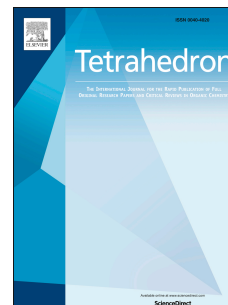


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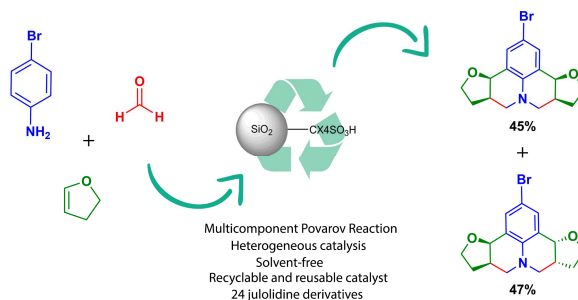
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Graphical Abstract

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^a Grupo de Química Supramolecular e Biomimética (GQSB), Departamento de Química, CCE, Universidade Federal de Viçosa, Viçosa, MG, 36570-900, Brazil.

^b Centro de Investigación y Desarrollo en Ciencias Aplicadas "Dr. Jorge J. Ronco" (CINDECA-CCT-CONICET), Universidad Nacional de La Plata, Calle 47 No 257, B1900AJK La Plata, Argentina.

^c Instituto de Química, Universidade Federal de Goiás, Campus Samambaia, Goiânia, GO, CP 131, 74001-970, Brazil.

^d Departamento de Química, Universidade Federal de Juiz de Fora, Juiz de Fora, MG, 36036-900, Brazil.

*Corresponding author: sefernandes@gmail.com or santonio@ufv.br

ABSTRACT: The application of immobilizing calixarene onto the surface of silica using a sol-gel method, as an efficient heterogeneous catalyst (CX4SO₃HSi(*n*)) for multicomponent Povarov reaction has been described. Catalytic activity of the CX4SO₃HSi(*n*) for the synthesis of julolidines under greener and environmentally benign conditions in simple and efficient method was explored. Notably, only 0.5 mol% of the catalyst is sufficient to catalyze the Povarov solvent-free reaction under microwave-assistance. Besides, this protocol allows the construction of four new C-C bonds and two C-N bonds in a single step. To the best of our knowledge, this consists the first silica supported calix[4]arene as a heterogeneous catalyst for multicomponent synthesis of julolidines.

KEYWORDS: calixarenes, heterogeneous catalysis, julolidines, microwave-assisted, multicomponent reactions

1. Introduction

High-efficiency catalysis is an inevitable topic of discussion in our society given our heavy reliance on it. The for development and advances in technology in order to meet the demands of a growing population for a sustainable synthetic chemistry.¹ Although homogeneous acid catalysis has attracted greater attention, their applications in industrial processes are hindered by the high cost, recovery catalyst, corrosion, toxicity and environmental safety. Recently, the combination of the chemical properties of acid organocatalysts and different solid supports such as carbon, polymers, silica and other metal oxides have received significant attention.²

In the last years, research interest in calix[*n*]arene chemistry has increased dramatically due to their applications in several fields of chemistry, such as gels and films with fluorescent properties,³ molecular recognition,⁴ self-assembling systems,⁵ mechanically interlocked molecules,⁶ and nanoporous materials.⁷ The application of calix[*n*]arenes as organocatalysts in organic synthesis has become very popular.⁸ On the other hand, the application of calix[*n*]arenes as a heterogeneous catalyst for the chemical transformations remains largely unexplored.^{2c,9}

Julolidine and their derivatives are one of the most versatile and important classes of *N*-heterocyclic and have attracted enormous attention from the scientific community for the potential in many applications such as for metal sensing,¹⁰ dye-sensitized solar cells,¹¹ antiviral activity,¹² antidepressants,¹³ tranquilizers,¹⁴ fluorescent probe,¹⁵ and nonlinear optical materials¹⁶ (Figure 1).

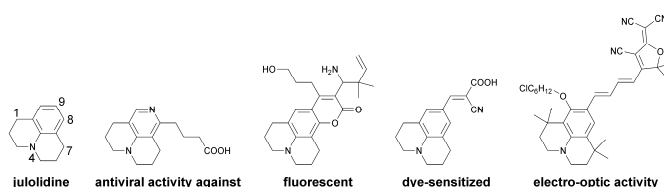


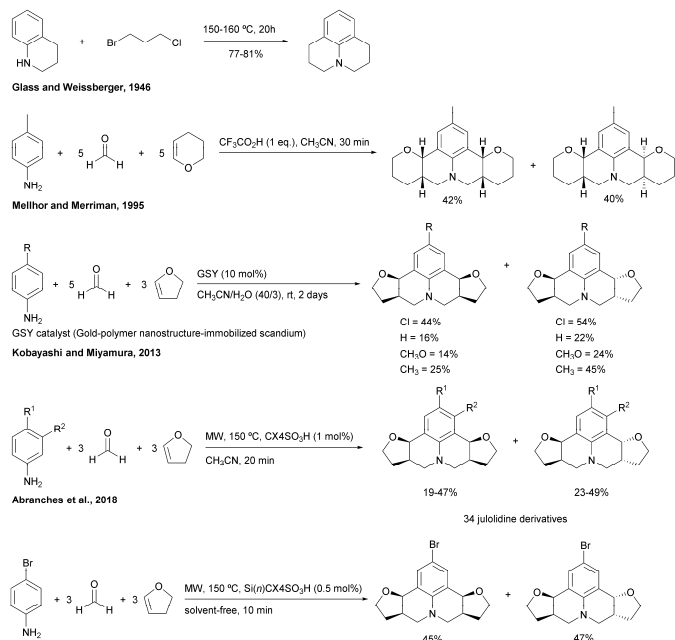
Figure 1. Some examples and application of julolidine derivatives.

