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Proceeding Paper

Semi-Synthesis of Imidazo-5*α*-Hydroxyvouacapane from *Caesalpinia pulcherrima* via a Groebke–Blackburn–Bienaymé Reaction †

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Abstract: A semi-synthetic strategy and operationally simple to obtain a new heterocyclic system imidazo-5*α*-hydroxyvouacapane in two-step reactions was developed. The first reaction step is a Vilsmeier-Haack formylation at the furan ring of the 5*α*-hydroxyvouacapane isolated from *Caesalpinia pulcherrima* stems to obtain the 5*α*-hydroxyvouacapane-aldehyde in 33% yield. The second reaction step is a Groebke–Blackburn–Bienaymé reaction to synthesize the imidazo-5*α*-hydroxyvouacapane by using 2-aminopyridine and *tert*-buthyl isocyanide in 75% yield. This work contributes significantly to semi-synthesis through multicomponent reactions, an area with limited literature coverage.

Keywords: 5*α*-hydroxyvouacapane; Groebke–Blackburn–Bienaymé reaction; *Caesalpinia pulcherrima*; isocyanides; semi-synthesis

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1. Introduction

Distinguished by their structural diversity and complexity [1], natural products or secondary metabolites have assumed a pivotal role in pharmaceutical research [2], primarily through their isolation, facilitating the discovery of bioactive compounds indispensable in drug development [3]. Nevertheless, these metabolites rarely find direct application without modification, necessitating the development of the semi-synthesis field [4], a scarcely explored that has been instrumental in synthesizing numerous derivatives with superior biological activities compared to their natural counterparts [5]. Thus, using powerful, rapid, and efficient synthetic tools becomes imperative to access these valuable natural product derivatives. Among them, isocyanide-multicomponent reactions (I-MCR) have gained prominence recently, particularly in synthesizing triterpenes and marine natural product derivatives [6,7]. However, the sparse literature on these reactions presents an enticing area for further investigation.

On the other hand, the genus *Caesalpinia* has a variety of secondary metabolites, such as diterpenes, triterpenes, flavonoids, aromatic phenols, phenylpropanoids, and others. Several *Caesalpinia* species have found utility in traditional medicine, with compounds isolated from these plants displaying significant biological activities [8]. Among these species, *Caesalpinia pulcherrima*, a small tropical tree commonly used as an ornamental plant

[9], has yielded metabolites with documented cytotoxic, antituberculosis, antibacterial, and antifungal properties. Isovouacapenol C **1** [10], pulcherrimin C **2** [11], pulcherrimin A **3** [12], 8,9,11,14-didehydrovouacapen-5α-ol **4** and 5α-hydroxyvouacapane **5** [10] are some of the metabolites isolated in this specie, the latter being the natural product under study in this work (Figure 1).

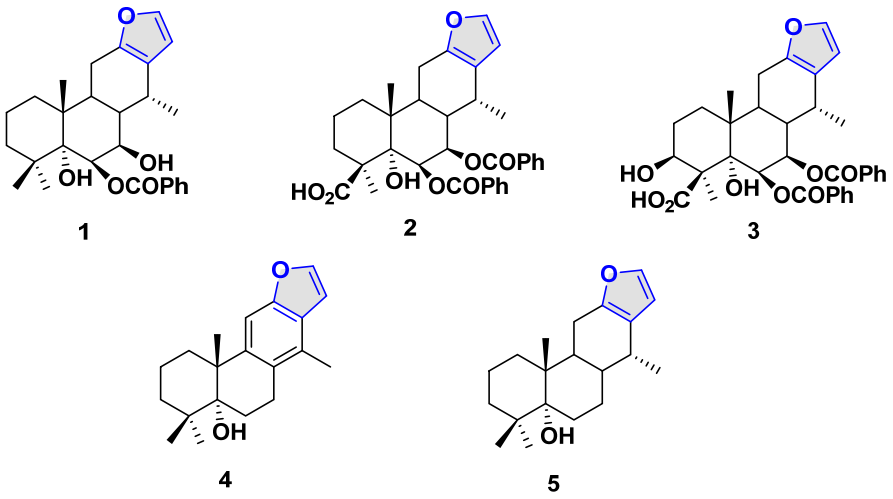


Figure 1. Vouacapanes isolated from *Caesalpinia pulcherrima*.

