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Proceeding Paper

Triterpenoid *bis*-Amide Analogs via Ugi Reaction [†]

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Abstract

Isocyanide-based multicomponent reactions such as Ugi four-component reaction, are among the most relevant synthetic tools in modern organic chemistry. They have been successfully applied in natural product science for the synthesis of natural product analogs, for example carbohydrates and steroids. However, the synthesis of analogs of other important groups like triterpenoids remain almost unstudied. In the present work, we report the synthesis of four bis-amides via Ugi reaction starting from masticadienonic acid, a triterpenoid isolated from *Pistacia mexicana*.

Keywords: isocyanide-based multicomponent reaction; Ugi reaction; bis-amide; natural products; triterpenoid

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1. Introduction

Since the discovery of the Ugi four-component reaction (Ugi-4CR) by Ivar Ugi in 1959, isocyanide-based multicomponent reactions (IMCRs) have gained recognition as one of the bests synthetic tools in modern organic chemistry [1].

IMCRs are domino processes in which three or more starting materials react through a sequence of reactions, leading to a complex product which contains all or most of the atoms of starting materials [2]. They are well acknowledged as the closest tools to the ideal synthesis, due to their numerous advantages in comparison to conventional multi-step syntheses, including a high atom economy, modularity, convergence, minimizing chemical waste, operational simplicity, high overall yields, bond-formation efficiency, improved reaction times, decreased costs, and less purification steps [3].

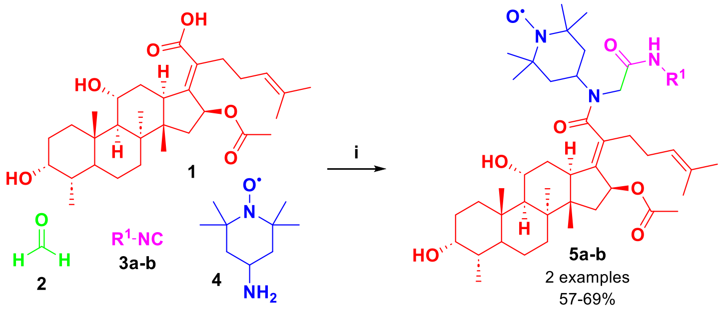
Ugi-4CR is nowadays the most studied IMCR due to its versatility, efficiency, and broad scope. In this reaction, an isocyanide, a primary amine, a carboxylic acid and a carbonyl compound react together, providing easy and efficient access to a complex peptide-like structure known as *bis*-amide, a peptidomimetic scaffold which is relevant for medicinal chemistry and organic synthesis [4]. Notably, this reaction has been mainly applied in combinatorial chemistry due to the possibility of varying the four components, leading to extensive libraries of compounds [5].

In recent years, due to Ugi-4CR versatility, it has been applied for the synthesis of complex natural product analogs with potential biological applications, mainly steroids [6]. Notably, the synthesis of triterpenoid analogs is almost unreported.

Triterpenoids are an important class of natural products, mainly isolated from higher plants [7]. These compounds are relevant because several studies have highlighted their potential applications such as antiviral, antibacterial, anti-inflammatory, and even more important, as antineoplastic [8]. The last property is the most studied, since the results are promising toward the development of cancer treatment alternatives.

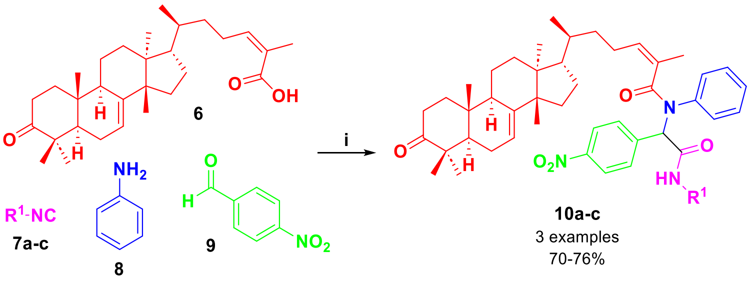
Two reports on the synthesis of triterpenoids analogs have been published, taking advantage of the natural carboxylic acid function naturally present in these compounds. The obtained results showed good cytotoxic properties when triterpenoid analogs were evaluated in vitro against various cancer cell lines [9,10].

(a) Previous work by Sultani et al.



R^1 = *tert*-butyl, 2,4,4-trimethoxybutyl; (i) MeOH, rt, 20 h.

(b) This work



R^1 = *tert*-butyl, 4-methoxyphenyl, benzyl; (i) EtOH, rt, 24 h.