The traditional strategies for syntheses of julolidines usually involve a reaction of an aniline or tetrahydroquinoline with 1-bromo-3-chloropropane¹⁷ (Scheme 1). Traditional method has the disadvantage of offering few alternatives for introducing substituents into the julolidine skeleton, in C-8 or C-9 and especially in the alkyl moiety.¹⁸

Multicomponent reactions (MCRs), defined as one-pot reactions, constitute an important group of transformations that combine many aspects of an ideal synthesis, such as operational simplicity, atom economy, bond forming efficiency, facile automation, reduction in the number of workup, extraction and purification processes, and hence minimize waste generation, rendering the green and sustainable transformations in synthetic chemistry.¹⁹ The modularity of this approach is extremely suitable for the synthesis of functional materials, and it is, therefore, widely used for the fast generation of molecules for high-tech applications.²⁰ The multicomponent Povarov reaction (MCPR) of an *in situ* generated imine and an electron-rich dienophile under acid catalysis conditions is a versatile and

widely used synthetic technique adding aspects of sustainability for the construction of tetrahydroquinolines,^{8a, 21} and quinolines.²²

The MCPR appears as a green alternative for the synthesis of julolidines derivatives and remains largely unexplored²³ (Scheme 1). Herein, a simple, effective and eco-friendly approach to the MCPR of julolidines derivatives using silica supported *p*-sulfonic acid calix[4]arene (CX4SO₃H*(n)*) as a recoverable and reusable heterogeneous catalyst under solvent-free conditions is presented.

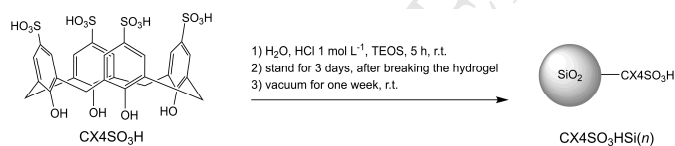


This work, transition-metal-free, solvent-free, Povarov Reactions (MCPRs)
Scheme 1. Different Variation on the Pathways for the Synthesis of Julolidines.

2. Results and Discussion

2.1. Catalysis synthesis CX4SO₃H*(n)*

Catalysts was synthesized using a sol-gel technique. A mixture of CX4SO₃H, water and a hydrochloric acid solution was added to tetraethyl orthosilicate. The mixture was stirred for 5 h at room temperature. Then, the mixture was allowed to stand for 3 days, and after breaking the formed hydrogel with a Teflon stick, the sample was dried in a vacuum for one week at room temperature.^{2e}



Scheme 2. Synthesis of the catalyst CX4SO₃H*(n)*.

2.2. Acid-based property

The ion exchange capacities of CX4SO₃H*(n)* were determined by acid-base titration and potentiometric titration. The acid capacity of the sample CX4SO₃H*(n)* catalyst was determined by titration with 5 x 10⁻³ M NaOH_(aq),²⁴ being found a value of 0.32 mmol H⁺/g of catalyst. The strength of the acid sites, obtained by potentiometric titration with *n*-butylamine, can be classified according to the following scale: E > 100 mV (very strong sites); 0 < E < 100 mV (strong sites); -100 < E < 0 mV (weak sites) and E < -100 mV (very weak sites).²⁵ The acid strength for CX4SO₃H*(n)* catalyst was 205 mV, indicating the presence of very strong sites.

2.3. X-Ray diffraction

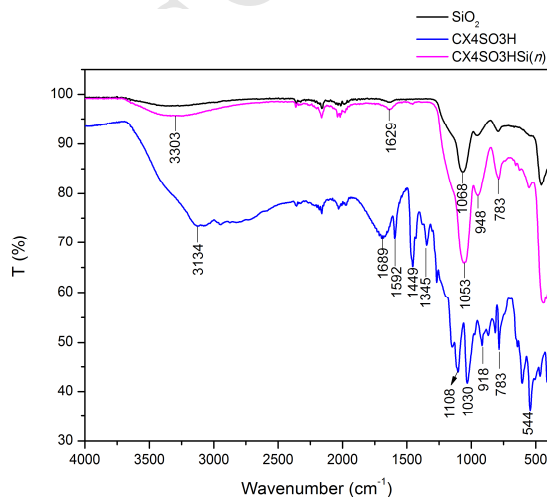
The XRD pattern peaks were obtained between 5° and 50°. Even though no X-ray diffraction peaks were detected in the XRD pattern of the supported samples, the presence of some ordering cannot be ruled out because they may be less than 40 Å in size, which is beyond the detection limit of the XRD technique. The broad X-ray diffraction patterns may indicate long-range disordered nature.^{2e}

2.4. Elemental analysis determination

The elemental analysis of the included CX4SO₃H show a carbon content of 5.92%, corresponding with a % w/w of active phase of the CX4SO₃H*(n)* catalyst in the silica matrix of 15.1%.

2.5. FT-IR analysis

Figure 2 shows the FTIR spectra of activated mesoporous silica, CX4SO₃H and CX4SO₃H*(n)*. The FTIR spectrum of unmodified mesoporous silica is relatively simple and well assigned.²⁶ The strong absorption band at 1068 cm⁻¹ is attributed to the Si–O–Si bending of silica, while the absorbance at 1629 and 3298 cm⁻¹ is assigned to the surface hydroxyl groups of the



mesoporous silica (Figure 2).

Figure 2. FTIR spectra of (—) SiO₂, (—) CX4SO₃H and (—) CX4SO₃H*(n)*.

A typical spectrum of CX4SO₃H (Figure 2) presents four main bands at 3134, 1449, 1030 and 783 cm⁻¹ which are assigned to the OH bond of the phenol group, the weak absorption peak of due to the methylene CH bending, the strong absorption peak of S–O bond and the CX4SO₃H aromatic hydrogen angular deformations, respectively.²⁷ The spectrum of CX4SO₃H*(n)* (Figure 2) presents four main bands at 3303, 1449, 1053 and 783 cm⁻¹ assigned to the stretching hydroxyl group stretching from both mesoporous silica and the CX4SO₃H molecule, the weak absorption peak of methylene bridges, the strong absorption peak of S–O which broadened the angular deformation band the peak of Si–O–Si and CX4SO₃H aromatic hydrogens, respectively.²⁸

2.6. ¹³C and ²⁹Si MAS-NMR

¹³C MAS-NMR of pure CX4SO₃H (Figure 3a) present the following peaks: 30.1 (-CH₂-); 127.9 (Ar); 137.0 (Ar); 150.6 (Ar). These signals are also present in the CX4SO₃H*(n)* (Figure 3b), which proves that the CX4SO₃H structure is maintained after the inclusion. Remaining ethoxy groups of the tetraethyl orthosilicate give peaks at 9.8 and 71.2 ppm; these peaks possess a small linewidth due to the high mobility of the ethoxy groups.²⁹

²⁹Si MAS-NMR of CX4SO₃H*(n)* catalyst are shown in Figure 3d. Three overlapping signals are present at -111.2 (53.7);

-101.7 (38.4); -91.8 (7.9) which can be assigned to Q4, Q3 and Q2, respectively.^{29,30} The same group of signals can be seen in pure silica (Figure 3c) showing that the support structure is maintained after the CX4SO₃H inclusion. The average distribution of Q4, Q3, and Q2 are according to literature.²⁹ The amount of geminal silanols (Q2) has a small increase when the CX4SO₃H is present.