In continuation of our studies of natural product derivatives and the synthesis of biologically relevant compounds by using I-MCR such as Ugi-azide and the Groebke-Blackburn-Bienaymé reaction (GBB) [13–17], herein, we report the isolation of 5α-hydroxyvouacapane **5** and the semi-synthesis of imidazo-5α-hydroxyvouacapane through the GBB reaction.

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 a mixture of hexanes-EtOAc was used as eluent. The NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C on a Varian Mercury 400 spectrometer, using $CDCl_3$ as the solvent and TMS as the internal standard. The chemical shift (δ) is reported in ppm, and the *J* values are given in Hertz. HRMS spectra were acquired on a Bruker MicroTOF-II spectrometer. The chemical names and drawings were obtained using ChemDraw Professional (version 15.0.0.106).

2.2. Plant Material

Specimens of *Caesalpinia pulcherrima* were collected from Huetamo de Núñez, Michoacán state, Mexico, in October 2022.

2.3. Extraction and Isolation

Air-dried stems (500 g) of *C. pulcherrima* were treated under reflux with CH_2Cl_2 (5 L) for 12 h. Filtration and evaporation of the CH_2Cl_2 extract afforded a brown viscous oil (40 g, 8%), from which a portion (10 g) was subjected to silica gel column chromatography (cc) with hexanes–CH_2Cl_2 mixtures as the eluent. Fractions 20–25 (hexanes–CH_2Cl_2; 95:5) gave purified vouacapane 5 (96 mg).

Colorless crystals; m.p. 98–100 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 1.1 Hz, 1H), 6.18 (d, *J* = 1.6 Hz, 1H), 2.58 (dd, *J* = 6.8, 4.1 Hz, 1H), 2.49–2.43 (m, 1H), 2.37–2.35 (m, 1H), 2.35–2.32 (m, 1H), 1.85–1.82 (m, 1H), 1.81–1.80 (m, 1H), 1.80–1.77 (m, 1H), 1.68–1.66 (m,

1H), 1.66–1.65 (m, 1H), 1.61–1.58 (m, 1H), 1.59–1.56 (m, 1H), 1.49–1.46 (m, 1H), 1.44–1.42 (m, 1H), 1.39–1.35 (m, 1H), 1.20–1.17 (m, 1H), 1.08 (s, 3H), 1.06 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 149.7, 140.2, 122.5, 109.5, 76.8, 41.1, 38.4, 37.6, 36.3, 34.5, 32.4, 31.5, 28.0, 25.6, 24.7, 24.4, 22.3, 18.2, 17.5, 17.6.

2.4. Synthesis of (4aR,7R,11bR)-9-(3-(Tert-butylamino)imidazo[1,2-a]pyridin-2-yl)-4,4,7,11b-tetramethyl-1,3,4,5,6,6a,7,11,11a,11b-decahydrophenanthro[3,2-b]furan-4a(2H)-ol

The 5α-hydroxyvouacapane 5 (100 mg, 1.0 equiv.) was dissolved in dimethylformamide (0.5 M) in a 5 mL round bottom flask. Next, a previously prepared mixture of $POCl_3$ (160 μL, 6.0 equiv.) was added dropwise to DMF (80 μL, 3.5 equiv.). The reaction mixture was stirred at room temperature for 2 h. Then, the reaction mixture was cooled to 0 °C, and crushed ice was added and stirred vigorously until the formation of a precipitate, which was filtered, washed with water (5 mL), and dried under vacuum to give a yellow powder. Finally, it was purified by flash column chromatography with hexanes:EtOAc 8:2 (*v*/*v*) to give the vouacapane-aldehyde 6 as a yellow oil (37%).

