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Short Note

7,7′-(1,4-Phenylene)*bis*(2-benzyl-3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-6-(4-methoxybenzyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one)

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Abstract

The multicomponent synthesis of a novel and highly symmetric polyheterocycle based on the pyrrolo[3,4-*b*]pyridin-5-one core incorporating the privileged tetrahydroisoquinoline moiety is described. The target compound was synthesized as an inseparable mixture of stereoisomers through a pseudo-repetitive Ugi–Zhu five-component reaction (PR-UZ-5CR) coupled to a double post-transformation sequence involving an intermolecular *aza* Diels–Alder cycloaddition, an intramolecular *N*-acylation, and a final tandem aromatization step. The product was prepared in 63% overall yield, and with an excellent atom economy of 85%, within a total reaction time of 85 min, and a temperature range from 25 to 65 °C. Structural elucidation and molecular mass confirmation were successfully achieved through NMR and FT-IR spectroscopy, and high-resolution mass spectrometry (HRMS), respectively.

Keywords: molecular symmetry; tetrahydroisoquinoline; one pot; multiple bond-forming transformations; pseudo-repetitive multicomponent reaction

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1. Introduction

The design of new molecules with pharmacological potential nowadays involves multiple theoretical, computational, and experimental considerations. However, the role of molecular symmetry and its potential influence on biological target recognition have been comparatively underexplored. Bai and Wang identified some guidelines to classify dimer-type molecules with high symmetry from a synthetic perspective [1]. When two chemical fragments connected by a linker are identical and share the same mode of connectivity to that linker, the resulting structure is defined as a bilaterally symmetric molecule (Figure 1A). In such cases, global symmetry becomes evident, and the molecules commonly exhibit C_2, C_S, or C_{2V} symmetry elements. Conversely, when the fragments are chemically identical but differ in their connectivity to the linker, the molecules are classified as non-bilaterally symmetric pseudo-dimers (Figure 1B). A relevant example of a dimer with bilateral symmetry is the commercial drug Daclatasvir (Figure 1A), an antiviral used for the treatment of hepatitis C by inhibiting its NS5A protein [2].

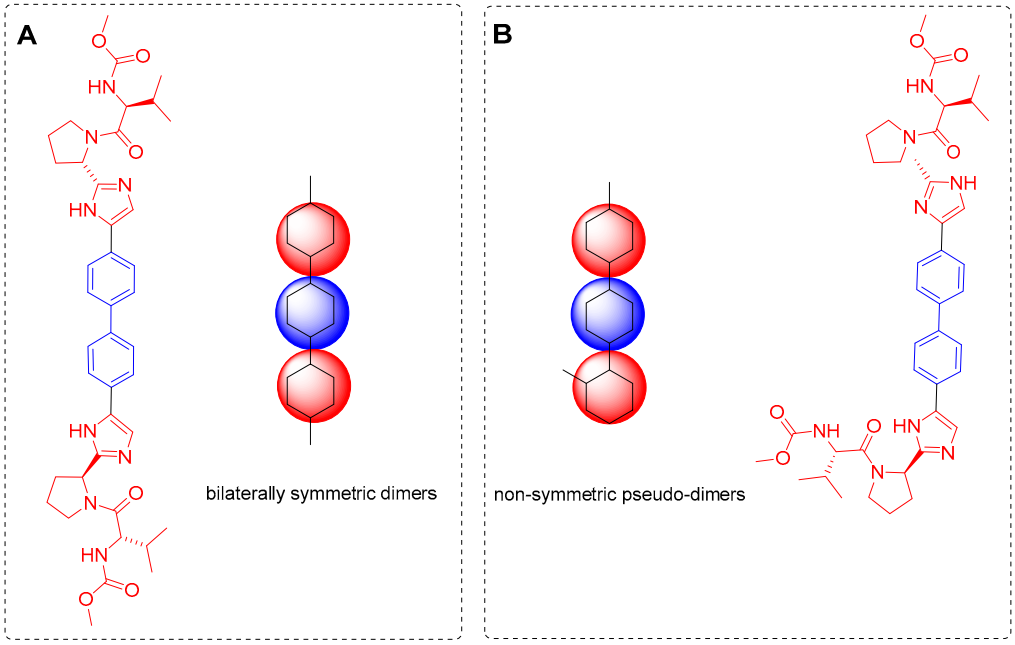
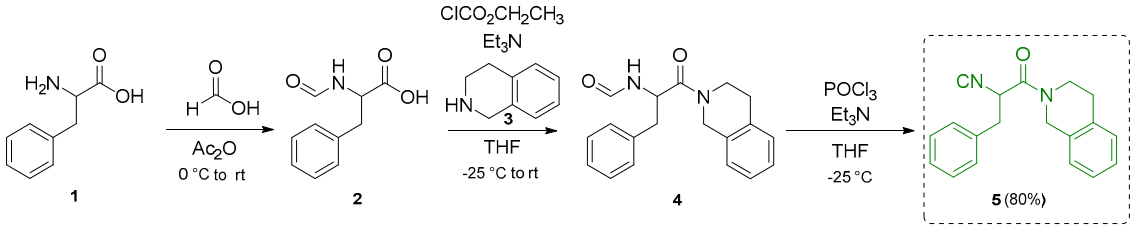


