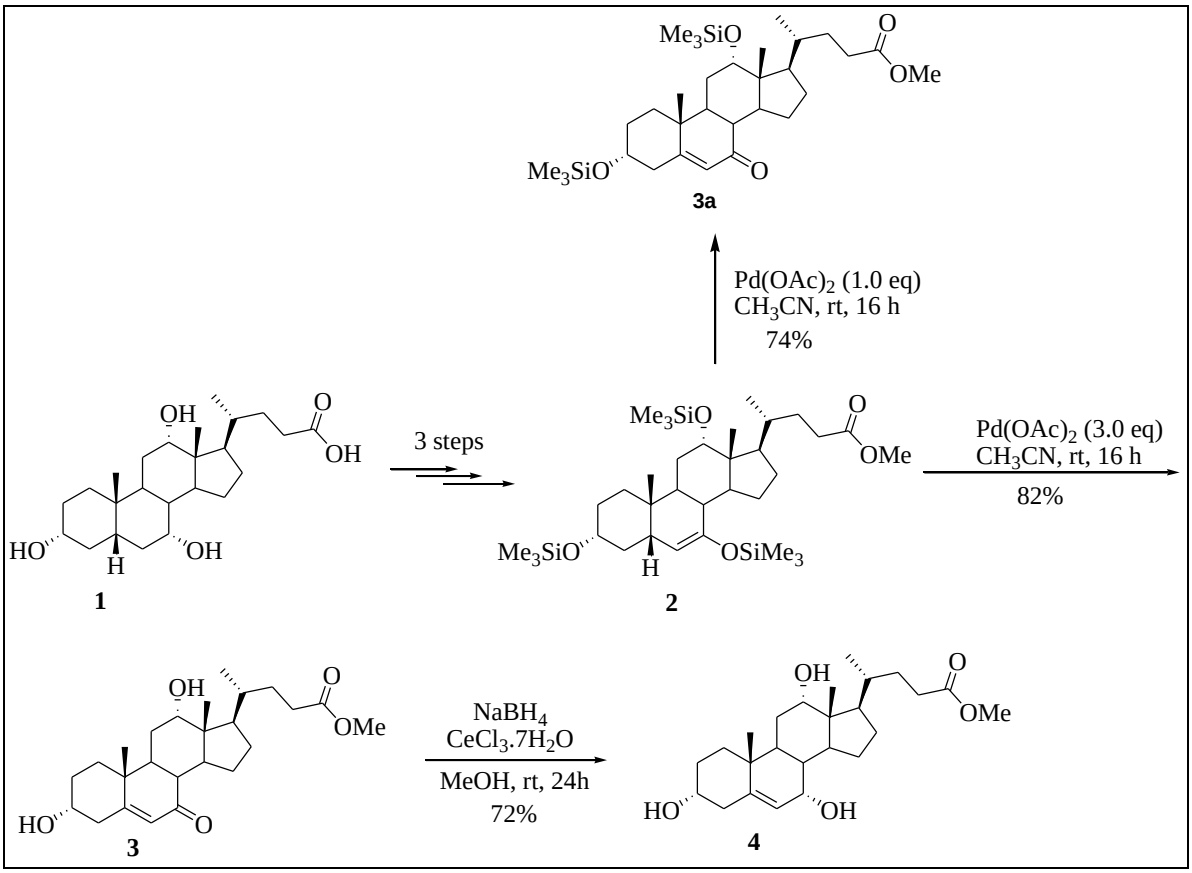
Cholic acid (ChA)

On the other hand, Saegusa oxidation extensively utilized for the conversion of enol silyl ethers to corresponding α,β-unsaturated ketones [9]. Also, has been used in total synthesis of natural products [10]. In addition, Luche reduction [11] has been applied for stereo selective reduction of α,β-unsaturated ketones. Furthermore, Vedejs reagent [12] (i.e., Oxodiperoxymolybdeenum (pyridine) (hexamethyphospotriamide) well know reagent for α-hydroxylation of ketones as well as enol ethers.

Herein, we first time successfully utilized "Saegusa oxidation" and "Vedejs reagent" for the syntheses of new cholic acid derivatives. In this short communication, we describe our success on the first syntheses of new four cholic acid derivatives.