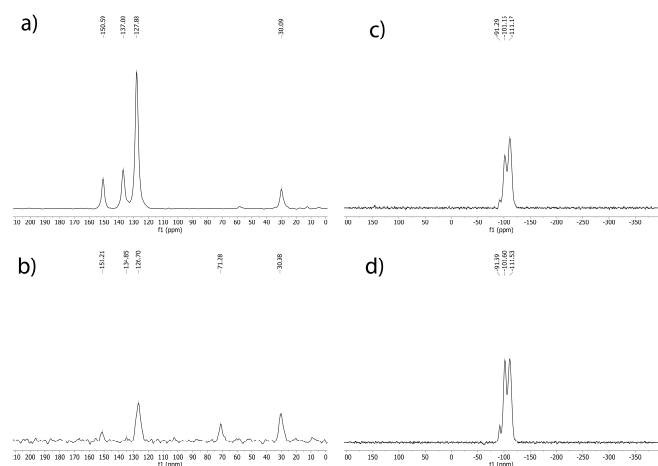
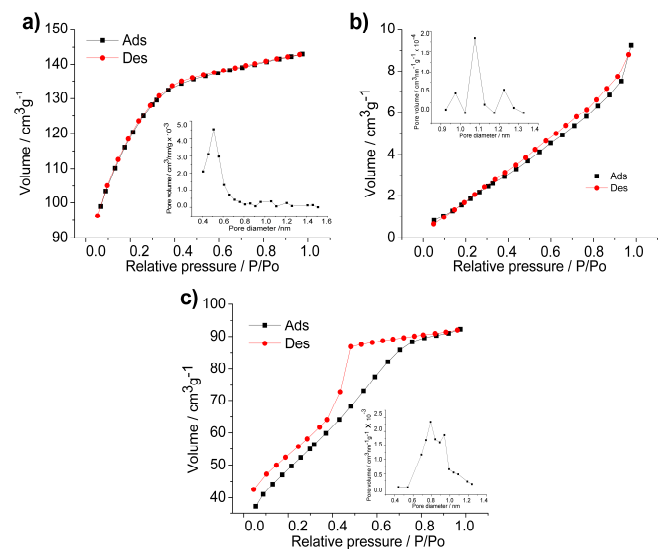


Figure 3. Solid-state NMR spectra: a) ¹³C NMR of CX4SO₃H; b) ¹³C NMR of CX4SO₃HSi(*n*); c) ²⁹Si NMR of support; d) ²⁹Si NMR of CX4SO₃HSi(*n*).

2.7. Textural properties

The porosity of a) silica, b) CX4SO₃H and c) CX4SO₃HSi(*n*) was measured using nitrogen physisorption and the adsorption-desorption isotherms are compared in Figure 4. The Barrett-Joyner-Halenda (BJH) pore size distribution (*i.e.*, insert on Figure 4) shows that the silica has a higher range of pore diameter (ca. 0.4 to 1.6 nm) with maximum at ca. 0.5 nm (Figure 4a), while CX4SO₃H has range of pore diameters (ca. 0.9 to 1.35 nm), with a well-defined maximum at 1.1 nm (Figure 4b). Conversely, the CX4SO₃HSi(*n*) presented an intermediate range of pore diameter (ca. 0.4 to 1.25 nm), with a maximum of 0.8 nm. The bimodal BJH pore size distribution was observed for CX4SO₃HSi(*n*), whereas the unimodal mesoporous distribution of silica before immobilization is an evidence of this material of its microporosity. This behavior was previously noticed by Katz et al, which immobilized calixarenes derivatives onto surface of



silica.³¹

Figure 4. a) BJH method of pore size distribution for silica, b) CX4SO₃H and c) CX4SO₃HSi(*n*).

On the other hand, the adsorption-desorption isotherms obtained from silica and CX4SO₃H (Figure 4a and b) were substantially different from that obtained from silica-supported CX4SO₃HSi(*n*) (Figure 4c). Typically, the BET isotherms obtained from silica were of type I, typical of microporous solids. The isotherms of calix[4]arene were type III, typical of solids with low porosity (*i.e.*, nonporous or microporous materials).³² Conversely, the silica-supported calix[4]arene presented isotherms typical of mesoporous solids (Type V).³³ Indeed, the hysteresis observed in the isotherms of Fig 5c was generated by differences in the processes of adsorption/desorption. This behavior may be assigned to the capillary condensation phenomena, triggered by inclusion of calix[4]arene (a solid with lower porosity) into silica (*i.e.* a microporous solid). The supporting of calix[4]arene on the silica surface generated a mesoporous solid, where the adsorption on mesoporous solids proceeds via multilayer adsorption followed by capillary condensation, resulting in a Type V isotherm.

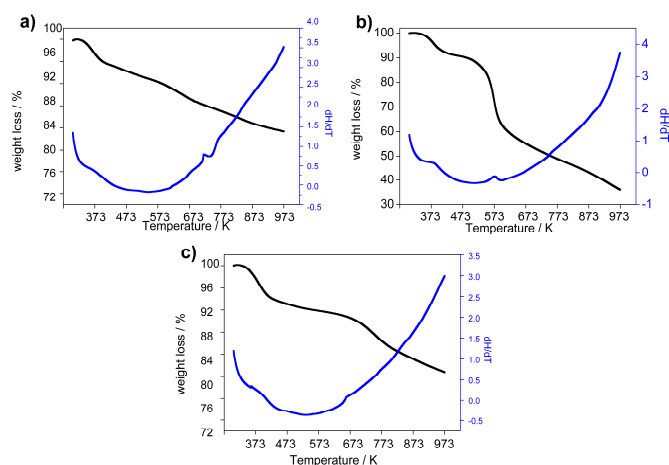
Table 1 shows the surface area and porous volume of the support, CX4SO₃H and CX4SO₃HSi(*n*) catalyst, respectively. The inclusion of CX4SO₃H in the silica matrix generates a material with an area 10 times larger than the bulk CX4SO₃H (Table 1).

