ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Syntheses of New Derivatives Derived from Cholic Acid.

Venkata Suryanarayana Ch[1], O Surendranatha Reddy[2], B Hari Babu[2] and V Anuradha[1]*

[1]Department of Chemistry, Vignan School of P.G Studies, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India.
[2]Department of Chemistry, Nagarjuna Nagar, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India.

ABSTRACT

First syntheses of two new functionalized derivatives of cholic acid have been reported. We have applied first time well known Saegusa oxidation and reduction with $NaBH_4$ for the syntheses of subjected cholic acid analogues.

Keywords: synthesis, cholic acid, Saegusa oxidation

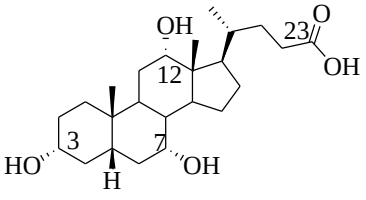
Corresponding author

ISSN: 0975-8585

INTRODUCTION

Cholic acid, along with chenodeoxycholic acid, is one of the two major bile acids produced by the liver where it is synthesized from cholesterol and they are the most important human bile acids. Cholic acid is a relatively inexpensive bile acid and can be used for synthesis of multi step synthetic product like ursodeoxycholic acid.[1] O. Bortolini et al. reported a simple and efficient synthesis of bile acids derived hydroxyl-bisphosphonates from the two human primary bile acids (cholic and chenodeoxycholic acids) and from ursodeoxycholic acid, compounds of well established pharmacological activity.[2] Cholic acid and its 7 β epimer have three hydroxyl groups present at different positions and study of their oxidation would give some insights into the chemistry of IBX and outcome may also have some practical utility.[3] Three common bile acids were degraded to the corresponding C_{22} aldehyde by an oxidative decarboxylation followed by ozonolysis. The side chain was subsequently regenerated via a Horner–Emmons reaction using an ylide generated from $^{13}C_2$-labeled bromoacetic acid.[4] 7β-HSDH is an efficient NADH-dependent reductase towards various 7-keto bile acid derivatives and a crude mixture of 7β- and 7α-HSDH allows obtaining on preparative scale UCA and UDCA in very good yields using cofactor in catalytic amount.[5] A series of synthetic derivatives of 6-□-alkylated chenodeoxycholic acid (CDCA) exhibits various biological properties such as potential farnesoid-X receptor (FXR) ligands[6] and potent and selective agonists of TGR5.[7]

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-3□, C-7□□, and C-12□□) on one face of the steroid nuclei.[8] Synthetic analogues of cholic acid have been widely explored in different scientific areas such as combinatorial and supramolecular chemistry,[9] various receptors syntheses,[9] as well as antimalarials and antiproliferatives.[10] In addition, it has been used for the first synthesis of 3-oxa-5□-steroid.[11] 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[7] identified the C-6- and C-23-alkylated cholic acid derivative as a novel and selective TGR5 agonist with remarkable in vivo activity.

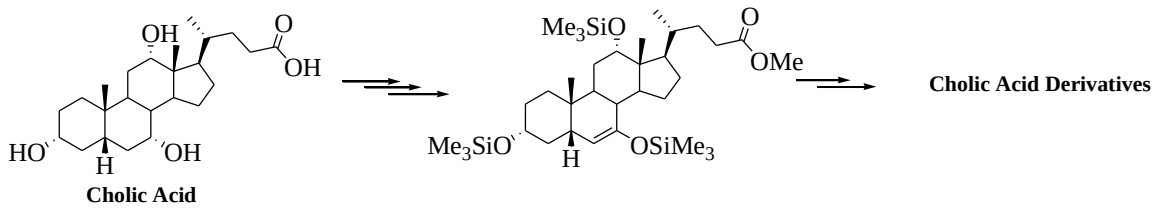


1

Cholic acid (ChA)

ISSN: 0975-8585

Table of Contents Graphic



Cholic Acid

On the other hand, Saegusa oxidation extensively utilized for the conversion of enol silyl ethers to corresponding □,□-unsaturated ketones.[12] Also, has been used in total synthesis of natural products.[13] In addition, NaBH4 reduction has been applied on □,□-unsaturated ketones. Herein, we first time successfully utilized "Saegusa oxidation" for the syntheses of new cholic acid derivatives. In this communication, we describe our success on the first syntheses of new cholic acid derivatives.

