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Synthesis, crystal structure, conformational analysis, nonlinear optical property and computational study of novel pregnane derivatives

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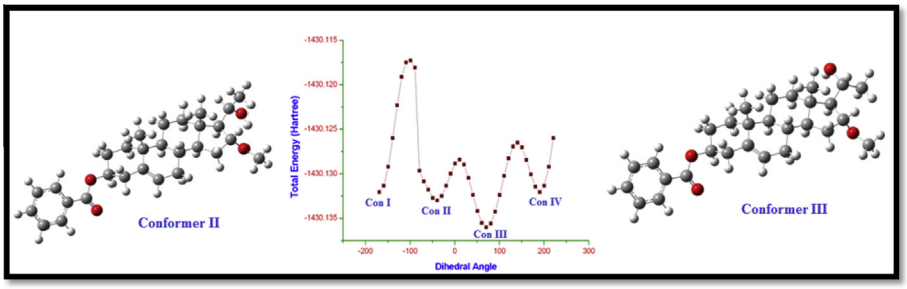
HIGHLIGHTS

- Compounds characterized with the help of ^{1}H, ^{13}C NMR, NOESY, FT-IR and ESI-MS.
- The structure and stereochemistry of **3** has been established by XRD.
- Relative stereochemistry of **4** elucidated by NOESY.
- Global electrophilicity index (2.82 eV) shows that **1** behaves as good electrophile.
- All the synthesized compounds can be used as non-linear optical (NLO) material.

GRAPHICAL ABSTRACT



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ABSTRACT

The molecular structure and detailed spectroscopic analysis of some novel newly synthesized pregnane derivatives have been performed using experimental techniques like ^{1}H, ^{13}C NMR, NOESY, FT-IR, UV–visible spectroscopy, mass spectrometry, crystallography, as well as theoretical calculations. The structure and stereochemistry of 3β-benzoyloxy 16α-methoxy pregn-5-ene-20-one (**3**) has been confirmed by single crystal X-ray diffraction, which crystallized in orthorhombic form having $P2_12_12_1$ space group with unit cell parameters $a = 6.395(5)$ Å, $b = 19.872(17)$ Å, $c = 19.898(16)$ Å and $Z = 4$. Quantum chemical calculations have been performed by density functional theory (DFT) using B3LYP functional and 6-31G (d,p) basis set. The electronic properties such as frontier orbitals and band gap energies have been calculated using time dependent density functional theory (TD-DFT). The strength and nature of weak intramolecular interactions have been studied by AIM approach. The vibrational wavenumbers have been calculated using DFT method and assigned with the help of potential energy distribution (PED). Global and local reactivity descriptors have been computed to predict reactivity and reactive sites in the molecule. First hyperpolarizability values have been calculated to describe the nonlinear optical (NLO) property of the synthesized compounds. Molecular electrostatic potential (MEP) analysis has also been carried out.

Introduction

Pregnanes are important class of steroid known for possessing remarkable biological activities like anti-inflammatory [1], anti-asthmatic [2], anti-viral [3] and anti-feedant [4]. *β-oxy* ketones derivatives of pregnanes, synthesized by Michael addition reaction on α, β-unsaturated pregnanes [5], have been reported to exhibit anti-hyperlipidemic and anti-oxidant activity [6]. Ester derivatives of steroids have also been reported to exhibit potential anti-hyperlipidemic, anti-oxidant [5], anti-diabetic [7] and anti-adipogenic activities [8].

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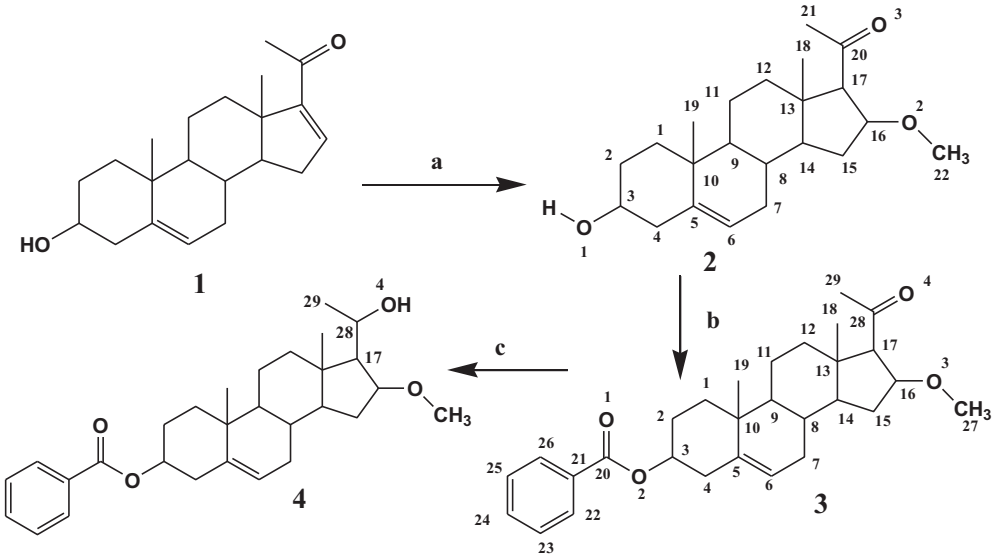

Scheme 1. (a) MeOH/KOH/reflux, yield 87.5%, (b) $C_6H_5COOH/CHCl_3$/DCC/DMAP, yield 90.6% and (c) $NaBH_4/CH_3COOC_2H_5$, yield 80%.

