

Proceeding Paper

Semisynthesis of 6 β -Acetoxycouacapanone Derivates via the Ugi-Azide Multicomponent Reaction [†]

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Abstract: A semisynthesis of 6 β -acetoxycouacapanone-1,5-disubstituted tetrazoles derivatives from the leaves of *Caesalpinia platyloba* by using the Ugi-azide multicomponent reaction as a key step reaction is described. To our knowledge, this is the first report where a non-natural product such as 1,5-disubstituted tetrazole is linked to a natural product or derivative of a natural product, and beyond the biological relevance that the target molecules present, this work contributes to the area of natural products as well as multicomponent reactions.

Keywords: 6 β -acetoxycouacapanone; 1,5-disubstituted tetrazoles; ugi-azide; isocyanides; semisynthesis

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1. Introduction

Natural products, besides their complex molecular architecture and structural diversity, exhibit several biological properties, thus they have become a source of inspiration in the development of drug substances [1]. Likewise, extracts from natural sources play an important role as additives to food, cosmetic, textile and perfumery industries [2]. On the other hand, the greatest source of natural products is terrestrial vascular plants, followed by marine plants and microorganisms such as bacteria and fungi, of which only 1% of the total microbial world has been studied. It has been calculated that around 75,000 species of higher plants on the earth, only 10% have been used in traditional medicine. Only 1 to 5% has been studied scientifically and is known to have therapeutic value [3].

Nowadays, it has become a challenging task to synthesize chemical libraries for drug discovery based on natural products in a simple and efficient way. There are many strategies to accomplish this challenge, of which multicomponent reactions are one of the most important. Multicomponent reactions are synthetic tools well known for their potential to generate complexity and structural diversity under a one pot process, which means, the formation of at least three new bonds per operation and high atomic economy [4–6].

On the other hand, the *Caesalpinia* genus constitutes a potential source of bioactive natural products due to its more than 205 species distributed throughout the world [7]; many of which have not yet been investigated for potential pharmacological activity. Several species are endemic to Mexico and exhibit a diversity of biological activities such as

cytotoxic, antioxidant, antimalarial, anti-inflammatory and antiviral [8]. The *Caesalpinia* genus is distinguished by the presence of diterpenes, with a vouacapane skeleton, which are characterized by containing a furan ring in their skeletal structure. Some examples of natural products (1–6) isolated from this genus are shown in Figure 1, where 6 β -acetoxyvouacapane 7 is the natural product under study in this work, and it was isolated from *Caesalpinia platyloba* [9].