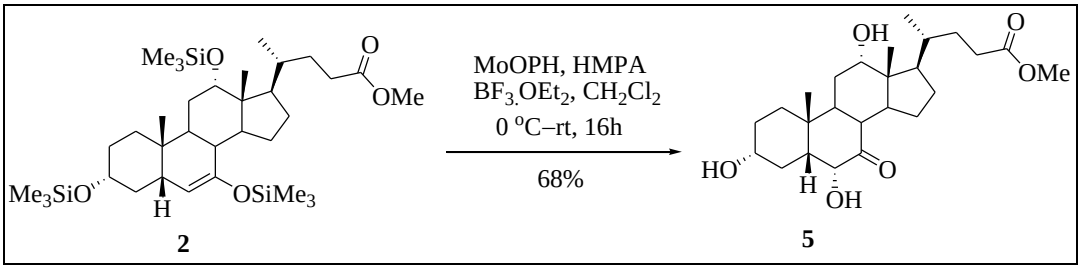
Results and Discussion

Our synthesis commenced with commercially available cholic acid (1), which can be converted into silylated enol ether intermediate 2[6b] in three steps by Pellicciari's[6b] procedure (Scheme 1). Saegusa oxidation [9] of silylated enol ether 2 with palladium acetate (3.0 equiv) in dry acetonitrile at room temperature for 16 h provided α,β-unsaturated ketone 3 in 82% yield. This compound exhibited characteristic singlet at 5.50 ppm in its ^{1}H NMR spectrum corresponds to the olefinic proton of α,β-double bond. In its ^{13}C NMR spectrum, resonance occurred at 127.01 and 174.58 ppm for the α,β-unsaturated α,β-unsaturated ketone motif. Moreover, its exact mass was detected as 419.13, which well agreed to the theoretical value 418.27 for $C_{25}H_{38}O_5$. These spectroscopic data clearly confirm the formation of α,β-unsaturated ketone 3. When the same reaction repeated with palladium acetate (3.0 equiv) under same reaction conditions exclusively delivered the di-silyl protected compound 3a in 74% yield. The resultant compound has been well characterized with all the spectral data. Then, reduction of compound 3 with ($NaBH_4$, $CeCl_3$.7 H_2O) in methanol at room temperature afforded the dihydro cholic acid derivative 4 as light brown solid in 72% yield. We have confirmed the formation of compound 4 by presence of characteristic singlet at 5.05 ppm in its ^{1}H NMR spectrum for C_5=C_6 double bond. The resultant double bond in compound 4 can be further functionalized to *cis*-polyhydroxy derivatives of cholic acid by dihydroxylation with OsO_4 [13].



Scheme 1: Synthesis of cholic acid analogue 4.

Our next stage was to introduce hydroxy group at C-6 position of the cholic acid. As shown in Scheme 2, α-hydroxylation of silylated enol ether 2 with chromyl chloride [14] in dichloromethane at room temperature for 16 h provided 6–hydroxy ketone 5 in 25% yield. On the other hand, same reaction repeated with oxygen (O_2) [15] balloon in water yielded compound 5 in only 40% yields. Then, by employing Vedejs reagent (MoOPH) in the presence of boron trifluoride diethyl etherate allowed us to improve the yield to 68%. The new compound has been characterized with all spectral data.



Scheme 2: Synthesis of 6-hydroxy analogue of cholic acid 5.

Conclusion

In conclusion, we accomplished the first synthesis of dihydro cholic acid derivative 4 in 5 steps from commercially available cholic acid. The well known Saegusa oxidation, Luche reductions were utilized for the synthesis of dihydro cholic acid 4. In addition, we make use of Vedejs reagent (MoOPH) for preparation of 6–hydroxy ketone 5.

Experimental Section

General Methods: All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen unless as indicated otherwise. Ethyl acetate and hexanes from GM fine chemicals were dried and distilled from CaH_2. Diethyl ether and THF from GM fine chemicals were dried by distillation from sodium and benzophenone under an atmosphere of nitrogen. Acetonitrile, acetone, dichloromethane, and methanol were purchased from Avra labs. Boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$), Trimethyl silyl chloride (TMSCl), Palladium Acetate (Pd $(OAc)_2$, Cerium (III) chloride heptahydrate ($CeCl_3{\cdot}7\ H_2O$), were purchased from Aldrich Chemical Co. Analytical thin layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), which were purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Silicycle ultra pure silica gel (particle size 40–63 µm, 230–400 mesh). Infrared (IR) spectra were measured on a PerkinElmer model spectrum one B spectrophotometer. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; and w, weak. Proton NMR spectra were obtained on a Varian Mercury-400 (400 MHz) spectrometer by use of chloroform-*d* ($CDCl_3$) and DMSO-d_6 as solvents. Proton NMR chemical shifts are referenced to the $CHCl_3$ singlet (δ7.24 ppm). Carbon-13 NMR spectra were obtained on a Varian Mercury-400 (100 MHz) spectrometer by used of chloroform-*d* as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (hertz). A Perkin-Elmer 241 polarimeter with a sodium lamp was used for determination of specific rotations at room temperature. Melting points were obtained with a Fargo MP-2D melting point apparatus.