Table 1. Surface and porosity parameters of Silica, CX4SO₃H and CX4SO₃HSi(*n*).

Entry	Catalyst	Surface area (m ² g ⁻¹)	Pore volume (m ³ g ⁻¹)
1	Silica	52.729	0.199
2	CX4SO ₃ H	2.842	0.013
3	CX4SO ₃ HSi(<i>n</i>)	33.958	0.131

2.8. Thermogravimetric analysis (TGA)

The thermal stability of the organosilicas was examined by thermogravimetric analysis (TGA). TG curves of (a) silica, (b) CX4SO₃H and (c) CX4SO₃HSi(*n*) were determined (Figure 5). TG curves showed that silica and CX4SO₃HSi(*n*) exhibited a lower mass loss than CX4SO₃H (ca. 16 % for (a) and (c), and 65 % for (b), respectively). The stage of mass loss started below 100 °C due to loss of the adsorbed water. Differently than TG curve of silica that presented only a well-defined stage of mass loss (Figure 5a), CX4SO₃H (Figure 5b) and CX4SO₃HSi(*n*) (Figure 5c) had two steps where the decrease of mass was well noticed. The second decrease of mass observed in the last two TG curves should be of (b) and (c) should be attributed to the decomposition of CX4SO₃H.³⁴ This change in the TG curve of CX4SO₃HSi(*n*) relative to that of pure silica demonstrates that silica was successfully modified with CX4SO₃H. Furthermore, the profile of curves shown in Figure 5 agree with literature data.³⁵ The endothermic peak on DSC curve of CX4SO₃H may be assigned to the decomposition of sulfonic groups of CX4SO₃H, which was



less pronounced in the DSC curve of CX4SO₃HSi(*n*).

Figure 5. High-resolution thermogravimetric analysis (TG) of a) silica, b) CX4SO₃H and c) CX4SO₃HSi(*n*).

2.9. Application of CX4SO₃HSi(*n*) in the synthesis of julolidines

The excellent results for synthesis of julolidines employing CX4SO₃H,^{23a} mentioned above, inspired us to use CX4SO₃HSi(*n*) as a heterogeneous catalyst to obtain julolidines. The heterogeneous CX4SO₃HSi(*n*) catalyst, previously prepared, was employed in all reactions. In order to determine the best reaction condition, 4-bromoaniline (**1a**), formaldehyde (**2**) and 2,3-dihydrofuran (**3**) were used as substrates and the reactions were carried out in the presence of CX4SO₃HSi(*n*) as catalyst (0.5 mol%) under microwave irradiation. A series of solvents as well as solvent-free conditions (Table 2, entry 1-6) were tested to determine the best condition for obtaining julolidines in very good yields. The use of water^{8a}, methanol or ethanol as protic solvents yielded the julolidine 1[(±)-T+C] in 14%, 79% and 53%, respectively (Table 2, entries 1-3). The 1[(±)-T+C] was also obtained in good yield when aprotic solvents, such as acetonitrile or solvent-free were used (Table 2, entries 4 and 5). Once determined that a solvent-free reaction was the best condition to obtain 1[(±)-T+C], we further investigated what the minimum amount of catalyst CX4SO₃HSi(*n*) required to achieve the maximum reaction yield. The 1[(±)-T+C] yield decreased to 57% and 56% when the amount of CX4SO₃HSi(*n*) was increased from 0.5 mol% to 1.0 mol% and 2.0 mol% (Table 2, entries 5-7). By using the microwave irradiation and different power (50, 100, 200 and 300 W), the 1[(±)-T+C] yield decreased to 92%, 87%, 85% and 70% when the power was increased from 50 W, 100 W, 200 W and 300 W (Table 2, entries 5 and 8-10). The yield of 1[(±)-T+C] decreased to 59% when the reaction time was decreased to 5 min (Table 2, entry 11), and the yields also decrease for longer reaction times (Table 2, entries 12 and 13). The 1[(±)-T+C] yield in the catalyst-free reactions or in the presence of the support (TEOS) reactions was 25 and 9%, respectively (Table 2, entries 14 and 15). Overall, the use of solvent-free, a reaction time of 10 min, and 0.5 mol % of CX4SO₃HSi(*n*) catalyst provided 1[(±)-T+C] in excellent yield (92%).

Table 2. Effect of the solvents, catalyst loading, power and reaction time on the formation of julolidines^a.

Entry	Solvent	Power (W)	Catalyst loading (mol %)	Time (min)	Total yield ^b (%)
1	H ₂ O	100	0.5	10	14
2	MeOH	100	0.5	10	79
3	EtOH	100	0.5	10	53
4	MeCN	100	0.5	10	84
5	-	100	0.5	10	87
6	-	100	1.0	10	57
7	-	100	2.0	10	56
8	-	200	0.5	10	85
9	-	300	0.5	10	70
10	-	50	0.5	10	92
11	-	50	0.5	5	59

12	-	50	0.5	15	24
13	-	50	0.5	20	24
14	-	50	-	10	25
15	-	50	support	10	9

^aReaction conditions: 4-bromoaniline **1a** (0.5 mmol), formaldehyde **2** (1.5 mmol), 2,3-dihydrofuran **3** (1.5 mmol). ^bTotal yield 1[(±)-T+C] for the crude mixture of (±)-1T and 1C was determined by GC/MS analysis.