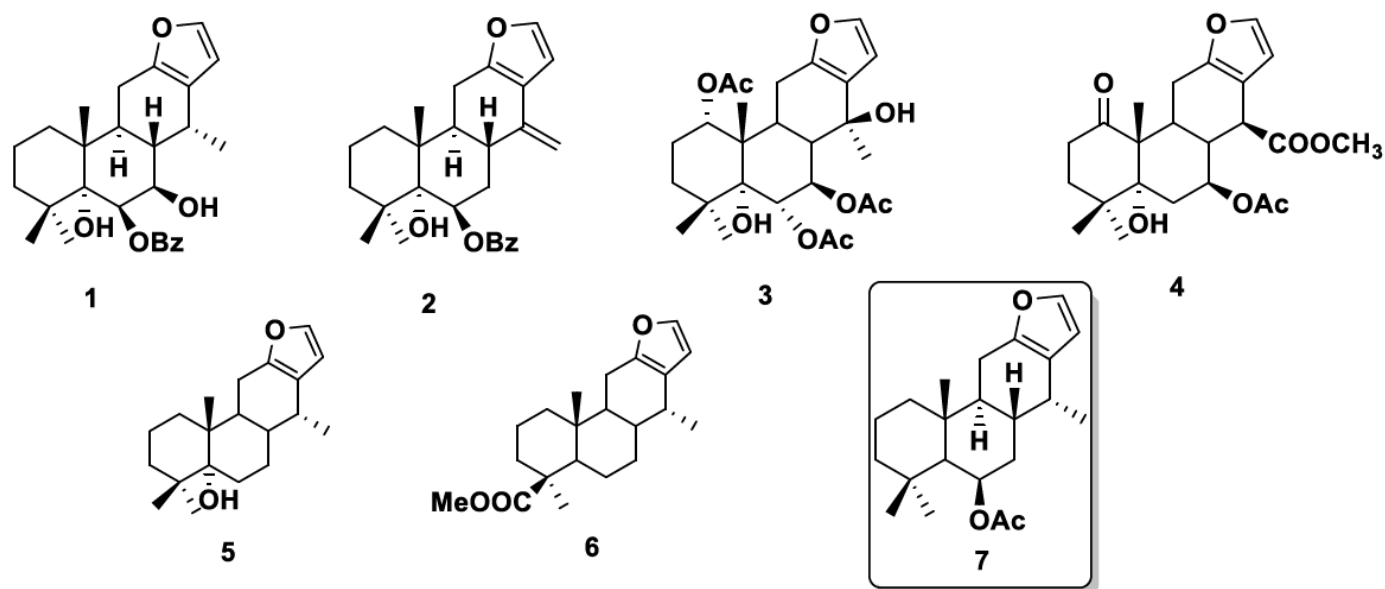


Figure 1. Vouacapanes isolated from the genus *Caesalpinia*.

Therefore, in this work the synthesis of a small series of derivatives of the natural product 6 β -acetoxyvouacapane 7, by using the Ugi-azide multicomponent reaction is described. It is important to mention that, within the state of the art, there are very few reports where a natural product is used as starting material making use of RMC-I and, particularly, there are no reports on the use of Ugi-azide reaction where a natural product or its derivatives are used as a starting material. Therefore, this work would contribute to the chemistry of natural products and the chemistry of multicomponent reactions.

2. Materials and Methods

2.1. Experimental Section

All reagents, reactants and solvents were purchased from Merck (before Sigma-Aldrich Co) without further purification. Thin-layer chromatography (TLC) was performed with silica gel plates from Merck (silica gel 60 F 254) and by using as eluent a mixture of hexanes-EtOAc, NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C on a Varian Mercury 400 spectrometer, using CDCl_3 as the solvent, and TMS as the internal standard. Chemical Shift (δ) is reported in ppm, and J values are given in Hertz. Chemical names and drawings were obtained using ChemDraw Professional (version 15.0.0.106).

2.2. General Procedure for 1,5-Disubstituted Tetrazoles-Vouacapane 12a-c

Aldehyde-6 β -acetoxyvouacapane 8 (1.0 equiv.) and amine (1.0 equiv.) were dissolved on 2,2,2-trifluoroethanol (1 M) in 5 mL round bottom flask and reacted for 5 min at room temperature. Then, isocyanide (1.0 equiv.) and TMSN_3 (1.3 equiv.) were sequentially added. The reaction mixture was stirred at room temperature until reaction consumption by TLC. Later, the reaction mixture was evaporated under reduce pressure. Then, the evaporated reaction crude was purified by flash column chromatographic (4:1 Hex:EtOAc v/v) to afford the 1,5-disubstituted tetrazoles-vouacapane 12a-c.

(5R,6aS,7R,11aS,11bR)-9-((1-(tert-butyl)-1H-tetrazol-5-yl)(p-tolylamino)methyl)-4,4,7,11b-tetramethyl-1,2,3,4,4a,5,6,6a,7,11,11a,11b-dodecahydrophenanthro [3,2-b]furan-5-yl acetate (**12a**):