Yellow oil; R_F = 0.80 (Hex:EtOAc 9:1 *v*/*v*); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.47 (s, 1H), 7.05 (s, 1H), 2.67 (dd, *J* = 7.0, 4.4 Hz, 1H), 2.60–2.54 (m, 1H), 2.50–2.40 (m, 2H), 1.88–1.85 (m, 1H), 1.83–1.82 (m, 1H), 1.81–1.78 (m, 1H), 1.67–1.66 (m, 1H), 1.65–1.63 (m, 1H), 1.63–1.57 (m, 2H), 1.45–1.40 (m, 1H), 1.37–1.35 (m, 1H), 1.33–1.30 (m, 1H), 1.22–1.19 (m, 1H), 1.09 (s, 3H), 1.05 (d, *J* = 9.0 Hz, 6H), 0.95 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 176.79, 158.61, 151.45, 126.85, 122.60, 41.08, 38.32, 37.01, 36.20, 34.33, 32.36, 31.24, 29.64, 27.90, 25.52, 24.64, 24.16, 22.74, 18.06, 17.48, 16.91. HRMS (ESI$^+$): *m*/*z*: Calcd. for $C_{21}H_{30}O_3$ [M + H]$^+$: 330.2195; Found: 331.2268.

2.5. Synthesis of (5R,11bS)-9-(3-(Tert-butylamino)imidazo[1,2-a]pyridin-2-yl)-4,4,7,11b-tetramethyl-1,2,3,4,4a,5,6,11b-octahydrophenanthro[3,2-b]furan-5-yl Acetate

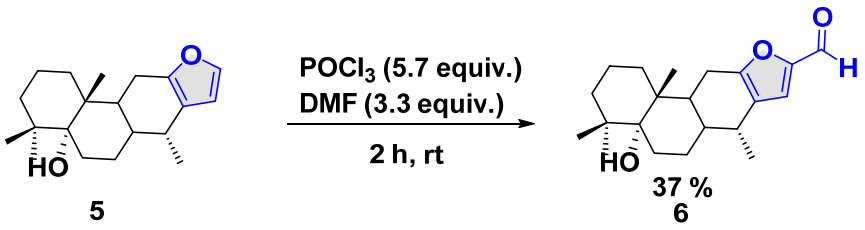
Vouacapane-aldehyde 6 (20 mg, 0.06 mmol), 2-aminopyridine (5.7 mg, 0.06 mmol), and $Sc(OTf)_3$ (10% mol) were dissolved in a mixture of MeOH/DCM (0.5 M, 2:3 *v*/*v*) in a 5 mL round bottom flask and reacted for 5 min at room temperature. Then, isocyanide (5.79 μL, 0.06 mmol) was added, and the reaction mixture was stirred at room temperature until reaction consumption (monitored by TLC). Next, the reaction mixture was evaporated under reduced pressure, and the residue was purified by flash column chromatography with hexanes:EtOAc (1:1) to afford 9 as an orange solid (21.8 mg, 74%).

Solid orange; mp = 94–97 C R_F = 0.20 (Hex:EtOAc 7:3 *v*/*v*); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.20 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.46 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.07 (ddd, *J* = 9.1, 6.6, 1.3 Hz, 1H), 6.73–6.68 (m, 2H), 2.70–2.55 (m, 1H), 2.57–2.46 (m, 1H), 2.46–2.35 (m, 2H), 1.84 (d, *J* = 8.5 Hz, 3H), 1.70–1.67 (m, 1H), 1.67–1.63 (m, 1H), 1.62–1.59 (m, 1H), 1.52–1.49 (m, 1H), 1.48–1.46 (m, 1H), 1.39–1.35 (m, 1H), 1.29–1.26 (m, 1H), 1.21–1.19 (m, 1H), 1.18 (s, 9H), 1.09 (s, 6H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 149.1, 148.0, 142.2, 131.2, 124.5, 123.8, 123.5, 123.3, 116.8, 110.9, 107.4, 56.5, 41.1, 38.3, 37.6, 36.3, 34.3, 32.4, 31.5, 30.1, 29.6, 28.0, 25.6, 24.7, 24.3, 24.0, 22.4, 18.2, 17.5, 17.1. HRMS (ESI$^+$): *m*/*z*: Calcd. for $C_{31}H_{43}N_3O_2$ [M + H]$^+$: 489.3355; Found: 490.3407.