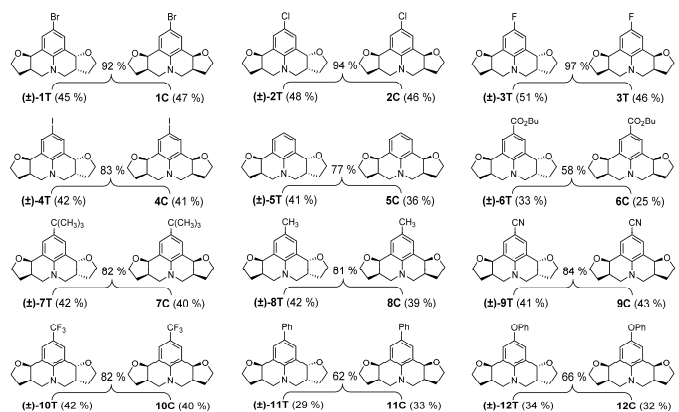
The catalytic activity of CX4SO₃HSi(*n*) was compared to that of two commercial heterogeneous Bronsted acids, Amberlyst and H₃PW₁₂O₄₀. Notably, the use of CX4SO₃HSi(*n*) was considerably more efficient than the other catalysts tested for this reaction (Table 3, entries 1-3).

Table 3. Effect of different heterogeneous catalysts on the formation of julolidines^a.

Entry	Catalyst	Yield ^b (%)
1	CX4SO ₃ HSi(<i>n</i>)	92
2	Amberlyst® IRA-400	23
3	H ₃ PW ₁₂ O ₄	31

^aReaction conditions: 4-bromoaniline **1a** (0.5 mmol), formaldehyde **2** (1.5 mmol), 2,3-dihydrofuran **3** (1.5 mmol). ^bTotal yield 1[(±)-T+C] for the crude mixture of (±)-1T and 1C was determined by GC/MS analysis.

Given the optimized reaction conditions for the synthesis of 1[(±)-T+C] (solvent-free, CX4SO₃HSi(*n*), 0.5 mol%, PW 50 W and 10 min), the generality of the MCPR was evaluated. For this purpose, aromatic anilines containing electron-donating and electron-withdrawing groups at *para*-position aromatic ring were evaluated (Scheme 3). The best yields were obtained for the *p*-halogen-substituted anilines (F (97%), Cl (94%), Br (92%) and I (83%)). These yields were very similar than those obtained by other methods for *p*-fluor, *p*-bromine and higher for anilines Cl, I, H and CH₃ for *p*-substituted.^{23a} The substituents on the aniline ring had no noticeable effect on the diastereomeric excess (Scheme 3). In general, low stereoselectivity is observed in the reaction.^{23a, 23b, 23d, 23e, 36} The *cis/trans* isomerism of the synthesized compounds was determined by ¹H NMR based on the values of the coupling constants (*J*_{cis} and *J*_{trans}) and the chemical shift values (compared to the previously reported results).^{23a} Despite the low selective ratio between diastereomers, the reactivity was impressive and both diastereomers could be characterized.



Suitably-shaped crystals of the (\pm)-*trans* diastereomer could be isolated and allowed for its structure elucidation by the single-crystal X-ray diffraction technique. As can be viewed in Figure 6, its relative configuration was unambiguously determined from this experiment. All methine carbons have *S*-stereochemistry in the chosen asymmetric unit, which is shown in this picture, even though the enantiomeric counterpart with *R*-stereochemistry for these four carbons is also present in the crystal lattice due to the crystallization in a centrosymmetric space group (monoclinic $C2/c$).

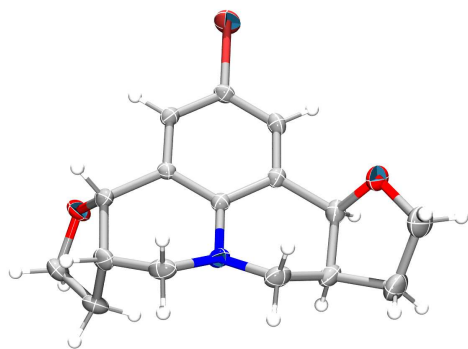
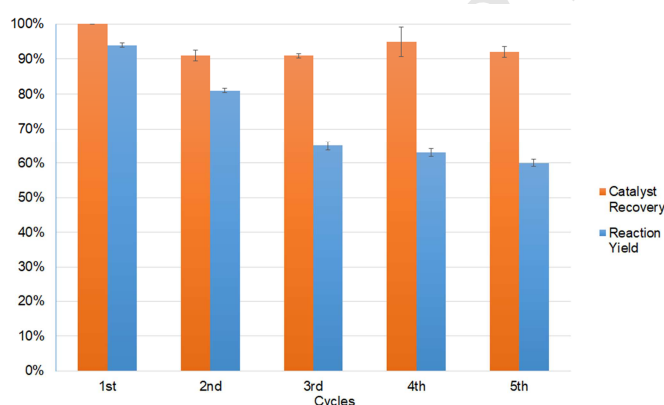


Figure 6. View of the chosen asymmetric unit of the (\pm)-*trans* diastereomer with non-hydrogen atoms represented by their corresponding 30% probability ellipsoids.

2.10. Catalyst Recycling

According to the principles of green chemistry that seek to sustainable synthetic chemistry, the recovery and reuse of the catalyst is quite important. The catalyst recycling experiment was conducted using the model reaction of 4-bromoaniline (1a), formaldehyde (2), 2,3-dihydrofuran (3), and $CX_4SO_3HSi(n)$ catalyst in solvent-free under microwave irradiation, conditions optimized. These results are summarized in Figure 7. After completion of the reaction, dichloromethane was added, and the catalyst recovered for upon filtration. After recovery, the catalyst was obtained as a solid residue in approximately 90% crude yield (Figure 7). The catalyst a significant decrease in yields with consecutive catalytic cycles was observed, which can be



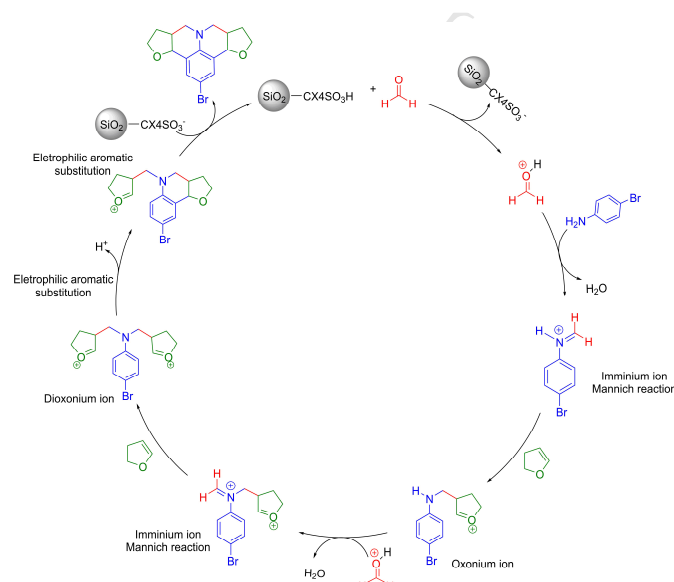
attributed to deactivation of the catalyst.