Yellow oil; $R_F = 0.40$ (Hex:EtOAc 8:2 v/v); $^1\text{H-NMR}$ (400 MHz, CDCl_3): **Diast a.** δ 6.99 (d, $J = 8.3$ Hz, 1H), 6.67 (d, $J = 8.3$ Hz, 1H), 6.13 (s, 1H), 5.99 (s, 1H), 5.48 (s, 1H), 2.59–2.36 (m, 3H), 2.22 (s, 1H), 2.03 (s, 1H), 2.02 (s, 3H), 1.80 (dt, $J = 6.7, 3.6$ Hz, 1H), 1.74 (s, 1H), 1.72 (s, 9H), 1.61 (d, $J = 13.2$ Hz, 1H), 1.57–1.54 (m, 1H), 1.53–1.48 (m, 1H), 1.46–1.42 (m, 1H), 1.40–1.36 (m, 1H), 1.18 (s, 3H), 1.16–1.14 (m, 1H), 1.06 (s, 1H), 1.01 (s, 1H), 0.97 (s, 3H), 0.86 (d, $J = 7.4$ Hz, 3H). **Diast b.** δ = 6.99 (d, $J = 8.2$ Hz, 1H), 6.67 (d, $J = 8.3$ Hz, 1H), 6.11 (s, 1H), 5.96 (s, 1H), 5.48 (s, 1H), 2.59–2.36 (m, 3H), 2.22 (s, 1H), 2.03 (s, 1H), 2.02 (s, 3H), 1.80 (dt, $J = 6.7, 3.6$ Hz, 1H), 1.74 (s, 1H), 1.72 (s, 9H), 1.61 (d, $J = 13.2$ Hz, 1H), 1.57–1.54 (m, 1H), 1.53–1.48 (m, 1H), 1.46–1.42 (m, 1H), 1.40–1.36 (m, 1H), 1.18 (s, 3H), 0.86 (d, $J = 7.4$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): (mixture of diastereomers) δ 170.5, 154.08, 154.06, 150.3, 150.2, 148.7, 148.6, 143.3, 130.1, 129.8, 128.89, 128.88, 123.3, 123.2, 121.0, 115.0, 114.9, 113.5, 108.8, 108.7, 69.5, 69.3, 69.1, 61.8, 61.7, 55.33, 55.30, 55.2, 55.1, 53.8, 53.5, 49.74, 49.68, 45.5, 45.1, 43.7, 43.64, 43.62, 42.22, 42.20, 42.0, 41.9, 37.92, 37.89, 37.85, 37.8, 37.7, 36.19, 36.17, 36.0, 35.9, 35.50, 35.45, 35.3, 35.2, 33.8, 33.79, 33.69, 33.65, 30.9, 30.84, 30.80, 30.0, 29.6, 29.2, 29.1, 29.0, 23.4, 21.8, 21.76, 21.70, 20.4, 18.8, 18.7, 17.5, 17.4, 17.20, 17.14.

(5R,6aS,7R,11aS,11bR)-9-((1-(tert-butyl)-1H-tetrazol-5-yl)(prop-2-yn-1-ylamino)methyl)-4,4,7,11b-tetramethyl-1,2,3,4,4a,5,6,6a,7,11,11a,11b-dodecahydrophenanthro [3,2-b]furan-5-yl acetate (**12b**):

Yellow oil; $R_F = 0.46$ (Hex:EtOAc 6:4 v/v); $^1\text{H-NMR}$ (400 MHz, CDCl_3): **Diast a.** δ = 5.94 (s, 1H), 5.62 (s, 1H), 5.49 (s, 1H), 3.54 (dt, $J = 16.8, 2.6$ Hz, 2H), 2.61–2.40 (m, 3H), 2.23 (t, $J = 2.4$ Hz, 1H), 2.03 (s, 1H), 2.02 (s, 3H), 1.81 (dt, $J = 6.5, 4.2$ Hz, 1H), 1.73 (d, $J = 2.6$ Hz, 1H), 1.72 (s, 9H), 1.64–1.59 (m, 1H), 1.56–1.51 (m, 1H), 1.50–1.48 (m, 1H), 1.47–1.46 (m, 1H), 1.42–1.38 (m, 1H), 1.19 (s, 3H), 1.17–1.14 (m, 1H), 1.06 (s, 1H), 1.02 (s, 3H), 0.98 (s, 3H), 0.89 (d, $J = 7.1$ Hz, 3H). **Diast b.** δ = 5.90 (s, 1H), 5.62 (s, 1H), 5.49 (s, 1H), 3.45–3.39 (m, 2H), 2.61–2.40 (m, 3H), 2.23 (t, $J = 2.4$ Hz, 1H), 2.03 (s, 1H), 2.02 (s, 3H), 1.81 (dt, $J = 6.5, 4.2$ Hz, 1H), 1.73 (d, $J = 2.6$ Hz, 1H), 1.71 (s, 9H), 1.64–1.59 (m, 1H), 1.56–1.51 (m, 1H), 1.50–1.48 (m, 1H), 1.47–1.46 (m, 1H), 1.42–1.38 (m, 1H), 1.18 (s, 3H), 1.17–1.14 (m, 1H), 1.06 (s, 1H), 1.02 (s, 3H), 0.98 (s, 3H), 0.86 (d, $J = 7.1$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): (mixture of diastereomers) δ 170.5, 153.8, 150.5, 148.6, 123.2, 109.1, 80.7, 72.6, 69.5, 61.6, 55.4, 55.3, 51.1, 45.5, 43.6, 42.2, 37.9, 36.2, 33.8, 33.7, 30.90, 30.88, 30.0, 29.9, 29.7, 23.4, 21.8, 18.7, 17.5, 17.2, 17.1.