3. Results and Discussion

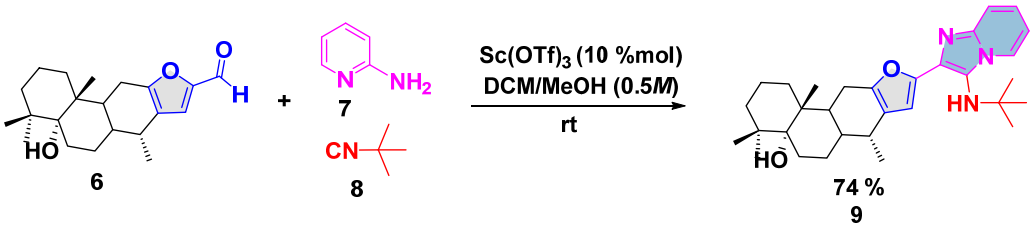
We began by isolating 5α-hydroxyvouacapane 5 from the dichloromethane extract of *C. pulcherrima* stem through column chromatography using mixtures of hexanes:EtOAC (9:1 *v*/*v*). This process yielded 96 mg (0.02% yield) of 5α-hydroxyvouacapane 5 as colorless crystals from 400 g of stem material. Spectroscopic characterization agreed with the data reported by Yodsaoue et al. [9]. Subsequently, 5α-hydroxyvouacapane 5 was subjected to a Vilsmeier-Haack formylation, resulting in the formation of vouacapane-aldehyde 6 in 37% yield (Scheme 1), which served as the starting material for the GBB reaction. 1D-NMR techniques (^{1}H and ^{13}C) confirmed the presence of the aldehyde proton at δ 9.47 and the carbonyl group at δ 176.8. The yield obtained for this compound was lower than that

reported by Servin et al. under the same formylation conditions [17]. This variation can be attributed to the fact that the starting material 5 contains a hydroxyl group, which may react with $POCl_3$, causing an alcohol dehydration reaction that leads to the formation of alkenes as byproducts.



Scheme 1. Formylation of 5α-hydroxyvouacapane vía Vilsmeier-Haack.

Thus, aiming to evaluate the synthetic potential of vouacapane-aldehyde **6**, a preliminary assessment of the reaction GBB by using as model reaction formyl-5α-hydroxyvouacapane **6**, 2-aminopyrimidine **7**, and *tert*-butyl isocyanide **8** under the conditions recently reported by our research group [13], yielded the imidazo-5α-hydroxyvouacapane **9** in 74% yield.



Scheme 2. Synthesis of imidazo-5α-hydroxyvouacapane **9** via GBB reaction.

The structure of imidazo-5α-hydroxyvouacapane **9** was elucidated by ^{1}H NMR, ^{13}C NMR and and HRMS. Inspection of the ^{1}H NMR spectroscopic data revealed four new aromatic proton resonances that belong to the fused imidazole. Thus, doublets of triplets signal at δ 8.20 (dt, J = 6.9, 1.2 Hz, 1H) and δ 7.46 (dt, J = 9.1, 1.2 Hz, 1H) were observed, as well as a doublet of doublets of doublets signal at δ 7.07 (ddd, J = 9.1, 6.6, 1.2 Hz, 1H). One signal overlapped with the proton resonance from the furan ring between δ 6.73–6.68 was observed, while a singlet signal at δ 1.18 was assigned to the *tert*-butyl group from isocyanide moiety. The ^{13}C NMR spectrum revealed a signal at δ 123.3 assigned to the carbon bound to the furan ring. At δ 142.2, a signal from the carbon bridgehead of the fused system was observed, and at δ 149.1, the signal corresponds to C-N from the isocyanide group.

4. Conclusions

In summary, we have demonstrated the initial utility of the GBB multicomponent reaction as a potent synthetic tool for the semi-synthesis of a novel heterocyclic system, imidazo-5α-hydroxyvouacapane **9**. This compound was efficiently obtained with good yield, showcasing the rapid and straightforward nature of the synthesis. This work represents a valuable contribution to the field of natural products and the realm of multicomponent reactions.

Author Contributions: Conceptualization, C.J.C.-G. and R.E.d.R.; methodology, G.S.-G. and A.A.F.-L.; software, L.C.G.; validation, G.R.-G.; formal analysis, L.C.G.; 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 A.A.F.-L.; writing—original draft preparation, C.J.C.-G. and G.S.-G.; writing—review and editing C.J.C.-G. and L.C.G.; visualization, A.A.F.-L.; and G.R.-G.; supervision, C.J.C.-G.; project administration, C.J.C.-G. and L.C.G.; and

funding acquisition, C.J.C.-G. All authors have read and agreed to the published version of the manuscript.

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

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