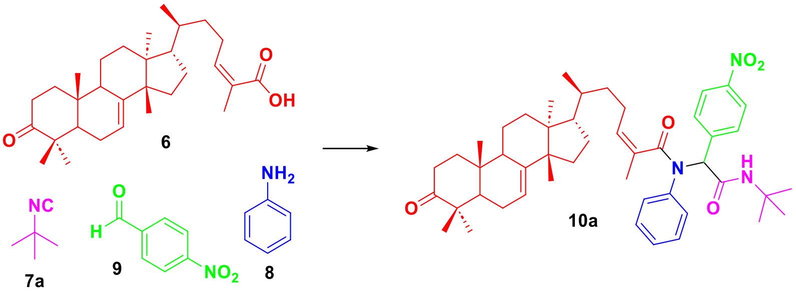
Due to the limited reports, in the present work, a small series of triterpenoid bis-amide analogs were synthesized from masticadienonic acid, a triterpenoid isolated from *Pistacia mexicana*, a plant species endemic to the Americas.

2. Results and Discussion

Herein, masticadienonic acid (**6**) was employed as carboxylic acid component in the Ugi-4CR for synthesizing *bis*-amide analogs (**10a–c**) at millimole scale. This natural product was isolated from peduncles of *Pistacia mexicana*, by solid-liquid extraction, and purified by recrystallization. For target molecule **10a**, equimolar amounts of **6**, isocyanides (**7a–c**), aniline (**8**) and 4-nitrobenzaldehyde (**9**) were placed in a capped vial along with a magnetic stirring bar. In the first experiment, methanol was employed as solvent taking into consideration previous reports of our group (Table 1, Entry 1). However, in this experiment, several side products were identified via TLC and **10a** was isolated in a 38% overall yield.

The solvent was changed to ethanol in a subsequent experiment and a better yield of 72% was afforded (Table 1, Entry 2). Also, the reaction profile was cleaner, and no side products were observed in TLC. Finally, an experiment employing water as solvent for attempting to develop a greener procedure was performed (Table 1, Entry 3), however, the reaction did not proceed. Employing the conditions from Entry 2, a small series of *bis*-amides were synthesized in good overall yields.

Table 1. Screening conditions for the synthesis of target molecule **16a**.



Entry	Solvent	Time	Yield
1	MeOH	24 h	38%
2	EtOH	24 h	72%
3	H_2O	48 h	NR
4	H_2O (80 °C)	12 h	traces
5	Solvent free	24 h	NR

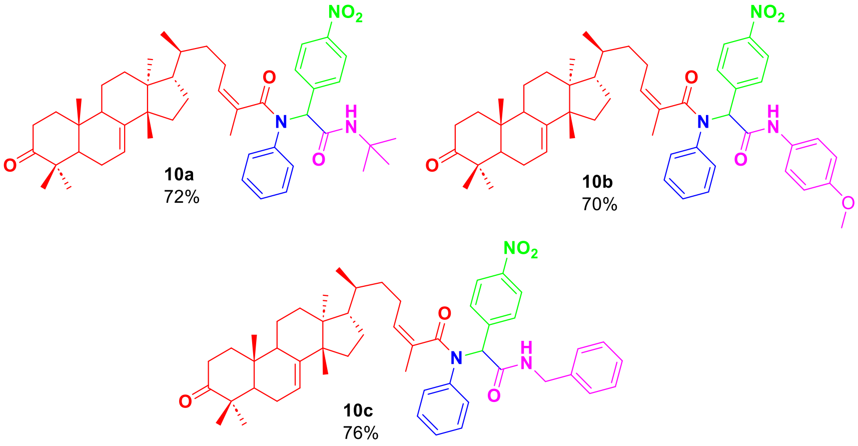


Figure 1. Synthesized *bis*-amides.

3. Experimental Section

3.1. General Information, Instrumentation and Chemicals

General Information, Chemicals and Instrumentation

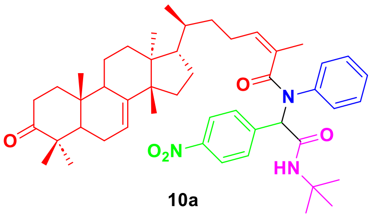
Bruker Avance III spectrometers (500 and 125 MHz, respectively) were used for ^{1}H and ^{13}C NMR spectra acquisition. Deuterated chloroform (CDCl3) was used as the solvent for NMR experiments. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS). Coupling constants are reported in Hertz (Hz). Multiplicities of the signals are described using standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using MestReNova software version 12.0.0-20080. Reaction progress was monitored by thin-layer chromatography (TLC) on precoated silica gel F254 aluminum sheets. The spots were visualized under UV light at 254 nm. Column chromatography was performed using silica gel (230–400 mesh) as stationary phase. Mixtures of hexanes and ethyl acetate were used as mobile phase for column chromatography and in TLC for reaction progress monitoring and measuring retention factors (R_f). All reagents were purchased from Sigma Aldrich and were used without further purification. Chemical names and drawings were obtained using the ChemDraw 22.2.0.3300 software package.