Ethyl 5-(((5R,6aS,7R,11aS,11bR)-5-acetoxy-4,4,7,11b-tetramethyl-1,2,3,4,4a,5,6,6a,7,11,11a,11b-dodecahydrophenanthro [3,2-b]furan-9-yl)(1-(tert-butyl)-1H-tetrazol-5-yl)methyl)amino)benzofuran-2-carboxylate (**12c**):

Yellow oil; $R_F = 0.56$ (Hex:EtOAc 6:4 v/v); $^1\text{H-NMR}$ (400 MHz, CDCl_3): **Diast a.** δ 7.43–7.37 (m, 2H), 6.97–6.93 (m, 2H), 6.15 (s, 1H), 6.00 (s, 1H), 5.49 (s, 1H), 4.42 (q, $J = 7.1$ Hz, 2H), 2.59–2.41 (m, 3H), 2.05.2.02 (m, 1H), 2.01 (s, 3H), 1.80 (dt, $J = 5.8, 2.5$ Hz, 1H), 1.72 (s, 1H), 1.68–1.65 (m, 1H), 1.64–1.61 (m, 1H), 1.55–1.53 (m, 1H), 1.50–1.47 (m, 1H), 1.44–1.42 (m, 1H), 1.41 (t, $J = 7.1$ Hz, 3H), 1.22–1.20 (m, 1H), 1.18 (s, 3H), 1.06 (s, 1H), 1.01 (s, 3H), 0.98 (s, 3H), 0.88 (d, $J = 7.3$ Hz, 3H). **Diast b.** δ 7.43–7.37 (m, 2H), 6.97–6.93 (m, 2H), 6.15 (s, 1H), 5.97 (s, 1H), 5.49 (s, 1H), 4.42 (q, $J = 7.1$ Hz, 2H), 2.59–2.41 (m, 3H), 2.05.2.02 (m, 1H), 2.01 (s, 3H), 1.80 (dt, $J = 5.8, 2.5$ Hz, 1H), 1.72 (s, 1H), 1.68–1.65 (m, 1H), 1.64–1.61 (m, 1H), 1.55–1.53 (m, 1H), 1.50–1.47 (m, 1H), 1.44–1.42 (m, 1H), 1.41 (t, $J = 7.1$ Hz, 3H), 1.22–1.20 (m, 1H), 1.18 (s, 3H), 1.06 (s, 1H), 1.01 (s, 3H), 0.98 (s, 3H), 0.86 (d, $J = 7.1$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): (mixture of diastereomers) δ 170.5, 159.5, 153.8, 150.8, 150.54, 150.47, 148.5, 148.4, 148.3, 146.1, 142.5, 127.7, 123.4, 123.3, 118.1, 118.1, 113.5, 113.1, 109.0, 108.9, 106.24, 106.15, 69.5, 61.8, 61.4, 55.33, 55.30, 50.6, 45.5, 43.6, 42.2, 37.92, 37.89, 36.2, 33.8, 33.7, 30.9, 30.8, 30.00, 29.99, 29.7, 23.4, 21.8, 21.7, 18.7, 17.4, 17.2, 17.1, 14.3.

3. Results and Discussion

First, we start with the isolation and purification of 6 β -acetoxyvouacapane **7** from the *Caesalpinia platyloba* leaves [8]. Then it was subjected a formylation reaction to obtain the

aldehyde-6 β -acetoxyvouacapane **8**, which their synthesis and procedure will be published soon.