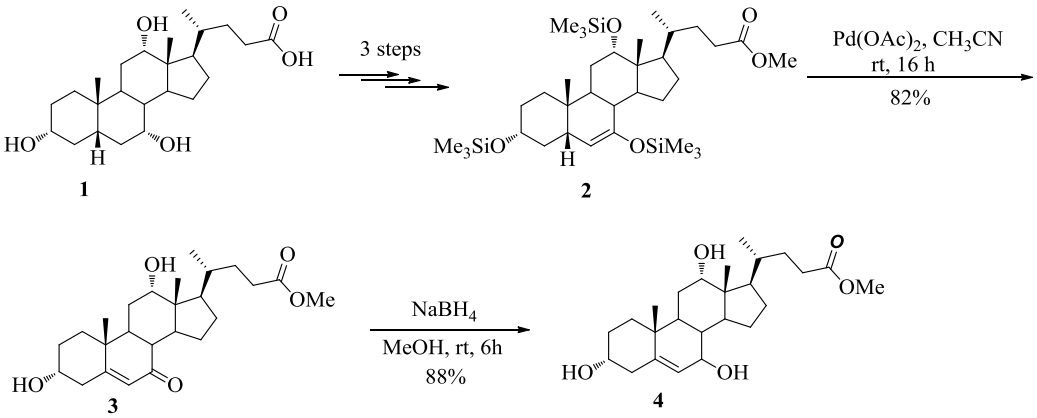
RESULTS AND DISCUSSION

Our synthesis commenced with commercially available cholic acid (**1**), which can be converted into silylated enol ether intermediate **2**[7b] in three steps by Pellicciari's[7b] procedure (Scheme 1). Saegusa oxidation[12] of silylated enol ether **2** with palladium acetate in dry acetonitrile at room temperature for 16 h provided □,□-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 □,□-double bond. In its ^{13}C NMR spectrum, resonance occurred at 127.01 and 174.58 ppm for the □, □-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 □,□-unsaturated ketone **3**. Then, reduction of compound **3** with $NaBH_4$ in methanol at room temperature afforded the dihydro alcohol derivative **4** as in 88% 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.[14]

CONCLUSION

In conclusion, we accomplished the first synthesis of dihydro alcohol derivative **4** in 5 steps from commercially available cholic acid. The well known Saegusa oxidation and $NaBH_4$ reduction were utilized for the synthesis of dihydro alcohol **4**.

ISSN: 0975-8585



Scheme 1: Synthesis of cholic acid analogue 4.

EXPERIMENTAL

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. Trimethyl silyl chloride (TMSCl), Palladium Acetate ($Pd(OAc)_2$ 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-300&400 (300 MHz & 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 (? 7.24 ppm). Carbon-13 NMR spectra were obtained on a Varian Mercury-300 (300MHz) 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 polmon 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

ISSN: 0975-8585

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); Melting Point: 84-86ºC ^{1}H NMR (DMSO; 300 MHz) 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 ($CDCl_3$; 300 MHz) 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, 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.

(4*R*)-methyl4-((3*R*,10*R*,12*S*,13*R*,17*R*)-3,7,12-trihydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12, 13,14,15,16,17-tetradecahydro-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 (226 mg, 6.0 mmol, 5.0 equiv). After the reaction mixture was stirred at room temperature for 6 h, methanol was evaporated by vacuum, 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 88 % yield: TLC R_f 0.1 (50% EtOAc in hexanes as the eluent); ^{1}H NMR (DMSO; 300 MHz) ; 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), 3.57(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 ($CDCl_3$; 400 MHz) 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, 127.16 , 141.24, 174.37; IR (KBr) ; 1461.2, 1632.11 ,3430.2 cm^{-1} : MS (FAB) m/z calcd for 392.5, found 393.4 $(M+H)^+$.

ACKNOWLEDGEMENTS

We thank the department of Chemistry, Vignan School of P.G Studies, Acharya Nagarjuna University, Guntur, Andhra Pradesh for financial support.

REFERENCES

[1] Liu Z, Advance in methods for preparation of ursodeoxicholic acid. Yaoxue Tongbao 1988; 23: 583–5.
[2] Olga Bortolini, et al. European J Med Chem 52 (2012) 221-229.
[3] Prasad S. Dangate, Chetan L. Salunke, Krishnacharya G. Akamanchi. Steroids 2011; 76: 1397–1399.

[4] Gregory P Tochtrop, Gregory T DeKoster, David P Cistola and Douglas F Covey. Bioorg Med Chem Lett 2002; 12: 433–435.
[5] Paola Pedrinia, et al. Steroids 2006; 71: 189–198.
[6] Pellicciari R, et al. J Med Chem 2002; 45: 3569-3572.
[7] Gioiello A, et al. Bioorg Med Chem 2011; 19: 2650-2658.
[8] Pellicciari R, et al. J Med Chem2007; 52: 4265-4268.
[9] Pellicciari R, et al. J Med Chem 2009; 52: 7958-7961.
[10] Mukhopadhyay S, Maitra U. Curr Sci 2004; 12 : 1666-1683.
[11] Ito Y, Hirao T, Saegusa TJ. Org Chem1978; 4: 1011-1013.
[12] Terzic N, et al. Med Chem 2007; 50: 5118-5127.
[13] Ibrahim-Ouali M, Nkomendi NB, Rocheblave L. Tetrahedron Lett 2010; 51: 93–95.
[14] Williams DR, Turske RA. Org Lett 2000; 02: 3217−3219.
[15] Chi S. Heathcock H. Org Lett 1999; 01: 3-6.
[16] Ida T, Momose T, Chang, FC, Goto J, Nambara T. Chem Pharm Bull 1989; 37: 3323-3329.