Figure 7. Recovery and reuse of $CX_4SO_3HSi(n)$ as the catalyst in the synthesis of 1[(\pm)-T+C]. Yield determined by GC/MS.

2.11. Reaction Mechanism

Based on the recently published work by Abranches et al.^{23a} and on the interception and the interception of oxonium and dioxonium ion by methanol, the catalytic cycle for the formation of the julolidine is presented in Scheme 4. The first step consists of the reaction between 4-bromoaniline and the

activated formaldehyde to provide the iminium ion *via* a Mannich reaction (Scheme 4). The addition of 2,3-dihydrofuran to the iminium ion forms the corresponding oxonium ion (Scheme 4). Then, the formation of a second iminium ion occurs, which subsequently leads to the formation of the dioxonium ion (Scheme 4). That is followed by an intramolecular electrophilic aromatic substitution to furnish the tetrahydroquinoline oxonium ion, which undergoes a second electrophilic aromatic substitution reaction to form the final julolidine and regenerate the $CX_4SO_3HSi(n)$ catalyst.



Scheme 4. Proposed Catalytic Cycle for the Synthesis of Julolidines.

3. Conclusions

In the present article, we have successfully functionalized the surface of mesoporous silica *via* sol-gel by *p*-sulfonic acid calix[4]arene heterogeneous catalyst $CX_4SO_3HSi(n)$ and characterized by BET, FT-IR, TGA, ^{13}C and ^{29}Si NMR. The catalyst then applied in the multicomponent reaction of Povarov under solvent-free conditions with high catalytic activity in the synthesis of julolidines. Two main diastereomers, *cis* and (\pm)-*trans*, were obtained and fully characterized. Moreover, the method allows the formation of four new C-C and two C-N bonds in a one-step stepwise transformation. Recyclability and reuse of the $CX_4SO_3HSi(n)$ catalyst was established for up to five successive runs without no dramatic loss in the reaction profile. The relative configurations of the product 1-(\pm)-*trans* was determined by X-ray crystallographic experiments. This consists the first silica support calix[4]arene as a heterogeneous catalyst for multicomponent synthesis of julolidines.

4. Experimental

4.1. General Information

Analytical grade commercial solvents and reagents included *p*-sulfonic acid calix[4]arene (CX_4SO_3H) were purchased from Sigma Aldrich, Fluka, and Merck, and used as received. Column chromatography was carried out using 0.063–0.2 mm silica gel (DavisilR LC60A 40–63 Micron) with the indicated solvent. Thin layer chromatography (TLC) was carried out using 0.2 mm Kieselgel F₂₅₄ (Merck) silica plates, and compounds were visualized using UV irradiation at 365 nm.

Infrared spectra were recorded as neat using a FT-IR Varian 660 Fourier transform infrared spectrometer. Values are expressed in wavenumbers (cm^{-1}) and recorded in a range of 4000–400 cm^{-1} .

NMR spectra were recorded at 25 °C in CDCl₃ on a Varian Mercury 300 spectrometer operating at 300 MHz for ¹H and 75 MHz for ¹³C, and on a Bruker Avance III HD 500 spectrometer operating at 500 MHz for ¹H and 125 MHz for ¹³C. Solid-state NMR spectra were performed a Bruker Avance III HD 300 spectrometer operating at 75 MHz for ¹³C and 60 MHz for ²⁹Si.

All chemical shifts are reported in parts per million (ppm) and were measured relative to the solvent in which the sample was analyzed (CDCl₃ δ = 7.26 for ¹H NMR and δ = 77.0 for ¹³C NMR). Coupling constants (*J*) are reported in hertz (Hz).

Mass spectrum and diastereoselectivity were determined by gas chromatography coupled to a mass spectrometer using a SHIMADZU GCMS-QP2010C Ultra mass spectrometer and the method with the following specifications: column RTx-5 MS, 30 m, DI 0.25 mm; carrier gas helium; injector temperature of 290 °C; oven temperature of 40 °C (2 min), ramped at 20 °C min⁻¹ up to 300 °C (held for 15 min).

4.2. CX₄SO₃H included in silica sol-gel framework synthesis

The CX₄SO₃HSi(*n*) catalyst was prepared following a procedure reported in the literature with some minor modification.²⁶ A mixture of CX₄SO₃H (0.600 g), water (4.5 mL) and 1 mol L⁻¹ hydrochloric acid (0.5 mL) was added to tetraethyl orthosilicate (12.50 mL). The mixture was stirred for 5 h at room temperature. Then, the mixture was allowed to stand for 3 days, and after breaking the formed hydrogel with a Teflon stick, the sample was dried under vacuum for one week at room temperature. The powdered sample was washed with distilled water (3 x 10 mL) and dried under vacuum.

4.3. Catalytic characterization

4.3.1. Acidity determination in aqueous media

The acid capacity was determined by titration with 5 x 10⁻³ M NaOH_(aq). In a typical experiment, 30 mg of solid CX₄SO₃HSi(*n*) was added to 10 mL of deionized water. The resulting suspension was allowed to equilibrate and the titrated by dropwise addition of a 5 x 10⁻³ M NaOH solution using phenolphthalein (0.2 %) as the pH indicator.²⁴

4.3.2. Acidity determination in non-aqueous media

The catalyst acidity of CX₄SO₃HSi(*n*) catalyst (50 mg) was determined by potentiometric titration of a suspension consisting of the solid catalyst in acetonitrile using a solution containing *n*-butylamine in acetonitrile (0.025 N) in a Metrohm 794 Basic Titrino apparatus with a double junction electrode.²⁵

4.3.3. Textural Properties

The specific surface area of the solids was determined from the N₂ adsorption-desorption isotherms at liquid nitrogen temperature. They were obtained using Micromeritics ASAP 2020 equipment. The samples were previously degassed at 100 °C for 12 h. The specific surface area (SBET) was determined by the BET method. The samples were degassed prior the analyses.

