(22E,24S)-24-Propylcholest-5en-3α-acetate: A New Steroid from the Stembark Aglaia angustifolia (Miq.) (Meliaceae)

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Submission date: 24-Feb-2020 10:19AM (UTC+0700)
Submission ID: 1262736224
File name: molbank-2020-M1112.pdf (363.25K)
Word count: 3526
Character count: 16526

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Short Note

(22*E*,24*S*)-24-Propylcholest-5en-3α-acetate: A New Steroid from the Stembark *Aglaia angustifolia* (Miq.) (Meliaceae)

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Received: 18 December 2019; Accepted: 22 January 2020; Published: 28 January 2020

Abstract: A new propylcholesterol-type steroid, namely (22*E*,24*S*)-24-propylcholest-5en-3α-acetate (**1**) has been isolated from the stembark of *Aglaia angustifolia* (Miq.). The structure of **1** was determined on the basis of spectroscopic data including 1D- and 2D-NMR as well as high resolution mass spectroscopy analysis. Compound **1** showed weak activity against the MCF-7 breast cancer cell line.

Keywords: *Aglaia angustifolia*; Meliaceae; MCF-7; propylcholesterol

1. Introduction

The genus *Aglaia* is the largest genus in subtropical and tropical angiosperm plants belonging to the Meliaceae family, which consists of more than 130 species and is widely distributed in the Southern mainland of China, the Indo-Malaysian region, and the Pacific Islands [1,2]. Some parts of the stem of the *Aglaia* plant have been used in traditional medicine for the treatment of skin diseases, fever, and wounds [3,4]. During the course of our continuous investigation for biologically active compounds from Indonesian *Aglaia* plants, we already isolated several bioactive compounds from *A. smithii* [5], *A. eximia* [6–8], *A. argentea* [9,10], and *A. elliptica* [11,12]. In further investigation on *Aglaia* plants that grow in Indonesia, we found that *A. angustifolia* has not been studied phytochemically previously. In this paper, we report the isolation and structural elucidation of a new propylcholesterol-type steroid, (22*E*,24*S*)-24-propylcholest-5en-3α-acetate (**1**) (Figure 1), along with its cytotoxic activity against MCF-7 breast cancer lines.

2. Results

Extraction and Isolation

The dried stembark of *A. angustifolia* (1.97 kg) was extracted successively with *n*-hexane (3 × 4 L), ethyl acetate (3 × 4 L), and methanol (3 × 4 L) at rt to give a crude *n*-hexane extract (19.5 g), ethyl acetate (20.4 g), and methanol (35 g) after removal of the solvent. The *n*-hexane extract (19.0 g) was separated by vacuum liquid chromatography on Merck GF_{254} silica gel using a 10% gradient of *n*-hexane-ethyl acetate-methanol solvent to give eight fractions (A–G). Fraction B (1.3 g) was subjected to column chromatography on silica gel using *n*-hexane:ethyl acetate (90:2) as a solvent to give ten subfractions (B1–B10). Subfraction B5 (44.2 mg) was further separated by column chromatography on silica gel using *n*-hexane:dichloromethane:ethyl acetate (90:9:1) to give **1** (5.6 mg).