Figure 1. Classification of molecules with evident symmetry: (**A**) Daclatasvir, a drug that serves as a dimer with bilateral symmetry; (**B**) An isomer of daclatasvir, exemplifying non-symmetric pseudo-dimers.

It is important to highlight that molecules with high symmetry exhibit exceptional stability, along in some cases with a significant degree of electronic delocalization [3]. These features are characteristic of compounds with potential antioxidant activity [4]. However, the synthesis of dimer-type molecules with bilateral symmetry may pose a synthetic challenge in the laboratory. In this context, multiple bond-forming transformations (MBFTs) offer attractive strategies to rapidly access structures with high molecular symmetry [5]. An important class of such transformations is the multicomponent reactions (MCRs), which are highly convergent one-pot processes in which the reagents undergo a sequence of elementary steps to produce a sole product with high structural complexity that retains most or all the atoms from the initial components [6]. This manuscript describes the synthesis and characterization of a new polyheterocycle bearing a pyrrolo[3,4-*b*]pyridin-5-one core (aza-analog of isoindolin-2-one core, a heterocycle of broad pharmacobiological relevance [7]), incorporating the privileged tetrahydroisoquinoline moiety. The target structure corresponds to a bilateral-symmetry dendrimer, obtained as an inseparable mixture of stereoisomers through the combination of two multiple bond-forming processes. These involve a pseudo-repetitive Ugi–Zhu five-component reaction (PR-UZ-5CR) [8] and a double cascade process: intermolecular *aza* Diels–Alder cycloaddition/intramolecular *N*-acylation/aromatization (decarboxylation–dehydration) steps.

2. Results and Discussion

The target polyheterocycle **17** was synthesized through two multiple-bond-forming transformations. The first one involves a PR-UZ-5CR, which produces the *bis*-oxazole **13**. In this reaction, terephthalaldehyde **6,** acting as a bi-functional reagent, 4-methoxybenzylamine **7**, and an α-isocyanoacetamide **5** functionalized with the tetrahydroisoquinoline scaffold were sequentially combined. Since the latter component is not commercially available, it was synthesized through a three-step sequence involving an initial formylation, an *N*-acylation, and a Ugi-type dehydration, following the methodology reported by Bienaymé (Scheme 1) [9].



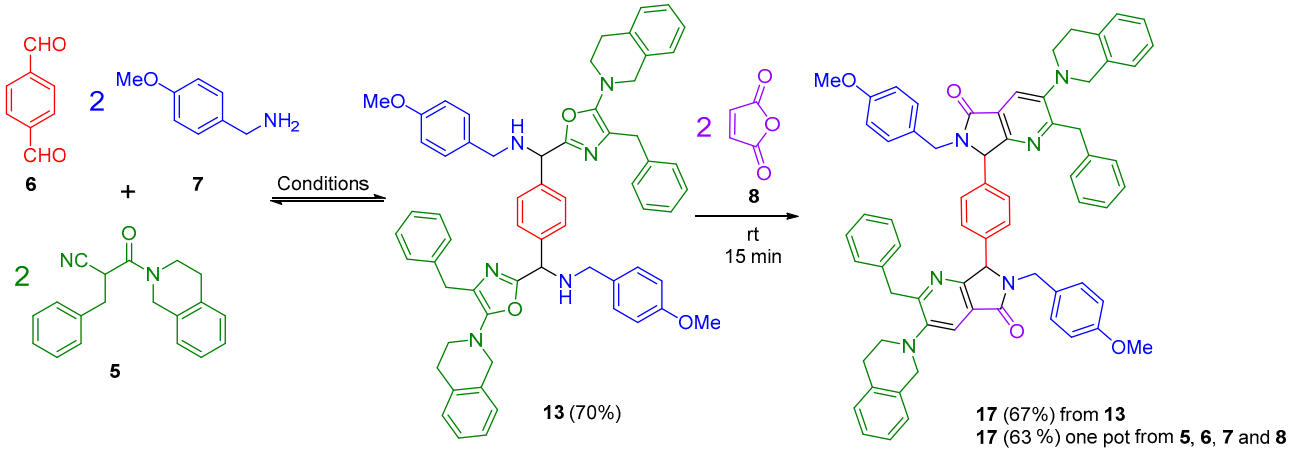
Scheme 1. Synthesis route to access the α-isocyanoacetamide component.

