Short Note

Trans-11-(3,4-Dimethoxyphenyl)-2,3,8,9-tetramethoxy-6-oxo-11,12-dihydro-6H-dibenzo[c,h]chromene-12-carboxylic Acid

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Trans-11-(3,4-Dimethoxyphenyl)-2,3,8,9-tetramethoxy-6-oxo-11,12-dihydro-6*H*-dibenzo[*c,h*]chromene-12-carboxylic acid

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Abstract: The title compound, *trans*-11-(3,4-dimethoxyphenyl)-2,3,8,9-tetramethoxy-6-oxo-11,12-dihydro-6H-dibenzo[*c,h*]chromene-12-carboxylic acid (4), was synthesized for the first time via a two-step protocol from 3,4-dimethoxyhomophthalic anhydride (1) and 3,4-dimethoxybenzaldehyde (DMBA). In the first step, 1 reacts with DMBA to give *trans*-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-oxo-3,4-dihydro-1*H*-2-benzopyran-4-carboxylic acid (2), which further reacts with additional two equivalents of 1 to give 4. Compound 4 was characterized by means of spectral methods - ^{1}H-, ^{13}C-, DEPT-135-NMR, and HRMS.

Keywords: 6*H*-dibenzo[*c,h*]chromenes; domino reaction; anhydride; methoxy groups

1. Introduction

Homophthalic anhydride (HA) possesses both nucleophilic and electrophilic properties, allowing it to react specifically with various reagents [1-3]. Previous research on tandem reactions utilizing HA as a building block has shown that most proceed through detectable and stable intermediates [4,5]; consequently, exploring their reactivity allows for studying the scope and limitations of these domino reactions and the synthesis of novel complex compounds in a controlled manner. A previous article showed that a domino reaction between unsubstituted HA with aromatic aldehydes results in tetracyclic, steroid-like compounds containing dibenzo[*c,h*]chromene moiety [6]. Such compounds have been shown to possess important bactericidal properties [7, 8-10] and potential antiestrogen activity [11].

The methoxy group is frequently presented as a fragment in various natural products, and medicinal chemists have increasingly incorporated this functional group into synthetic pharmaceuticals, acknowledging its benefits concerning ligand-target binding, physicochemical characteristics, and essential ADME (Absorption, Distribution, Metabolism, and Excretion) properties [12]. Attempting to find novel compounds with antiestrogenic activity, herein we present for the first time the synthesis of highly methoxy-substituted *trans*-11-(3,4-dimethoxyphenyl)-2,3,8,9-tetramethoxy-6-oxo-11,12-dihydro-6*H*-dibenzo[*c,h*]chromene-12-carboxylic acid (4).

2. Results and Discussion

The synthesis of 4 was accomplished via a two-step synthetic procedure, as depicted in Schemes 1 and 2. In the first step (Scheme 1), we obtained *trans*-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-oxo-3,4-dihydro-1H-2-benzopyran-4-carboxylic acid (2) by reacting 6,7-dimethoxyhomophtalic anhydride (**1**) with 3,4-dimethoxybenzaldehyde in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) [13]. This step proceeds smoothly, giving a diastereomeric mixture of *cis*- and *trans*-**2** in a ratio of 1:4 in favor of *trans*-2.

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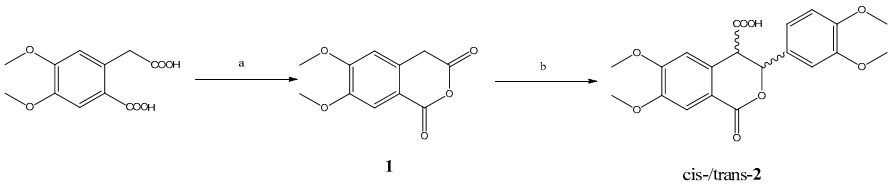
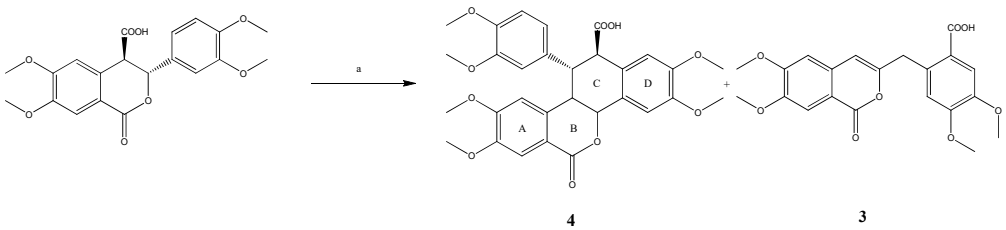


Scheme 1. Preparation of *cis*-/*trans*-**2.** a) AcCl, reflux, 2.5h; b) 3,4-dimethoxybenzaldehyde (DMBA), DMAP, $CHCl_3$, r.t., 10 min [6,13];.



Scheme 2. Synthesis of **4** and dimeric compound **3**. a) 2 eq. **1,** Pyridine, 100° C.