(22E,24S)-24-propylcholest-5en-3α-acetate (**1**), white amorphous powder, $[\alpha]^{D}_{29.4}$ −0.56° (*c*, 0.26, $CHCl_3$), IR (KBr) ν_{max}: 2928, 2852, 1731, 1463, 1374, 1262, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ_H (ppm): 5.37 (1H, d, *J* = 6.0 Hz, H-6), 4.60 (1H, m, H-3), 2.34 (1H, m, H-4b), 2.13 (1H, m, H-4a), 2.03 (3H, s, Me-32), 2.01 (1H, m, H-12b), 1.97 (1H, m, H-7b), 1.87 (1H, m, H-2b), 1.86 (1H, m, H-1b), 1.84 (1H, m, H-16b), 1.67 (1H, m, H-25), 1.61 (1H, m, H-23b), 1.60 (1H, m, H-11b; H-15b), 1.59 (1H, m, H-2a), 1.57 (1H, m, H-28b), 1.54 (1H, m, H-7a), 1.46 (1H, m, H-11a),1.45 (1H, m, H-8), 1.36 (1H, m, H-20), 1.32 (1H, m, H-22a:H-29b), 1.26 (1H, m, H-28a), 1.25 (1H, m, H-29a), 1.19 (1H, m, H-16a), 1.17 (1H, m, H-12a;H-23a), 1.13 (1H, m, H-1a), 1.12 (1H, m, H-17), 1.08 (1H, m, H-15a), 1.03 (3H, s, Me-19), 1.01 (1H, m, H-22b), 1.00 (1H, m, H-14), 0.95 (1H, m, H-9), 0.93 (1H, m, H-24), 0.91 (3H, d, *J* = 6.2 Hz, Me-27), 0.91 (3H, d, *J* = 6.0 Hz, Me-21), 0.84 (3H, t, *J* = 6.8 Hz, Me-30), 0.81 (3H, d, *J* = 6.2 Hz, Me-26), 0.68 (3H, s, Me-18); ^{13}C NMR and DEPT-135 ($CDCl_3$, 150 MHz), δ_C (ppm): 170.9 (s, C-31), 139.8 (s, C-5), 122.8 (d, C-6), 74.2 (d, C-3), 56.9 (t, C-14), 56.3 (d, C-17), 50.2 (d, C-9), 46.0 (d, C-24), 42.5 (s, C-13), 39.9 (t, C-12), 38.3 (t, C-4), 37.2 (t, C-1), 36.8 (s, C-10), 36.3 (d, C-20), 34.1 (t, C-22), 32.1 (t, C-7), 32.0 (d, C-8), 29.9 (t, C-28), 29.3 (d, C-25), 28.4 (t, C-16), 28.0 (t, C-2), 26.2 (t, C-23), 24.4 (t, C-15), 23.3 (t, C-28), 21.2 (t, C-11), 21.6 (q, C-32), 20.8 (q, C-27), 19.5 (q, C-19), 19.2 (q, C-26), 19.0 (q, C-21), 12.2 (q, C-30), 12.0 (q, C-18); HR-TOFMS *m/z* 493.4088 $[M + Na]^+$ (calcd. for $C_{32}H_{54}O_2Na$, *m/z* 493.4022).

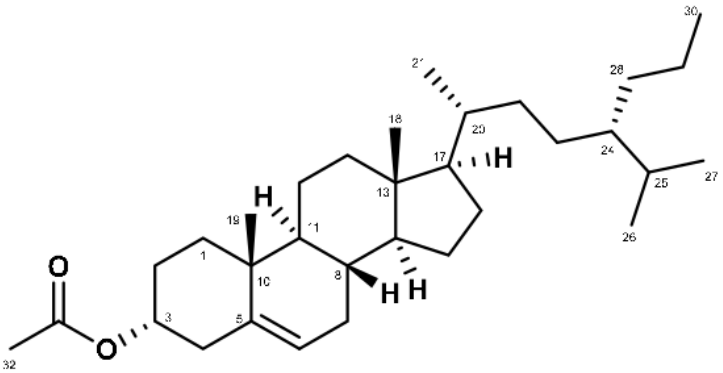

Figure 1. Chemical Structure of Compound **1.**

3. Discussion

Compound **1** was isolated as a white amorphous powder with $[\alpha]^{D}_{29.4}$ −0.56° (*c*, 0.26, $CDCl_3$). Its molecular composition was established to be $C_{32}H_{54}O_2$ from HRTOFMS *m/z* 493.4088 $[M + Na]^+$, calculated for $C_{32}H_{54}O_2Na$ (*m/z* 493.4022) and NMR spectral data. The Index of Hydrogen Deficiency (HD) was obtained from equation, HD = ΣC − ΣH/2 + 1, so the HD index of compound **1** was six. The IR spectrum displayed bands that were ascribed to C–H stretching of aliphatic (2928 and 2852 cm^{-1}), C–H stretching of olefinic (3117 cm^{-1}), carbonyl ester (1731 cm^{-1}), and ether group (1262 and 1039 cm^{-1}).