The pseudo-repetitive Ugi-Zhu five-component reaction (PR-UZ-5CR) was performed by reacting terephthalaldehyde **6** with two equivalents of 4-methoxybenzylamine **7** in PhMe under continuous stirring (Scheme 2). The progress of the reaction was monitored using TLC, which indicated complete consumption of the aldehyde **6** after 30 min. Subsequently, $Yb(OTf)_3$ (8 mol%) was added to the reaction mixture to facilitate the conversion of the imine **9** into the corresponding Lewis-type iminium cation **10**. The coordination between the ytterbium center and the imine nitrogen was enhanced by microwave irradiation at 65 °C for 5 min at 65 W. The next step was to promote the reaction between the preformed intermediate **10** and the α-isocyanoacetamide **5** to yield the PR-UZ-5CR product (*bis*-oxazole **13**) (Scheme 3). Initially, this step was performed at room temperature under constant stirring (Table 1, entry 1), resulting in a yield of 16%. To improve conversion efficiency, the effect of temperature was systematically evaluated using microwave irradiation as the heating source. At 50 °C, the yield increased to 58% (Table 1, entry 2), and further elevating the temperature to 60 °C (Table 1, entry 3) provided the optimal yield of 70% in 25 min. However, at temperatures above 60 °C, a gradual decrease in yield was observed (Table 1, entry 4).

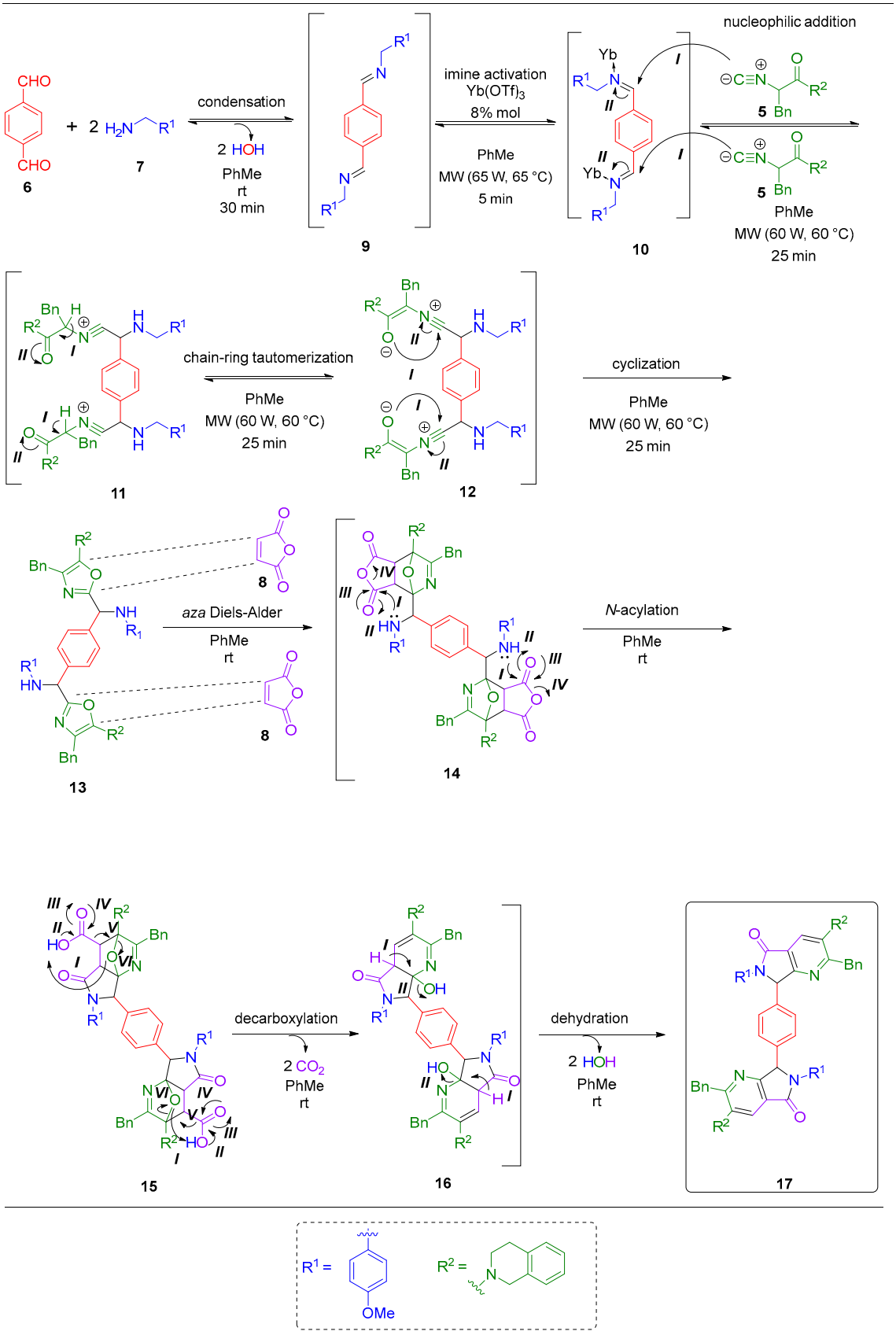
Table 1. Optimization of the reaction conditions.