4.3.4. Thermogravimetric analysis

The thermogravimetric analysis was performed on a Perkin Elmer Simultaneous Thermal Analyzer (STA) 6000. The masses of the samples used were between 5-10 mg, with a heating rate of 10 °C min⁻¹ under nitrogen flow. The temperatures of the thermograms were recorded at each variation of 0.1 °C in a range of 30 °C to 700 °C. This technique allows to verify the loss of mass at different temperatures and verify the degree of hydration of the catalysts.

4.3.5. Elemental analysis determination

Elemental analyses were obtained by using a CHN Perkin-Elmer 2400 instrument.

Room temperature X-ray diffraction intensity data were measured employing MoK α beam from an I μ S microsource with multilayer optics (Bruker-AXS Kappa Duo diffractometer with an APEX II CCD detector). The diffraction images were acquired upon rotation of the ϕ and ω axes. After integration, reduction and scaling of raw X-ray intensity data, the structure was solved with SIR2004³⁷ using direct methods of phase retrieval. The Br, C, O, and N atoms were found directly from the solved Fourier map. In sequence, the initial model was refined by the full-matrix least squares method with SHELXL-2014³⁸ on F2. Non-hydrogen and hydrogen atoms were refined with anisotropic and isotropic [$U_{iso}(H) = 1.2U_{eq}$] atomic displacement parameters, respectively. Hydrogens coordinates were stereochemically calculated following a riding model [C—H bond lengths of either 0.93 Å (aromatic), 0.97 Å (methylene), or 0.98 Å (methine)]. The program ORTEP-3³⁹ was used to prepare the molecular drawing. The final crystallographic information file (CIF) has been deposited with the Cambridge Structural Data Base under deposit code 1898736.

4.5. General procedure for the synthesis of julolidines (1-12[(±)-T+C])

A mixture of aniline (0.5 mmol), formaldehyde (1.5 mmol), 2,3-dihydrofuran (1.5 mmol) and CX₄SO₃HSi(*n*) (15 mg, 0.5 mol %) was added to a vial sealed and placed in a CEM Discover microwave oven. The reaction mixture it was subjected to microwave irradiation for 10 min under stirring, the temperature of 150 °C and power of 50 W, solvent-free. Subsequently, dichloromethane was added to the reaction mixture and then filtered for recovery and reuse of the solid (catalyst). The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography. Twenty-four julolidines were obtained. ¹H, ¹³C NMR, GC/MS and Infrared characterized all the julolidines 1-12[(±)-T+C].

4.5.1. (3*bR*,6*aR*,9*aR*,12*aR*)-2-bromo-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline ((±)-**1T**).

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 6:2:1 v/v) afforded 75.3 mg of the title product in 45% yield as a yellow solid. Mp: 111.1 – 112.3 °C. ¹H NMR (300 MHz; CDCl₃): δ 1.83-1.95 (m, 2H); 2.10-2.22 (m, 2H), 2.53-2.64 (m, 2H), 2.81 (dd, *J* = 7.6, 11.4 Hz, 2H), 2.98 (dd, *J* = 4.2, 11.4 Hz, 2H), 3.79 (td, *J* = 7.2, 8.4 Hz, 2H); 3.88 (td, *J* = 5.4, 8.4 Hz, 2H), 4.68 (d, *J* = 6.6 Hz, 2H), 7.36 (s, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 29.3 (CH₂), 36.1 (CH), 51.1 (CH₂), 65.8 (CH₂), 75.0 (CH), 110.2 (CH), 124.4 (C), 133.0 (C), 142.7 (C). IR (neat): 2960, 2920, 2851, 1590, 1047, 865, 616. GC/MS *m/z* (abundancy %): 335 (49, M⁺), 337 (46, M+2), 292 (100), 55 (46).

4.5.2. (3*bR*,6*aR*,9*aS*,12*aS*)-2-bromo-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline (**1C**).

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 6:2:1 v/v) afforded 78.7 mg of the title product in 47% yield as a yellow solid. Mp: 89.4 – 89.9 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.68-1.80 (m, 2H); 2.20-2.32 (m, 2H), 2.44-2.53 (m, 2H), 2.56 (dd, *J* = 9.6, 12 Hz, 2H), 2.94 (dd, *J* = 3.8, 9.6 Hz, 2H), 3.80 (td, *J* = 6.3, 9.0 Hz, 2H), 3.95 (td, *J* = 6.3 e 8.4 Hz, 2H), 4.47 (d, *J* = 4.5 Hz, 2H), 7.41 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 30.0 (CH₂), 35.3 (CH), 51.0 (CH₂), 65.2 (CH₂), 75.3 (CH), 109.8 (CH), 123.7 (C), 133.6 (C), 143.2 (C). IR (neat): 2918, 2855, 2825, 1591, 1050, 871, 618. GC/MS *m/z* (abundancy %): 335 (54, M⁺), 337 (54, M+2), 292 (100), 55 (47).

4.5.3. (3*bR*,6*aR*,9*aR*,12*aR*)-2-chloro-110.4 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.82-1.93 (m, 2H), 2.10-2.21 (m, 2H), 2.51-2.62 (m, 2H), 2.81 (dd, J = 7.6, 11.4 Hz, 2H), 2.98 (dd, J = 4.5, 11.4 Hz, 2H), 3.78 (td, J = 7.5, 8.4 Hz, 2H), 3.87 (td, J = 5.4, 8.4 Hz, 2H), 5.16 (d, J = 6.3 Hz, 2H), 7.52 (s, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 29.3 (CH₂), 36.0 (CH), 51.0 (CH₂), 65.8 (CH₂), 74.8 (CH), 79.6 (CH), 124.8 (C), 138.9 (C), 143.3 (C). IR (neat): 2912, 2864, 1584, 1489, 1453, 1294, 1034, 732. GC/MS m/z (abundance %): 383 (100, M⁺), 338 (98), 55 (24).