(*R*)-methyl4-((3*R*,10*R*,12*S*,13*R*,17*R*)-2,3,4,7,8,9,10,11,12,13,14,15,16,17tetradecahy-dro-3,12-dihydroxy-10,13-dimethyl-7-oxo-1Hcyclopenta[a]phenanthren-17-yl)pentanoate (3): To a solution containing compound 2 (3 g, 4.69 mmol, 1.0 equiv) in dry acetonitrile (30 mL) was added Pd $(OAc)_2$ (3.16 g, 14.07 mmol, 3.0 equiv). After the reaction mixture was stirred at room temperature for 16 h, the organic solvent completely distilled off and it was diluted with water and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl solution (15 mL), dried over $MgSO_4$ (s), filtered, and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (27% EtOAc in hexane as the eluent) gave **3** (1.60 g, 3.82 mmol) in 82% yield as a white solid: TLC R_f 0.2 (50% EtOAc in hexanes as the eluent); ^{1}H NMR (DMSO; 300 MHz) δ 0.61 (s, 3 H, 21-CH3), 0.83-0.93 (m, 5 H), 1.11-1.29 (m, 10 H), 1.51-1.80 (m, 9 H), 2.15-2.27 (m, 5 H), 3.57 (s, 3 H, CO_2CH_3), 3.81 (s, 1 H), 3.97 (s, 1 H), 4.27 (d, *J*= 3.9 Hz, 1 H), 4.45(d, *J* = 2.7 Hz, 1 H), 5.50 (s, 1 H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 12.29, 16.51, 17.23, 25.64, 27.67, 28.02, 29.48, 30.78, 30.93, 31.78, 34.95, 38.26, 39.41, 41.07, 42.81, 45.17, 45.79, 46.34, 46.83, 51.30, 66.86, 71.66, 127.01, 166.12, 174.58, 201.69;); IR (KBr) ; 1739.2 (s, COCH3), 1651.4 (s, C=O), 2927 cm^{-1}; MS (FAB) *m*/*z* calcd for 418.27, found 419.13 (M+H) $[\alpha]^{25}_{589}$: -58.710°, C=0.62 in EtOH.

(*R*)-methyl4-((3*R*,10*R*,12*S*,13*R*,17*R*)-2,3,4,7,8,9,10,11,12,13,14,15,16,17tetradecahy-dro-3,12-dihydroxy-10,13-dimethyl-7-oxo-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (3a). To a solution containing compound **2** (3 g, 4.69 mmol, 1.0 equiv) in dry acetonitrile (30 mL) was added Pd $(OAc)_2$ (3.16 g, 4.69 mmol, 1.0 equiv). After the reaction mixture was stirred at room temperature for 16 h, the organic solvent completely distilled off and it was diluted with water and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl solution (15 mL), dried over $MgSO_4$ (s), filtered, and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (10-15% EtOAc in hexane as the eluent) gave 3a (1.98g, 3,53 mmol) in 74.7% yield as a white solid: TLC R_f 0.5 (40% EtOAc in hexanes as the eluent);^{1}H NMR (DMSO; 300 MHz) δ 0.1(d,18H,SiMe),0.61 (s, 3 H, 21-CH3), 0.83-0.93 (m, 5 H),1.05(d, 3H), 1.11-1.29 (m, 6 H), 1.42-1.98 (m, 9 H), 2.1-2.27 (m, 2 H), 2.3-2.55 (m, 3 H), 3.6 (s, 3 H,CO2Me), 4.0 (s, 1 H), 4.15(s, 1 H), 5.6 (s, 1 H); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 0.28 ,12.47, 16.04, 17.74, 25.74, 27.81, 29.28, 30.78, 30.93, 31.78,35.22, 38.28,40.34, 41.20, 45.37, 46.31,47.24,49.47,51.37, 67.06,71.42 73.28, 127.01, 165.89, 174.58, 201.69); IR (KBr); 1740 (s, COCH3), 1712 (s, C=O), 2952 cm^{-1}; MS (FAB) *m*/*z* calcd for 562.35, found 563.23 (M+H).