Entry	Conditions [a,b] T (°C)	Yield (%) [c] for 13
1	rt	16
2	μW (50)	58
3	μW (60)	70
4	μW (70)	64

[a] PhMe was used as the solvent, and $Yb(OTf)_3$ (8 mol%) served as the catalyst. The imine formation proceeded quantitatively under constant stirring. [b] Double cascade process between the *bis*-oxazole **13** and maleic anhydride (**8**) proceeded quantitatively at room temperature in 15 min. [c] Yield was measured after purification by silica gel column chromatography.



Scheme 2. Synthetic methodology.



Scheme 3. Reaction mechanism for polyheterocyclic *bis*-pyrrolo[3,4-*b*]pyridin-5-one **17**.

After establishing the optimal conditions for the pseudo-repetitive Ugi-Zhu five-component reaction (PR-UZ-5CR), the focus shifted to the post-transformation step to

achieve the highly symmetric polyheterocycle **17**. This transformation involved a double cascade sequence: intermolecular *aza* Diels-Alder cycloaddition/intramolecular *N*-acylation/aromatization, this latter one including a tandem decarboxylation-dehydration process. Thus, the *bis*-oxazole **13** reacted with maleic anhydride (**8**), serving as the dienophile. Remarkably, with constant stirring, the reaction reached completion within 15 min, resulting in a polyheterocyclic product **17** with a yield of 67%. Alternatively, the same compound **17** was synthesized in a one-pot process, yielding a comparable result of 63%, which is considered satisfactory, especially since it only required a straightforward work-up.

The polyheterocycle **17** was characterized by 1D NMR (^{1}H, ^{13}C) and 2D NMR (COSY, HMBC, and HSQC) spectroscopy, allowing for the unequivocal assignment of each proton and carbon signal (see the Electronic Supplementary Material and Materials and Methods section for further details). The molecular weight was confirmed by high-resolution mass spectrometry (HRMS), with the molecular cation $(C_{68}H_{61}N_6O_4)^+$ detected within an error margin of 0.1 ppm.

The proposed reaction mechanism leading to polyheterocycle **17** begins with the condensation of aldehyde **6** and benzylamine **7**, resulting in the formation of *bis*-imine **9**. This intermediate is then converted into the *bis*-iminium cation **10** through coordination with the ytterbium catalyst. This activation promotes the nucleophilic addition of the divalent carbon from α-isocyanoacetamide **5** to the electrophilic carbon of intermediate **10**, which generates a *bis*-nitrilium cation **11**. This one subsequently undergoes intramolecular tautomerization and cyclization to yield the *bis*-oxazole **13**, which then reacts with maleic anhydride **8** via a double *aza* Diels–Alder cycloaddition, resulting in the formation of the oxa-bridged intermediate **14**. This intermediate undergoes a rapid intramolecular acylation, followed by a tandem decarboxylation-dehydration step, which ultimately produces the polyheterocyclic *bis*-pyrrolo[3,4-*b*]pyridine-5-one **17** (Scheme 3).