The ^{13}C NMR spectrum showed 32 carbon resonances, which were classified by their chemical shifts, DEPT, and HMQC spectra as 7 methyl groups (2 tertiary, 3 secondary, 1 primary, and 1 acetyl), 12 methylene carbons, 9 methane carbons (1 oxygenated and 1 olefinic carbons), and 4 quaternary carbons (1 olefinic and 1 oxygenated carbons). These functionalities accounted for 2 out of the total 6 hydrogen deficiency indexes. The remaining four hydrogen deficiency indexes were consistent with the tetracyclic steroidal structure [13] with acetyl and olefinic as additional groups. The significant difference side chain structure of **1** with other sterol type steroids was the *n*-propyl side chain of **1** at C-24 instead of the ethyl group of other sterols like stigmasterol [10,11,13]. It was indicated by ^{13}C NMR spectrum of **1**, an additional chemical shift (29.9 ppm) at C-28 with δ_H (1.26 (1H, m, H-28a) and 1.57 (1H, m, H-28b)) and showed as CH_2 with DEPT spectra of **1**.

The ^1H NMR spectrum of **1** displayed the presence of two tertiary methyls at δ_H 0.68 (3H, *s*, Me-18) and 1.03 (3H, *s*, Me-19). Three secondary methyls of **1** were seen at δ_H 0.91 (3H, d, J = 6.0 Hz, Me-21), 0.81 (3H, d, J = 6.2 Hz, Me-26), and 0.91 (3H, d, J = 6.2 Hz, Me-27). One primary methyl of **1** was seen at δ_H 0.84 (3H, t, J = 6.8 Hz, Me-30); this ^1H NMR spectrum of primary methyl Me-30 corresponded to the C-30 methyl group of the n-propyl group side chain structure of compound **1** at C-24 [14]. The acetyl, olefinic, and oxygenated methine signals were also observed in ^1H-NMR at δ_H 2.03 (3H, s, Me-32), 5.37 (1H, d, J = 6.0 Hz, H-6), and 4.60 (1H, m, H-3), respectively.

A comparison of the NMR data of **1** with 24ε-*n*-propylcholesterol compounds, isolated from a cultured marine chrysophyte [14], and with (24*R*)-24-propylidenecholesterol isolated from *Aureoumbra lagunensis*, the Texas brown tide alga [15], and with a stereospecific synthesis 24-propylcholesterol isolated from the Texas brown tide [16], indicated that the structure of **1** is very similar to the synthetic compound (22*E*,24*S*)-24-propylcholest-5-en-3β-ol. The main difference was the absence of a hydroxyl group and the presence of an acetyl group, which suggested that **1** was an acetyl derivative of (22*E*,24*S*)-24-propylcholest-5-en-3β-ol. The ^1H-^1H COSY spectrum of **1** (Figure 2, see the Supplementary Materials), showed correlations in H_1-H_2-H_3-H_4, H_6-H_7-H_8-H_9-H_{11}-H_{12}-, H_{14}-H_{15}-H_{16}-H_{17}-H_{20}-H_{22}-H_{23}-H_{24}-H_{25}-H_{26}, and H_{24}-H_{28}-H_{29}-H_{30}, supporting the presence of propylcholesterol structure with acetoxyl group in **1**. The HMBC correlations from the tertiary, secondary, and primary methyl protons to their neighboring carbons enabled the assignment of the two tertiary methyls at C-10 and C-13, secondary methyls at C-20 and C-25 (2×), as well as a primary methyl at C-29, respectively. Furthermore, the olefinic proton at δ_H 5.37 (1H, d, J = 6.0 Hz, H-6) was correlated to olefinic carbon at δ_C 139.8 at methylene carbon at δ_C 32.1, indicating an olefinic moiety was located at C-5 and C-6 ($\Delta^{5,6}$), similar to stigmast-5en-3α-acetate [10,11].

