1. Introduction

Multicomponent reactions (MCRs) are efficient synthetic strategies in modern organic chemistry, which have multiple advantages over the traditional multistep synthesis. MCRs are defined as procedures in which three or more components react together in a one-pot reaction, to form a complex product characterized by containing all or nearly all the atoms of the reactants in its structure [1,2].

Some of the most relevant characteristic of MCRs are their high degree of atomic economy, bond-formation efficiency, high overall yields in short working time and being experimentally simple to perform, often without needing anhydrous reaction media or an inert atmosphere [2]. Isocyanide-based multicomponent reactions (IMCR) are one of the most prominent groups of MCRs, raising the interest of chemists in the last decades for their usefulness in the synthesis of bioactive molecules and/or potential drug candidate libraries [3].

In 1921, the Italian chemist Mario Passerini discovered the first IMCR, named Passerini three component reaction (P-3CR), which provides easy access to α-acyloxycarboxamides from carbonyl compounds such as an aldehyde or ketone, an isocyanide and a carboxylic acid [4,5]. This reaction is a perfect tool for the synthesis of large libraries of compounds through the variation of substituents, providing a scaffold with importance for its presence in bioactive drugs and peptidomimetics [1,5].

IMCRs like Passerini and Ugi reactions play an essential role in modern combinatorial chemistry, serving as a powerful tool for the easy synthesis of diversity-oriented libraries which can exhibit promising pharmacological properties [5,6]. An important example is their use in the synthesis of libraries from bioactive biomolecules such as peptides and steroids [7].

On the other hand, only two reports related to the use of Passerini reactions employing natural products such as triterpenoids can be found in the literature (Scheme 1), using either naturally functionalized compounds or semi-synthetic ones [6,8].
Triterpenoids have been studied intensively and stand out for their important biological properties such as antibacterial, antifungal, antiviral and antioxidant activities [6,9–12]. However, in recent years, the application of these natural compounds and their derivatives, as cytotoxic agents providing alternatives to modern treatments for cancer, has attracted great interest in the field of natural products chemistry, since various reports have indicated that triterpenoids and their derived amides are highly cytotoxic [13–15].

Due to the limited reports in this field, and the importance of natural products, herein we report the synthesis of four triterpenoid-derived α-acyloxycarboxamides employing a naturally functionalized triterpenic acid, with some relevant characteristics, such as being α,β-unsaturated and not being sterically hindered.

2. Results and Discussion

In this work, we describe the synthesis of a small library of triterpenoid-derived α-acyloxycarboxamides in moderate yields, via the Passerini three-component reaction under mild green conditions.

Our work began with the isolation of masticadienonic acid (9) from the plant material of *Pistacia mexicana*. Fruits collected in Cerro de Camataran, in the community of San Martín, Michoacán, Mexico, were dried and finely ground. The material was subjected to extraction by reflux with hexanes for a period of 4 h. The solvent was removed under reduced pressure to afford the crude hexanic extract, from which a solid precipitate was recovered. This precipitate was recrystallized from acetone and characterized by its $^1$H and $^{13}$C NMR spectrums.

The optimization of the Passerini reaction was carried out selecting 9, tert-butyl isocyanide (11) and 4-nitrobenzaldehyde (10a) to achieve our target molecule 12a (Table 1).

**Scheme 1.** Derivatization of triterpenoids by isocyanide-based multicomponent reactions.

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Due to the limited reports in this field, and the importance of natural products, herein we report the synthesis of four triterpenoid-derived α-acyloxycarboxamides employing a naturally functionalized triterpenic acid, with some relevant characteristics, such as being α,β-unsaturated and not being sterically hindered.
The first attempt employed DCM as solvent in a 0.5 M concentration, since the literature reports that P-3CR is accelerated in aprotic solvents in high concentrations [16]. The reaction was also carried out using water and solvent free as greener alternatives, but these efforts were not satisfactory as no product was identified in TLC analysis. Finally, the use of methanol as solvent, under the same conditions as previous attempts, led only to traces.

Table 1. Screening conditions for synthesis of α-acyloxycarbamide 12a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>r.t.</td>
<td>24 h</td>
<td>79%</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>r.t.</td>
<td>24 h</td>
<td>n.r.</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>r.t.</td>
<td>24 h</td>
<td>Traces</td>
</tr>
<tr>
<td>4</td>
<td>Solvent free</td>
<td>r.t.</td>
<td>24 h</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

Using the optimized conditions for P-3CR, we synthesized the series of α-acyloxycarbamides 12a–d depicted in Scheme 2. Products were obtained in moderate to good yields (25–79%) as we explored the versatility of this methodology employing aldehydes of different stereo-electronic nature, such as aliphatic and aromatic, both activated and deactivated.

Scheme 2. Substrate scope.