It is important to highlight that the polyheterocycle **17** was obtained as an inseparable mixture of four stereoisomers due to the presence of two stereogenic centers. The PR-UZ-5CR coupled to the further cascade sequence [intermolecular aza Diels-Alder cycloaddition/intramolecular *N*-acylation/aromatization] did not include any stereocontrolled strategy. In addition, it is worth noting that, probably due to the high symmetry degree of compound **17**, only one highly fluorescent purple spot was visualized by TLC under UV light at 254 nm and 365 nm. The presence of diastereomers is also not evident in the NMR spectra of compound **17** (See the Electronic Supplementary Material for further details).

3. Materials and Methods

3.1. General Information, Instrumentation, Sofware, and Chemicals

Hydrogen-1 (^{1}H) and Carbon-13 (^{13}C) Nuclear Magnetic Resonance (NMR) spectra were acquired on a Bruker Avance III 500 MHz spectrometer (Fällande, Uster, Switzerland), using deuterated chloroform ($CDCl_3$) as the solvent. Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS). Coupling constants (*J*) are expressed in Hertz (Hz), and signal multiplicities are described using the conventional abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). NMR data were processed and analyzed using MestReNova software (version 14.2.0-26256). Reaction progress was monitored by Thin-Layer Chromatography (TLC) on plastic plates pre-coated with silica gel F_{254}, with spot visualization under UV light at 254 nm and 365 nm. Flash column chromatography was carried out on silica gel (230–400 mesh), employing mixtures of hexane and ethyl acetate as the eluent system. These solvent mixtures were also used for TLC development and for the determination of retention factors (R_f). All chemicals and reagents were purchased from Sigma-Aldrich-Merck (Toluca, Estado de

México, Mexico) and used as received, without further purification and/or dehydration. Chemical structures were generated using ChemDraw Professional software (version 15.0.0.106, PerkinElmer Informatics, Cambridge, MA, USA).

3.2. One Pot Synthesis and Characterization of 7,7′-(1,4-Phenylene)bis(2-benzyl-3-(3,4-dihydroisoquinolin-2(1H)-yl)-6-(4-methoxybenzyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one) **17**

In a 10 mL microwave reactor tube (CEM Discover SP system, Matthews, NC, USA) equipped with a magnetic stirrer, 3 mL of toluene (PhMe) was added, followed by the addition of 0.5 mmol (1 equiv.) of benzene-1,4-dicarboxaldehyde and 1 mmol (2 equiv.) of 4-methoxy benzylamine. The reaction mixture was continuously stirred at room temperature for 30 min. Subsequently, 0.04 mmol (8% mol) of ytterbium triflate $Yb(OTf)_3$ was added, and the mixture was subjected to microwave heating at 65 °C and 65 W for 5 min. Then, 1 mmol (2 equiv.) of 1-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-isocyano-3-phenylpropan-1-one was added, and the reaction was continued at 60 °C and 60 W for an additional 25 min. Finally, 1 mmol (2 equiv.) of maleic anhydride was introduced, and the mixture was continuously stirred at room temperature for 15 min. Upon completion of the reaction, the crude mixture was transferred to a 100 mL separatory funnel, followed by the addition of 15 mL of saturated K_2CO_3 solution and 15 mL of ethyl acetate (EtOAc). The organic layer was separated, and liquid–liquid extractions were performed. The organic phase was evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using silica gel as the stationary phase and mixtures of hexane and ethyl acetate as eluents. Final purification was carried out by preparative chromatography, also using silica-gel as the stationary phase and a hexane/ethyl acetate mixture (3:1 *v*/*v*) as the eluent. A slightly yellow solid 0.321 g of the compound **17** (Figure 2) was obtained (63% yield).