(R)-methyl-4-((3*R*,7*S*,10*R*,12*S*,13*R*,17*R*)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3,7,12-trihydroxy-10,13-dimethyl-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (4). To a solution containing ketone 3 (500 mg 1.19 mmol, 1.0 equiv) in methanol (10 mL) was added NaBH4 (452 mg, 11.9 mmol, 10.0 equiv) and $CeCl_3$.7 H_2O (1.34 g, 3.57 mmol, 3.0 equiv). After the reaction mixture was stirred at room temperature for 24 h, it was quenched with aq NH_4Cl solution and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl solution (15 mL), dried over $MgSO_4$ (s), filtered, and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (35% EtOAc in hexane as the eluent) gave 4 (360 mg, 0.855 mmol) in 72% yield as light brown solid: TLC R_f 0.1 (50% EtOAc in hexanes as the eluent); ^{1}H NMR (DMSO; 300 MHz); δ 0.61 (s, 3 H, 21-CH3), 0.80-0.85 (m, 2 H), 0.90-0.92 (m, 5 H), 1.14-1.19 (m, 4 H), 1.23-1.50 (m, 10 H), 1-90-1.98 (m, 2 H), 2.20-2.27 (m, 2 H), 2.32 (s, 1 H), 2.36 (s, 1 H), 3.26(s,3H,OMe), 3.57 (s, 2 H), 3.79-3.85 (m, 2 H), 4.02 (m, *J*= 7.2 Hz, 3 H), 4.14 (d, *J*= 4.5 Hz, 2 H), 5.05 (s, 1 H); ^{13}C NMR ($CDCl_3$; 300 MHz) δ 12.50, 14.11, 17.24, 18.25, 20.72, 22.54, 26.63, 27.67, 29.21, 29.54, 30.81, 32.30, 34.61, 35.15, 36.52, 39.02, 39.28, 41.57, 46.24, 47.07, 60.13, 66.64, 72.55, 127.16, 141.24, 174.37; IR (KBr) ; 1733.11 cm^{-1} (s, COCH3): MS (FAB) m/z calcd for 420.27, found 421.15 (M+H).

(*R*)-methyl-4-((3*R*,5*R*,6*R*,10*R*,12*S*,13*R*,17*R*)-hexadecahydro-3,6,12-trihydroxy-10,13-dimethyl-7-oxo-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (5). To a solution containing Compound **2** (500 mg 0.782 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added MoOPH (221.8 mg, 1.173 mmol, 1.5 equiv) and boron trifluoride diethyl etherate (166.4 mg, 1.173 mmol, 1.5 equiv) After the reaction mixture was stirred at room temperature for 16 h, it was quenched with aq sat $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl solution (15 mL), dried over $MgSO_4$ (s), filtered, and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (35% EtOAc in hexane as the eluent) gave 5 (352 mg, 0.806 mmol) in 68% yield as pale brown solid: TLC R_f 0.1 (50% EtOAc in hexanes as the eluent); ^{1}H NMR (DMSO; 300 MHz) δ 0.570 (s, 3 H, 21-CH3), 0.81-1.05 (m, 10 H), 1.20-1.45 (m, 6 H), 1.45-1.95 (m, 9 H), 1.98-2.41 (m, 7 H), 2.85 (dd, 5-CH, *J* =6.0 Hz, 1 H), 3.55 (s, 3 H, CO_2CH_3), 3.78 (d, 1 H, 12CH-OH), 4.29 (d, *J* = 8.4 Hz, 1 H, 3CH-OH), 4.483 (d, *J* = 8.4 Hz, 1 H, 6CH-OH) ; ^{13}C NMR ($CDCl_3$; 300 MHz) δ 12.64, 17.16, 18.16, 22.61, 24.19, 27.52, 29.03, 29.32, 30.78, 30.98, 33.99, 34.98, 35.74, 37.01, 40.32, 45.25, 45.96, 46.09, 46.34, 49.44, 51.38, 57.97, 70.50, 71.86, 174.67 (COCH3), 212.36 (C=O); IR (KBr); 1736.4 (s, COCH3), 1710.6 (s, C=O) cm^{-1}; $[\alpha]^{25}_{589}$: $+3.333^0$, C=0.6 in EtOH; MS (FAB) m/z calcd for 436.28, found 437.42 (M+H).

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Supporting Information: Copies of ^{1}H and ^{13}C NMR spectra for compounds 3, 3a, 4 and 5.

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