3. Experimental Section

3.1. General Information, Instrumentation and Chemicals

1H and 13C NMR spectra were acquired using Varian Mercury Plus 400 (400 and 100 MHz, respectively). The solvent used for NMR spectroscopy was deuterated chloroform (CDCl₃). Chemical shifts (δ) are given in ppm relative to tetramethylsilane. Coupling constants are reported in Hertz (Hz). Multiplicities of the signals are reported 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 pre-coated silica gel F254 and the spots were visualized under UV light at 254 nm or using ceric ammonium sulphate stain under heating. 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 measuring retention factors.
(Rf). All reagents were purchased from Sigma Aldrich and were used without further purification. Chemical names and drawings were obtained using ChemOffice 17.0.0.206 software package.

3.2. General Procedure

Masticadienonic acid (9, 0.11 mmol, 1.0 equiv.), aldehyde 10a-d (0.11 mmol, 1 equiv.) and tert-butyl isocyanide (11) were dissolved in dichloromethane (0.22 mL, 0.5 M), and placed in a sealed vial with a magnetic stir bar. The mixture was stirred at room temperature for 24 h. Then, solvent was removed and the crude was purified by column chromatography using silica gel and a mixture of 15% ethyl acetate in hexanes, to afford the corresponding α-acyloxycarboxamides 12a–d.

3.3. Spectral Data

3.3.1. 2-(tert-butylamino)-1-(4-nitrophenyl)-2-oxoethyl 3-oxotirucalla-7,24Z-dien-26-oate (12a)

![12a](image)

White solid; Rf = 0.23 (15% ethyl acetate in hexanes): \(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C, TMS): \(\delta\) 8.23 (m, 2H), 7.63 (m, 2H), 6.18 (bs, 1H), 6.13 (td, \(J = 7.6, 1.6\) Hz, 1H), 6.09 (d, \(J = 1.8\) Hz, 1H), 5.30 (dd, \(J = 6.1, 3.2\) Hz, 1H), 2.76 (td, \(J = 14.5, 5.4\) Hz, 1H), 2.59 (m, 1H), 2.45 (m, 1H), 2.28 (dt, \(J = 14.1, 3.8\) Hz, 1H), 2.25 (m, 1H), 2.10 (m, 2H), 2.07 (d, \(J = 1.5\) Hz, 3H), 1.99 (m, 2H), 1.98 (m, 1H), 1.81 (m, 2H), 1.73 (t, \(J = 8.7\) Hz, 1H), 1.64 (m, 1H), 1.56 (m, 2H), 1.53 (m, 2H), 1.49 (m, 1H), 1.48 (m, 2H), 1.48 (m, 1H), 1.40 (m, 1H), 1.40 (s, 9H), 1.28 (m, 1H), 1.14 (m, 1H), 1.12 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.89 (d, \(J = 6.2\) Hz, 3H), 0.81 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 216.9, 166.2, 165.0, 148.9, 147.9, 145.7, 143.2, 127.9, 124.5, 123.7, 117.8, 74.2, 52.8, 52.2, 51.7, 51.1, 48.4, 47.8, 43.4, 38.4, 35.9, 35.4, 34.9, 34.9, 33.9, 33.5, 28.1, 27.3, 26.9, 24.5, 24.3, 21.9, 21.5, 20.6, 18.2, 18.1, 12.7.

3.3.2. 2-(Tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl 3-oxotirucalla-7,24Z-dien-26-oate (12b)

![12b](image)

Colorless oil; Rf = 0.21 (15% ethyl acetate in hexanes): \(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C, TMS): \(\delta\) 7.38 (m, 2H), 7.33 (m, 2H), 6.07 (bs, 1H), 6.05 (dt, \(J = 7.6, 1.6\) Hz, 1H), 5.99 (d, \(J = 2.6\) Hz, 1H), 5.30 (dd, \(J = 6.0, 3.2\) Hz, 1H), 2.77 (td, \(J = 14.5, 5.4\) Hz, 1H), 2.58 (m, 1H), 2.45 (m, 1H), 2.29 (dt, \(J = 14.1, 3.8\) Hz, 1H), 2.24 (m, 1H), 2.10 (m, 2H), 1.99 (m, 2H), 1.98 (d, \(J = 1.6\) Hz, 3H), 1.82 (m, 1H), 1.73 (t, \(J = 8.7\) Hz, 1H), 1.65 (m, 1H), 1.55 (m, 2H), 1.53 (m, 2H), 1.50 (m, 1H), 1.48 (m, 2H), 1.47 (m, 1H), 1.40 (m, 1H), 1.36 (s, 9H), 1.29 (m, 1H), 1.14 (m, 1H), 1.11 (s, 3H), 1.06 (s, 3H), 1.01 (s, 3H), 0.99 (d, \(J = 6.2\) Hz, 3H), 0.80 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 216.9, 167.1, 165.4, 147.0, 145.8, 134.7, 134.6, 128.8, 128.7, 125.1, 117.8, 74.6, 52.8, 52.2, 51.5, 51.1, 48.4, 47.8, 43.4, 38.5, 35.9, 35.4, 35.0, 34.9, 33.9, 33.5, 28.6, 28.1, 27.3, 26.8, 24.5, 24.3, 21.9, 21.5, 20.6, 18.2, 18.1, 12.7.
3.3.3. 2-(Tert-butylamino)-1-(4-methoxyphenyl)-2-oxoethyl 3-oxotirucalla-7,24Z-dien-26-oate (12c)