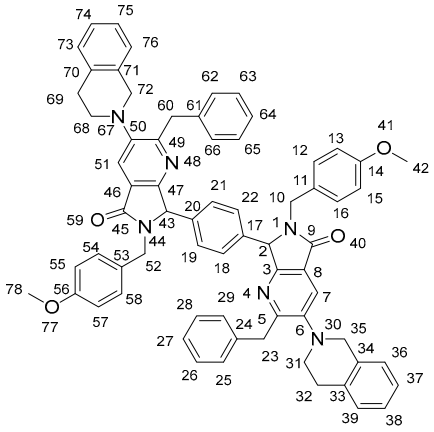


Figure 2. Structure of compound **17**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (s, 2H, H-7, H-51), 7.20–7.06 (m, 24H, aromatics), 7.00–6.95 (m, 2H, H-27, H-64), 6.85 (d, *J* = 8.8 Hz, 4H, H-13, H-15, H-55, H-57), 5.36 (d, *J* = 14.7 Hz, 2H, H-10, H-52), 5.28 (s, 2H, H-2, H-43), 4.28 (d, *J* = 14.0 Hz, 2H, H-23, H-60), 4.21 (d, *J* = 14.0 Hz, 2H, H-23′, H-60′), 4.08–3.99 (m, 4H, H-35, H-72), 3.78 (s, 6H, H-42, H-78), 3.37 (d, *J* = 14.7 Hz, 2H, H-10′, H-52′), 3.22–3.13 (m, 4H, H-31, H-68), 3.04–2.96 (m, 4H, H-32, H-69). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0 (C-9, C-45), 161.9 (C-5, C-49), 159.9 (C-3, C-47), 159.2 (C-14, C-56), 148.2 (C-6, C-50), 139.2 (C-24, C-61), 136.0 (C-17, C-20), 134.3 (C-33, C-70), 133.9 (C-34, C-71), 129.8 (C-12, C-16, C-54, C-58), 128.9 (C-11, C-53), 128.8 (C-25, C-29, C-62, C-66), 128.7 (C-36, C-76), 128.1 (C-26, C-28, C-62, C-65, C-18, C-19, C-21, C-22), 126.3 (C-37, C-75), 126.1 (C-27, C-64), 125.9 (C-38, C-74), 123.9 (C-8, C-46), 123.6 (C-7, C-51), 114.2 (C-13, C-15, C-55, C-57), 64.0 (C-2, C-43), 55.4 (C-35, C-72), 50.9 (C-31, C-68), 43.4 (C-10, C-52),

39.7 (C-23, C-60), 29.5 (C-32, C-69); HRMS (ESI$^+$): m/z calcd for $C_{68}H_{61}N_6O_4$ $[M + H]^+$ 1025.4749, found 1025.4748 (error = 0.1 ppm); IR (υ, cm^{-1}): 3429 (N-H), 1709 (C=O), 1430 (C-C), 1357 (C-O), 1220 (C=C).

4. Conclusions

The one-pot synthesis of the highly symmetric polyheterocycle **17** as an inseparable mixture of stereoisomers exemplifies the strategic coupling of multiple bond-forming transformations (MBFTs). Specifically, the current one that involves a pseudo-repetitive Ugi–Zhu 5C reaction (PR-UZ-5CR) followed by an intermolecular *aza* Diels–Alder/intramolecular *N*-acylation/tandem aromatization process, leading to the rapid formation of a bilaterally symmetric dimer that incorporates the privileged tetrahydroisoquinoline moiety. This methodology demonstrates impressive atom economy (85%), producing only four molecules of water and two molecules of carbon dioxide as byproducts. Furthermore, the reaction is conducted under mild reaction conditions, eliminating the need for elevated temperatures and highlighting the advantages of pseudo-repetitive-type multicomponent reactions over their non-pseudo-repetitive counterparts. Lastly, the inherent symmetry and the presence of privileged heterocyclic motifs within the final structure suggest that the resulting polyheterocycle may possess significant potential for biological activity against specific molecular targets.

Supplementary Materials: The following supporting information can be downloaded online. Figure S1. ^{1}H-NMR spectrum ($CDCl_3$, 500 MHz) of compound **17**; Figure S2. ^{13}C-NMR spectrum ($CDCl_3$, 125 MHz) of compound **17**; Figure S3. 2D-NMR (COSY) spectrum of compound **17**; Figure S4. 2D-NMR (HSQC-part I) spectrum of compound **17**; Figure S5. 2D-NMR (HSQC-part II) spectrum of compound **17**; Figure S6. 2D-NMR (HMBC-part I) spectrum of compound **17**; Figure S7. 2D-NMR (HMBC-part II) spectrum of compound **17**; Figure S8. 2D-NMR (HMBC-part III) spectrum of compound **17**; Figure S9. HRMS (ESI$^+$-TOF) spectrum of compound **17**; Figure S10. FT-IR (ATR) spectrum of compound **17**.

Author Contributions: Synthesis and characterization, R.E.B.-C.; data curation, A.I.-J.; investigation, E.G.-Z.; writing—original draft preparation, R.E.B.-C. and A.I.-J.; funding acquisition and writing—review and editing, A.I.-J. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

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