3.2. General Procedure

Masticadienonic acid (1.0 equiv.), 4-nitrobenzaldehyde (1.0 equiv.), aniline (1.0 equiv.) and the isocyanides (1.0 equiv.) were dissolved in ethanol (0.5 M) and placed in a capped vial with a magnetic stir bar. The mixture was stirred at room temperature for 24 h. Then, solvent was removed under reduced pressure, and the crude reaction mixture was purified by column chromatography, using silica gel as stationary phase and mixtures of ethyl acetate in hexanes, to afford the corresponding bis-amides **10a–c**.

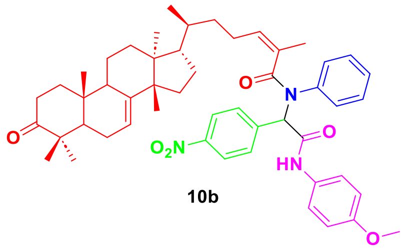
3.3. Spectral Data

(6S,Z)-N-(2-(tert-butylamino)-1-(4-nitrophenyl)-2-oxoethyl)-2-methyl-6-((10R,13S,14S,17S)-4,4,10,13,14-pentamethyl-3-oxo-2,3,4,5,6,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-N-phenylhept-2-enamide (***10a***): yellow viscous liquid, R_f = 0.35 (20% ethyl acetate in hexanes): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 6.09 (dt, *J* = 7.6, 1.6 Hz, H24), 5.31 (dd, *J* = 6.1, 3.4 Hz, H7), 2.75 (td, *J* = 14.5, 5.4 Hz, H2), 2.57 (m, H23), 2.45 (m, H23′), 2.29 (dt, *J* = 14.1, 3.8, H9), 2.25 (m, H2′), 2.10 (m, H6), 1.99 (m, H1), 1.99 (m, H16′), 1.92 (d, *J* = 1.4 Hz, H27), 1.82 (m, H12), 1.73 (t, *J* = 8.7 Hz, H5), 1.66 (m, H12′), 1.55 (m, H11), 1.55 (m, H22), 1.50 (m, H17), 1.50 (m, H15), 1.47 (m, H1′), 1.42 (m, H20), 1.28 (m, H16′), 1.16 (m, H22′), 1.12 (s, H29), 1.05 (s, H28), 1.01 (s, H19), 1.00 (s, H30), 0.89 (d, *J* = 6.2 Hz, H21), 0.81 (s, H18). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ 216.9 (C3), 172.6 (C26), 168.0 (C32), 145.9 (C8), 142.5 (C35), 132.4 (C24), 130.8 (C25), 129.1 (C37), 127.7 (C38), 126.5 (C36), 117.8 (C7), 55.2 (C31), 53.1 (C17), 52.3 (C5), 51.2 (C33), 51.2 (C14), 48.5 (C9), 47.9 (C4), 43.5 (C13), 38.5 (C1), 36.0 (C20), 35.1 (C22), 35.0 (C10), 34.9 (C2), 34.0 (C15), 33.6 (C12), 28.7 (C34-C34‴), 28.2 (C16), 27.4 (C30), 27.2 (C23), 24.6 (C28), 24.4 (C6), 22.0 (C18), 21.6 (C29), 20.8 (C27), 18.3 (C11), 18.2 (C21), 12.8 (C19).