In continuation of our synthesis of some novel pregnane derivatives, Michael reaction [6], followed by Steglich esterification [9] and reduction of 3β-benzoyloxy-16α-methoxy-pregn-5-ene-20-one was carried out, leading to the generation of a novel pregnane derivative. The synthesized pregnane derivatives are shown in Scheme 1.

X-ray studies not only helped in establishing the stereochemistry of compound **3**, but it also helped in predicting the orientation of groups present at C-3, C-16 and C-17 positions. An atom in molecule (AIM) theory has been extensively applied to classify and understand hydrogen bonding interactions and π-electron delocalization in the molecule [10]. Energy gap between HOMO and LUMO characterized the molecular chemical stability and charge transfer interaction. Development of materials with large NLO property has been of great interest because of their application in ultrafast image-processing, optical data processing, transmission, and storage [11].

Therefore, the present paper aims to give a complete description of the molecular geometry, conformational analysis, chemical shifts, vibrational assignments, intramolecular interactions, electronic transitions, global and local reactivity descriptors, MEP and NLO features of the synthesized compounds.

Experimental

Materials and physical measurements

All reagents for synthesis were purchased from Sigma Aldrich (St. Louis, MO) and used without further purification. Thin layer chromatography (TLC) was performed on silica gel G coated plates to detect completion of reaction. Compounds were purified by column chromatography using silica gel (60–120 mesh). ^{1}H NMR spectra and NOESY correlation were recorded on Bruker DRX-300 MHz and 400 MHz spectrometer using $CDCl_3$ as the solvent and TMS as an internal standard, chemical shifts were reported as δ (ppm) and ^{13}C NMR spectra were recorded on JOEL AL 300 FTNMR (75Mz) using TMS as an internal reference. FT-IR spectra were recorded on Perkin Elmer FT-IR spectrometer from 4000 to 450 cm^{-1} range. The spectra were analyzed using Spectrum™ Software suite. ESI–MS spectra were recorded on Agilent 6520 Q-TOF mass spectrometer. Ultraviolet absorption spectra were obtained (in the range of 200–450 nm) using ELICO BL-200 UV–vis spectrophotometer equipped with a 10 mm quartz cell in dichloromethane. Melting point was determined using open capillary tube method and uncorrected.

*Synthesis of 3β-hydroxy-16α-methoxy-pregn-5-ene-20-one (**2**)*

2 g (6.369 mmol) of 3β-hydroxy-pregn-5, 16-diene-20-one (**1**) in 150 mL of 3% methanolic potassium hydroxide solution was refluxed under nitrogen for 70 min. The completion of reaction was monitored with the help of thin layer chromatography (TLC). The solution was cooled and then poured in 100 mL of ice cold water. The precipitated derivative was extracted with dichloromethane (3 × 100 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulphate and filtered. The solvent was evaporated under vacuum and the crude reaction mixture was purified by column chromatography yielding 1.75 g (87.5%) of 3β-hydroxy-16α-methoxy-pregn-5-ene-20-one (**2**) [12] as solid. m.p = 481 K, Molecular formula: $C_{22}H_{34}O_3$, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.35–5.39 (1H, m, H-6), 4.32–4.36 (1H, m, H-16), 3.51–3.46 (1H, m, H-3), 3.21 (3H, s, OCH_3), 2.54 (1H, d, H-17, J = 6.0 Hz), 2.18 (3H, s, CH_3-21), 1.25 (3H, s, CH_3-19), 0.67 (3H, s, CH_3-18). IR νmax (in cm^{-1}): 3459, 3028, 2933, 2900, 2886, 2854, 1701, 1449, 1355, 1299, 1267, 1226, 1174, 1149, 1126, 1091, 1054, 1022, 982, 957, 895, 885, 861, 832, 809, 764, 735, 660, 609, 591, 481.

*Synthesis of 3β-benzoyloxy-16α-methoxy-pregn-5-ene-20-one (**3**)*

200 mg (0.578 mmol) of 3β-hydroxy-16α-methoxy-pregn-5-ene-20-one (**2**) was dissolved in 10 mL of chloroform and then benzoic acid (70.4 mg, 0.577 mmol), DCC (118.9 mg, 0.577 mmol) and DMAP (70.4 mg, 0.576 mmol) were added. The reaction mixture was stirred at room temperature. The completion of reaction was monitored with the help of thin layer chromatography (TLC). Reaction mixture was washed with 5% HCl and water, dried over anhydrous sodium sulphate and filtered. The organic layer was concentrated under reduced pressure and purified by column chromatography using ethyl acetate: hexane (2:98) yielding 245 mg (90.6%) of 3β-benzoyloxy-16α-methoxy-pregn-5-ene-20-one (**3**) as solid. m.p = 414 K, Molecular formula: $C_{29}H_{38}O_4$, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.05–8.02 (2H, m, H-22 & H-26), 7.57–7.52 (1H, m, H-24), 7.46–7.41 (2H, m, H-23 & H-25), 5.43