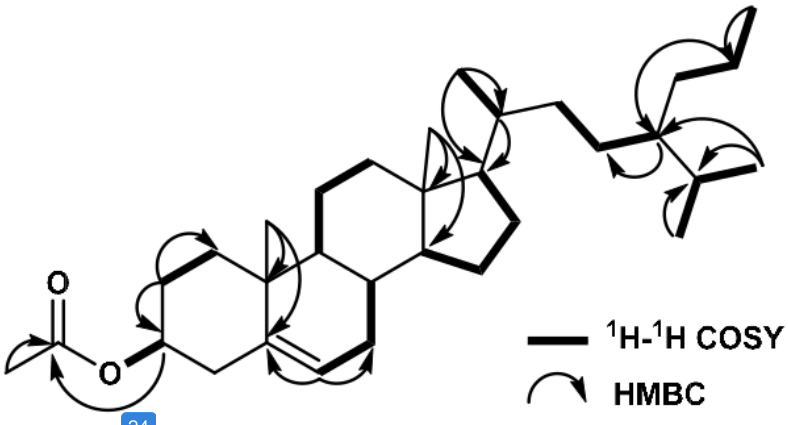

Figure 2. Selected ^1H-^1H COSY and HMBC correlations for **1**.

Correlations from oxygenated methine proton at δ_H 4.60 (H-3) and methyl acetyl at δ_H 2.03 (Me-32) to carbonyl ester at δ_C 170.9 (C-31) were used to assign an acetyl group that was located on C-3.

The relative configuration of compound **1** was identified by a ^{1}H-^{1}H NOESY experiment (Figure 3), which showed the NOESY correlations between Me-19 and H-8 as well as H-1 and H-3, which indicated that the acetyl group at C-3 was α-oriented. Similar to the observations from 1H-1H NOESY, the cross peak between Me-18 and H-20, and H-20 and H-24 indicated that H-20 and H-24 were β-oriented. This result was supported also by comparing it to those of stigmast-5en-3α-acetate [10,11], and the specific optical rotation of **1** (−0.26° (*c*, 0.26, $CDCl_3$) was the same negative sign to that of the previously reported (22*E*,24*S*)-24-propylcholest-5en-3β-ol ($[\alpha]_D^{21}$ = −29.5°(*c* 0,40, CH_2Cl_2) [16]. Therefore, compound **1** was elucidated to be a new derivative propylcholesterol-type steroid and was named (22*E*,24*S*)-24-propylcholest-5en-3α-acetate.

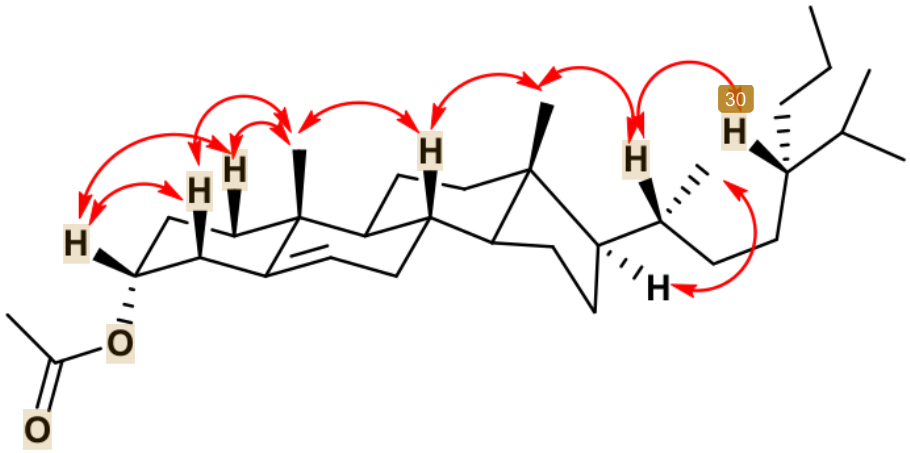

Figure 3. Selected NOESY correlations for **1**.

The compound (22*E*,24*S*)-24-propylcholest-5en-3α-acetate (**1**), was evaluated for its cytotoxicity against the MCF-7 breast cancer cell line according to a method described previously [17], and cisplatin (IC_{50} 38.06 µg/mL) was used as a positive control [18,19]. Compound **1** showed weak activity against MCF-7 with an IC_{50} value of 60.4 µM. This result is in line with previously investigations where a steroid derivative showed weak activity against the breast cancer line [10,11].