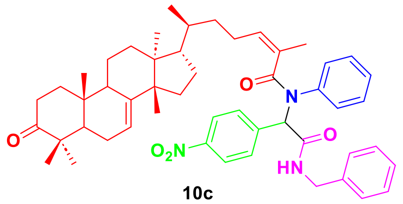
10a

(6S,Z)-N-(2-((4-methoxyphenyl)amino)-1-(4-nitrophenyl)-2-oxoethyl)-2-methyl-6-((10R,13S,14S,17S)-4,4,10,13,14-pentamethyl-3-oxo-2,3,4,5,6,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-N-phenylhept-2-enamide (***10b***): yellow viscous liquid, R_f = 0.24 (30% ethyl acetate in hexanes): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 6.09 (dt, *J* = 7.6, 1.6 Hz, H24), 5.31 (dd, *J* = 6.1, 3.4 Hz, H7), 2.75 (td, *J* = 14.5, 5.4 Hz, H2), 2.57 (m, H23), 2.45 (m, H23′), 2.29 (dt, *J* = 14.1, 3.8, H9), 2.25 (m, H2′), 2.10 (m, H6), 1.99 (m, H1), 1.99 (m, H16′), 1.92 (d, *J* = 1.4 Hz, H27), 1.82 (m, H12), 1.73 (t, *J* = 8.7 Hz, H5), 1.66 (m, H12′), 1.55 (m, H11), 1.55 (m, H22), 1.50 (m, H17), 1.50 (m, H15), 1.47 (m, H1′), 1.42 (m, H20), 1.28 (m, H16′), 1.16 (m, H22′), 1.12 (s, H29), 1.05 (s, H28), 1.01 (s, H19), 1.00 (s, H30), 0.89 (d, *J* = 6.2 Hz, H21), 0.81 (s, H18). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ 217.0 (C3), 173.3 (C26), 166.8 (C32), 156.4 (C36), 145.9 (C8), 142.4 (C38), 132.8 (C24), 131.0 (C33), 130.6 (C25), 129.2 (C40), 127.9 (C41), 126.6 (C39), 121.5 (C34), 117.8 (C7), 114.1 (C35), 55.4 (C37), 55.2 (C31), 53.0 (C17), 52.3 (C5), 51.1 (C14), 48.5 (C9), 47.9 (C4), 43.5 (C13), 38.5 (C1), 36.0 (C20), 35.2 (C22), 35.0 (C10), 34.9 (C2), 34.0 (C15), 33.6 (C12), 28.2 (C16), 27.4 (C30), 27.1 (C23), 24.6 (C28), 24.4 (C6), 22.0 (C18), 21.6 (C29), 20.8 (C27), 18.3 (C11), 18.2 (C21), 12.8 (C19).



10b

*(6S,Z)-N-(2-(benzylamino)-2-oxoethyl)-2-methyl-6-((10R,13S,14S,17S)-4,4,10,13,14-pentamethyl-3-oxo-2,3,4,5,6,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-N-phenylhept-2-enamide (**10c**):* colorless crystals, m.p.: 176–178 °C, R_f = 0.35 (20% ethyl acetate in hexanes): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 7.37–7.25 (m, H35–37), 6.41 (t, *J* = 6.05 Hz, NH) 6.03 (td, *J* = 7.6, 1.6 Hz, H24), 5.31 (dd, *J* = 6.1, 3.4 Hz, H7), 4.69 (s, H31), 4.51 (d, *J* = 7.6 Hz, H33) 2.75 (td, *J* = 14.5, 5.4 Hz, H2), 2.57 (m, H23), 2.45 (m, H23′), 2.29 (dt, *J* = 14.1, 3.8, H9), 2.25 (m, H2′), 2.10 (m, H6), 1.99 (m, H1), 1.99 (m, H16′), 1.92 (d, *J* = 1.4 Hz, H27), 1.82 (m, H12), 1.73 (t, *J* = 8.7 Hz, H5), 1.66 (m, H12′), 1.55 (m, H11), 1.55 (m, H22), 1.50 (m, H17), 1.50 (m, H15), 1.47 (m, H1′), 1.42 (m, H20), 1.28 (m, H16′), 1.16 (m, H22′), 1.12 (s, H29), 1.05 (s, H28), 1.01 (s, H19), 1.00 (s, H30), 0.89 (d, *J* = 6.2 Hz, H21), 0.81 (s, H18). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ 216.9 (C3), 167.3 (C32), 166.1 (C26), 146.9 (C24), 145.9 (C8), 137.6 (C34), 128.8 (C36), 127.7 (C37), 127.6 (C35), 125.1 (C25), 117.9 (C7), 62.8 (C31), 52.9 (C17), 52.3 (C5), 51.2 (C14), 48.5 (C9), 47.9 (C4), 43.5 (C13), 43.1 (C33) 38.5 (C1), 36.0 (C20), 35.6 (C22), 35.0 (C10), 34.9 (C2), 34.0 (C15), 33.6 (C12), 28.2 (C16), 27.4 (C30), 26.9 (C23), 24.6 (C28), 24.4 (C6), 22.0 (C18), 21.6 (C29), 20.7 (C27), 18.3 (C11), 18.2 (C21), 12.8 (C19).



10c

3. Conclusions

This work is an example of the efficiency and versatility of Ugi-4CR, which allows it to be successfully applied for the synthesis of triterpenoid analogs. This procedure stands out for using mild reaction conditions, affording good overall yields, employing a green solvent, and overcoming the disadvantages of the conventional multi-step techniques for functionalizing triterpenoids, such as the use of toxic reagents, excess of solvents and harsh reaction conditions and lower yields.

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Data Availability Statement: The present work is part of ongoing research and data is available upon request to the corresponding authors due to privacy concerns.

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

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