After separating from its *cis* isomer, we reacted *trans*-**2** with two additional equiv. of **1** (Scheme 2). The initial investigation of this reaction showed that **1** reacts preferably with itself, giving the dimeric compound **3** [1, 14]. However, the portion-wise addition of **1** (0.33 equiv. every 20 min) minimizes, to some extent, the self-dimerization reaction, thus allowing the formation of the target compound **4**. Notably, the somewhat harsh reaction conditions (100 °C, pyridine) lead to partial demethylation, resulting in a 3-8% compound loss. This phenomenon can be partially elucidated through existing literature [15]. As a result, the yield of compound **4** is additionally reduced; however, it was successfully isolated in pure crystalline form following column chromatography, and its structure was unequivocally confirmed using various NMR techniques (^{1}H-, ^{13}C-, DEPT-135), and mass spectrometry (HRMS), available as Supplementary materials. The *trans* configuration of compound **4** was validated by the singlet signals for the methyne protons (ring **C**) observed in the 1H-NMR spectrum. According to the Karplus equation [16], this observation suggests a torsion angle between the protons of approximately 80-90°, indicating an antiperiplanar (diaxial) conformation for the bulky substituents (aryl and carboxylate groups). This finding aligns with previously reported data [6].

To summarize, a steroid-like compound with a high degree of methoxy substitution—suggesting improved biological activity—was synthesized from readily available and inexpensive starting materials through a two-step protocol that involved two domino reactions. This research demonstrates the usefulness of homophthalic anhydride in constructing complex molecules with potential medicinal applications, particularly due to the advantageous methoxy group. Further studies on the biological activity of compound 4, especially its potential as an antiestrogen, are currently underway.

3. Materials and Methods

General: All NMR spectra were recorded in DMSO-d6 on a Bruker Avance III HD 500 operating at 500.13 MHz for 1H and 125.76 MHz for 13C. Chemical shifts are reported in ppm. Reactions were monitored by thin-layer chromatography (TLC) on silica gel aluminum sheets ALUGRAM SIL G/UV254 using an Ethyl Acetate/Petroleum Ether (3:2 v/v) eluent. Column chromatography was carried out with a 1:1 Ethyl Acetate/n-heptane mobile phase on silica gel (0.04 – 0.063 Kieselgel 60) as a stationary phase. High-Resolution Mass Spectra (HRMS) were obtained on a Shimadzu LCMS-9050. All chemicals used in this study were purchased from Sigma-Aldrich (FOT, Sofia, Bulgaria). The organic solvents were of analytical grade. 6,7-Dimethoxy-4H-isochromene-1,3-dione (1) and *trans*-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-oxoisochroman-4-carboxylic acid (*trans*-2) were obtained as shown on Scheme 1.

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3.1. trans-11-(3,4-dimethoxyphenyl)-2,3,8,9-tetramethoxy-6-oxo-11,12-dihydro-6H-dibenzo[c,h]chromene-12-carboxylic acid (4):

0.640 g (1.648 mmol) of *trans*-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-oxoisochroman-4-carboxylic acid (*trans*-**2**) were dissolved in 10 mL of pyridine and the reaction mixture was heated up to 100° C. 0.732 g (3.296 mmol) of 6,7-dimethoxy-4H-isochromene-1,3-dione (**1**) were then added portion-wise within 2 h (0.33 equiv. per 20 min) and the reaction mixture was left overnight. After cooling, the mixture was diluted with ethyl acetate and washed consecutively with 10% HCl, water, and 5% $NaHCO_3$. The bicarbonate layer was then acidified (10% HCl) and extracted with ethyl acetate. The organic layer was washed with water to pH ~7, dried over Na_2SO_4, and then subjected to column chromatography to yield 110 mg (14%) of *trans*-**4**. White solid, ^{1}H-NMR (500.13 MHz, DMSO) δ 3.61-3.62 (3H, s, OMe), 3.66-3.67 (3H, s, OMe), 3.75 (3H, s, OMe), 3.83-3.84 (3H, s, OMe), 3.87-3.88 (3H, s, OMe), 3.89-3.90 (3H, s, OMe), 3.92 (1H, s, 12-H), 4.97 (1H, s, 11-H), 6.47-6.50(1H, dd, ArH), 6.97 (1H, s, ArH) , 7.05 (1H, s, ArH), 7.07-7.08(1H, d, ArH), 7.31 (1H, s, ArH), 7,57 (1H, s, ArH), 12.52-12.71 (1H, s, COOH); ^{13}C-NMR: δ 173.7, 161.04, 155.6, 150.05, 149.55, 149.15, 148.85, 148.23, 147.21, 133.55, 132.8, 125.55, 121.03, 119.25, 114.60, 113.40, 112.21, 112.05, 110.17, 110.10, 105.45, 104.63, 56.54, 56.33, 56.11, 56.09, 55.89, 55.74, 51.26 m.p.: 135-137 °C; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{30}H_{29}O_{10}^+$: 549.1760, found ; [M+H]+ 549.17722.

Supplementary Materials: Figure S1 1H-NMR: Spectrum of Compound **4** in DMSO-d6, Figure S1a: 1H-NMR Spectrum of Compound **4** in DMSO-d6; Figure S2 13C-NMR Spectrum of Compound **4** in DMSO-d6; Figure S3 DEPT-135-NMR Spectrum of Compound 4 in DMSO-d6; Figure S4 HRMS ESI Spectrum of Compound **4**;.

Author Contributions: Conceptualization, M.B. and V.A.; methodology, M.B.; validation, V.A. and S.S.; investigation, V.A.; data curation, S.S.; writing—original draft preparation, V.A.; writing—review and editing, V.A., S.S. and M.B.; visualization, V.A.; supervision, S.S.; resources, M.B.; funding acquisition, M.B. All authors have read and agreed to the published version of the manuscript.

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

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