4. Materials and Methods

4.1. General Experimental Procedures

The optical rotation was obtained with an Autopol IV automatic polarimeter. Mass spectra were measured with a Waters Xevo QTOFMS (Waters, Milford, MA, USA). NMR data were recorded on a Bruker Avance-600 spectrometer at 600 MHz for ^{1}H and 150 MHz for ^{13}C using TMS as an internal standard (Billerica, MA, USA). Chromatographic separations were carried out on silica gel (60, 70–230, and 200–400 mesh) (Merck, Darmstadt, Germany). TLC plates were precoated with silica gel GF_{254} (Merck, Darmstadt, Germany, 0.25 mm), and detection was achieved by spraying with 10% H_2SO_4 in ethanol, followed by heating.

4.2. Plant Material

The stem bark of *A. angustifolia* (Miq.) was collected from Bogor Botanical Garden, Bogor, Indonesia in February 2017. The plant was identified by Mr. Ismail, the staff of the Bogoriense Herbarium, Indonesian Science Institute, Bogor, Indonesia. A voucher specimen (II.K.57a) was deposited at the herbarium.

4.3. Cytotoxic Bioassay

The cytotoxicity of the compounds against MCF-7 human breast cancer cells was measured using the PrestoBlue cell viability assay. The cells were maintained in a Roswell Park Memorial Institute (RPMI) medium supplemented with 10% (v/v) Fetal Bovine Serum (FBS) and 1 µL/mL antibiotics. Cultures were incubated at 37 °C in a humidified atmosphere of 5% CO_2. Tumor cells were seeded in 96-well microliter plates at 1.7×10^4 cells per well. After 24 h, compounds were added to the wells. After 96 h, cell viability was determined by measuring the metabolic conversion of resazurin substrate into pink fluorescent resorufin product resulting from reduction in viable cells. The PrestoBlue assay results were read using a multimode reader at 570 nm. All compounds were tested at eight concentration (7.81; 15.63; 31.25; 62.50; 125.00; 250.00; 500.00; 1000.00 µg/mL) in 100% DMSO with a final concentration of DMSO of 2.7% in each well. Each concentration of the compounds was tested in two parallels experiments. IC_{50} values were calculated by the linear regression method using Microsoft Excel software.

5. Conclusions

A new propyl cholesterol type-steroid, namely (22*E*,24*S*)-24-propylcholest-5en-3α-acetate (**1**), was isolated from the stembark of *A. angustifolia* (Miq.) belonging to the Meliaceae family. This propyl cholesterol type-steroid was found in the *Aglaia* genus for the first time.

Supplementary Materials: The following are available online, Figure 1.1a,b. ^{1}H-NMR Spectrum of **1** (600 MHz in $CDCl_3$), Figure 1.2. ^{13}C-NMR Spectrum of **1** (150 MHz in $CDCl_3$), Figure 1.3a,b. DEPT-135° Spectrum of **1** (in $CDCl_3$), Figure 1.4. HSQC Spectrum of **1**, Figure 1.5. HMBC Spectrum of **1**, Figure 1.6. ^{1}H-^{1}H COSY Spectrum of **1**, Figure 1.7. NOESY of Spectrum of **1** (600 MHz in $CDCl_3$), Figure 1.8. HR-TOF-MS Spectrum of **1**, Figure 1.9. TLC Profile of **1**.

Author Contributions: Conceptualization, U.S., K.A.; Data curation, D.G.K.; Formal analysis, Y.S.; Investigation, R.P.H., N.; Methodology, R.M., D.H., A.T.H.; Supervision, U.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Directorate General of Scientific Resources, Technology, and Higher Education, Ministry of Research, Technology, and Higher Education, Indonesia (Doctoral Grant, number, PRJ-5513/LPDP.3/2016, by R.P.H).

Acknowledgments: We thank also to Mr. Kansi Haikal at the Central Laboratory, Universitas Padjadjaran for QTOFMS Measurements.

Conflicts of Interest: The authors declare no conflict of interest.

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Judul karya ilmiah (artikel) : (22E, 24S)-24-Propylcholest-5en-3α-acetate: A New Steroid from the Stembark of *Aglaia angustifoli* (Miq.) (Meliaceae)

Jumlah Penulis : 9 orang

Status Pengusul : Penulis ke enam

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