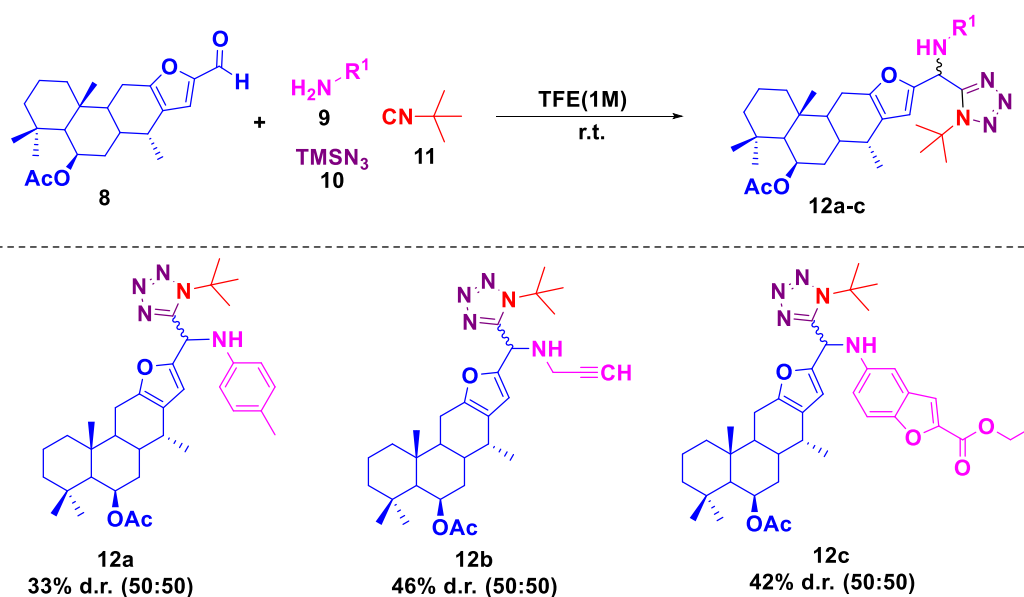
Thus, we started by searching for the optimal reaction conditions for the Ugi-azide reaction using as model reaction aldehyde-vouacapane **8**, *p*-toluidine (**9**), and *tert*-butyl isocyanide (**11**). We first performed the reaction using the classical Ugi-azide conditions [10–12], with MeOH as the solvent at room temperature. However, the product could not be identified because the aldehyde-6 β -acetoxyvouacapane **8** was not soluble in the reaction mixture and consequently the starting materials were not consumed (entry 1, Table 1). As second experiment we performed the reaction using 2,2,2-trifluoroethanol as solvent instead of MeOH because of the fact that, in recent years, Ugi-azide reactions have been carried out successfully using this solvent. The reaction proceeded well, affording the product in a 33% yield after purification by chromatographic column (entry 2, Table 1). At this point, it was decided to use these conditions, although there are more reaction conditions to be explored such as the use of microwave reactor [13], sonication [14] and the use of Lewis acids such as ZnCl₂ [15]. It is also important to mention that in the Ugi-azide reaction a stereogenic center is formed, so the product obtained was observed by ¹H NMR as a mixture of diastereomers in a 50:50 ratio.

Table 1. Optimization of RMC Ugi-azide conditions.

Entry ^a	Solvent	Yield (%)
1	MeOH (1M)	ND ^b
2	2,2,2-trifluoroethanol (1M)	33 ^c

^a The reaction time was 24 h. ^b Product no detected. ^c The isolated yields were determined after purification by flash column chromatography.

With the optimal reaction conditions previously explored, we proceeded to study the scope of the reaction using amines with different stereoelectronic properties. The tetrazole-vouacapanes **12a-c** were obtained in moderate yields (Scheme 1). We also observed by ¹H NMR a diastereomeric mixture for each of the target molecules in 50:50 ratio.



Scheme 1. Synthesis of 1,5-disubstituted tetrazoles-vouacapane **12a-c** via Ugi-Azide multicomponent reaction.

4. Conclusions

A small family of pseudo natural products 1,5-disubstituted tetrazoles-vouacapane **12a-c** were synthesized in moderate yields by Ugi-azide multicomponent reaction under a mild reactions condition. To date, this is the first work where a natural product or natural product derivative is joined to a non-natural product such as 1,5-disubstituted tetrazole and beyond the biological relevance that the target molecules present, this work contributes both to the area of natural products and in multicomponent reactions.

Author Contributions: Conceptualization, C.J.C.-G. and R.E.d.R.; methodology, G.S.-G. and J.G.M.; software, L.C.G. and M.M.-A.; validation, G.R.-G. and M.M.-A.; formal analysis, L.C.G. and J.G.M.; investigation, C.J.C.-G. and M.A.G.-H.; resources, C.J.C.-G. and R.E.d.R.; data curation, G.S.-G. and M.A.G.-H.; writing-original draft preparation, C.J.C.-G. and G.S.-G.; writing-review and editing C.J.C.-G., A.S.-C. and L.C.G.; visualization, M.M.-A. and G.R.-G.; supervision, C.J.C.-G.; project administration, C.J.C.-G. and L.C.G.; funding acquisition, C.J.C.-G. All authors have read and agreed to the published version of the manuscript.

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