Yellow oil; Rf = 0.29 (15% ethyl acetate in hexanes): $^1$H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): $\delta$ 7.36 (m, 2H), 6.88 (m, 2H), 6.08 (dt, $J = 7.5, 1.2$ Hz, 1H), 6.01 (bs, 1H), 5.99 (d, $J = 2.9$ Hz, 1H), 5.30 (dd, $J = 6.1, 3.4$ Hz, 1H), 3.80 (s, 3H), 2.74 (td, $J = 14.5, 5.4$ Hz, 1H), 2.59 (m, 1H), 2.44 (m, 1H), 2.28 (dt, $J = 14.1, 3.8, 1$ Hz), 2.25 (m, 1H), 2.11 (m, 2H), 1.98 (m, 1H), 1.99 (m, 1H), 1.97 (d, $J = 1.5$ Hz, 3H), 1.81 (m, 1H), 1.73 (t, $J = 8.7$ Hz, 1H), 1.65(m, 1H), 1.56 (m, 2H), 1.55 (m, 2H), 1.49 (m, 1H), 1.48 (m, 2H), 1.48 (m, 1H), 1.41 (m, 1H), 1.36 (s, 9H), 1.28 (m, 1H), 1.15 (m, 1H), 1.12 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H), 0.89 (d, $J = 6.2$ Hz, 3H), 0.81 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 216.8, 167.7, 165.7, 159.8, 146.2, 145.9, 128.8, 128.4, 125.5, 117.8, 114.0, 75.0, 55.2, 52.8, 52.3, 51.3, 51.1, 48.4, 47.8, 43.5, 38.5, 36.0, 35.9, 35.6, 35.0, 34.9, 34.0, 33.5, 28.6, 28.1, 27.3, 26.8, 24.5, 24.3, 21.9, 20.6, 18.2, 18.1, 12.7.

3.3.4. 1-(Tert-butylamino)-1-oxooctan-2-yl 3-oxotirucalla-7,24Z-dien-26-oate (12d)

Colorless oil; Rf = 0.39 (15% ethyl acetate in hexanes): $^1$H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): $\delta$ 7.38 (m, 2H), 7.33 (m, 2H), 6.07 (bs, 1H), 6.05 (dt, $J = 7.6, 1.6$ Hz, 1H), 5.99 (d, $J = 2.6$ Hz, 1H), 5.30 (dd, $J = 6.0, 3.2$ Hz, 1H), 2.77 (td, $J = 14.5, 5.4$ Hz, 1H), 2.59 (m, 1H), 2.45 (m, 1H), 2.28 (dt, $J = 14.1, 3.8, 1$ Hz), 2.25 (m, 1H), 2.10 (m, 2H), 1.99 (m, 2H), 1.97 (m, 1H), 1.98 (d, $J = 1.6$ Hz, 3H), 1.82 (m, 1H), 1.76 (m, 2H), 1.73 (t, $J = 8.7$ Hz, 1H), 1.64 (m, 1H), 1.56 (m, 2H), 1.53 (m, 2H), 1.49 (m, 1H), 1.48 (m, 2H), 1.48 (m, 1H), 1.47 (m, 2H), 1.40 (m, 1H), 1.36 (s, 9H), 1.31 (m, 2H), 1.29 (m, 2H), 1.28 (m, 1H), 1.26 (m, 2H), 1.16 (m, 1H), 1.11 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.89 (d, $J = 6.2$ Hz, 3H), 0.88 (t, $J = 6.7$ Hz, 3H), 0.81 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 216.9, 167.1, 165.4, 147.0, 145.8, 134.7, 134.6, 128.8, 128.7, 125.1, 117.8, 74.6, 52.8, 52.2, 51.5, 51.1, 48.4, 47.8, 43.4, 38.5, 35.9, 35.5, 35.0, 34.9, 33.9, 33.5, 28.6, 28.1, 27.3, 26.8, 24.5, 24.3, 21.9, 21.5, 20.6, 18.2, 18.1, 12.7.

4. Conclusions

In the present work, a new example of the versatility of IMCRs was developed by synthesizing a series of novel triterpenoid-derived $\alpha$-acyloxy-carboxamides under mild conditions with good overall yields using aliphatic and deactivated aromatic aldehydes. It was observed for compound 12c that the use of an activated aromatic aldehyde leads to lower yields, showing that the stereo-electronic nature of this component is relevant for the outcome of the reaction. Finally, it was identified that reports on this type of compound are limited but promising, opening the possibilities for a more complex contribution in the future.

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

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