Column chromatography on silica gel (dichloromethane/ethyl acetate = 2:0.1 v/v) afforded 69.8 mg of the title product in 48% yield as a brown solid. Mp: 104.3 – 104.8 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.83-1.95 (m, 2H), 2.10-2.22 (m, 2H), 2.54-2.64 (m, 2H), 2.81 (dd, J = 7.5, 11.4, 2H), 2.98 (dd, J = 4.2, 11.4 Hz, 2H), 3.79 (td, J = 7.5, 8.4 Hz, 2H), 3.88 (td, J = 5.4, 8.4 Hz, 2H), 4.68 (d, J = 6.6 Hz, 2H), 7.22 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 29.4 (CH₂), 36.2 (CH), 51.2 (CH₂), 65.8 (CH₂), 75.0 (CH), 122.9 (CH), 124.0 (C), 130.2 (C), 142.3 (C). IR (neat): 2933, 2891, 2858, 2823, 1487, 1452, 1052, 860, 637. GC/MS m/z (abundance %): 291 (62, M⁺), 246 (100), 55 (42).

4.5.4. (3*bR*,6*aR*,9*aS*,12*aS*)-2-chloro-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline (2*C*).

Column chromatography on silica gel (dichloromethane/ethyl acetate = 2:0.1 v/v) afforded 66.9 mg of the title product in 46% yield as a brown solid. Mp: 83.6 – 84.5 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.67-1.77 (m, 2H), 2.20-2.32 (m, 2H), 2.47-2.57 (m, 2H), 2.57-2.61 (m, 2H), 2.93 (dd, J = 3.6, 9.6 Hz, 2H), 3.80 (td, J = 6.0, 8.9 Hz, 2H), 3.94 (td, J = 6.0, 8.4 Hz, 2H), 4.46 (d, J = 4.8, 2H), 7.27 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 30.0 (CH₂), 35.4 (CH), 51.1 (CH₂), 65.2 (CH₂), 75.3 (CH), 122.6 (CH), 123.3 (C), 130.7 (C), 142.8 (C). IR (neat): 2926, 2865, 2828, 2803, 1490, 1452, 1049, 856, 644. GC/MS m/z (abundance %): 291 (65, M⁺), 246 (100), 55 (40).

4.5.5. (3*bR*,6*aR*,9*aR*,12*aR*)-2-fluoro-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline ((±)-3*T*).

Column chromatography on silica gel (dichloromethane/ethyl acetate = 2:0.1 v/v) afforded 70.1 mg of the title product in 51% yield as a brown solid. Mp: 115.8 – 116.4 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.86-1.97 (m, 2H), 2.10-2.21 (m, 2H), 2.55-2.66 (m, 2H), 2.78 (dd, J = 7.5, 11.4 Hz, 2H), 2.95 (dd, J = 4.2, 11.4 Hz, 2H), 3.79 (td, J = 7.2, 8.4 Hz, 2H), 3.87 (td, J = 5.4, 8.4 Hz, 2H), 4.70 (d, J = 6.6 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 29.4 (CH₂), 36.4 (CH), 51.6 (CH₂), 65.9 (CH₂), 75.2 (d, J_{C-F} = 1.5 Hz, CH), 116.8 (d, J_{C-F} = 21.8 Hz, CH), 124.0 (d, J_{C-F} = 6.4 Hz, C), 140.5 (d, J_{C-F} = 1.5 Hz, C), 155.7 (d, J_{C-F} = 236.3 Hz, C). IR (neat): 2937, 2868, 2827, 1493, 1284, 855, 701. GC/MS m/z (abundance %): 275 (61, M⁺), 230 (100), 55 (34).

4.5.6. (3*bR*,6*aR*,9*aS*,12*aS*)-2-fluoro-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline (3*C*).

Column chromatography on silica gel (dichloromethane/ethyl acetate = 2:0.1 v/v) afforded 63.2 mg of the title product in 46% yield as a brown solid. Mp: 93.6 – 94.2 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.69-1.77 (m, 2H), 2.21-2.32 (m, 2H), 2.47-2.58 (m, 2H), 2.52 (dd, J = 7.5, 11.4 Hz, 2H), 2.95 (dd, J = 4.2, 11.4 Hz, 2H), 3.80 (td, J = 6.0, 8.9 Hz, 2H), 3.95 (td, J = 6.0, 8.4 Hz, 2H), 4.49 (d, J = 3.9 Hz, 2H), 4.04 (d, J = 8.7 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 30.1 (CH₂), 35.6 (CH), 51.6 (CH₂), 65.3 (CH₂), 75.6 (d, J_{C-F} = 1.3 Hz, CH), 117.3 (d, J_{C-F} = 21.8 Hz, CH), 123.3 (d, J_{C-F} = 6.6 Hz, C), 140.7 (d, J_{C-F} = 1.7 Hz, C), 155.4 (d, J_{C-F} = 236.5, C). IR (neat): 2933, 2869, 2825, 1492, 1282, 864, 714. GC/MS m/z (abundance %): 275 (63, M⁺), 230 (100), 55 (34).

4.5.7. (3*bR*,6*aR*,9*aR*,12*aR*)-2-iodo-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline ((±)-4*T*)

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 6:2:1 v/v) afforded 80.4 mg of the title product in 42% yield as a brown solid. Mp: 109.7

110.4 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.82-1.93 (m, 2H), 2.10-2.21 (m, 2H), 2.51-2.62 (m, 2H), 2.81 (dd, J = 7.6, 11.4 Hz, 2H), 2.98 (dd, J = 4.5, 11.4 Hz, 2H), 3.78 (td, J = 7.5, 8.4 Hz, 2H), 3.87 (td, J = 5.4, 8.4 Hz, 2H), 5.16 (d, J = 6.3 Hz, 2H), 7.52 (s, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 29.3 (CH₂), 36.0 (CH), 51.0 (CH₂), 65.8 (CH₂), 74.8 (CH), 79.6 (CH), 124.8 (C), 138.9 (C), 143.3 (C). IR (neat): 2912, 2864, 1584, 1489, 1453, 1294, 1034, 732. GC/MS m/z (abundance %): 383 (100, M⁺), 338 (98), 55 (24).

4.5.8. (3*bR*,6*aR*,9*aS*,12*aS*)-2-iodo-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline (4*C*).

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 6:2:1 v/v) afforded 78.5 mg of the title product in 41% yield as a brown solid. Mp: 87.1 – 87.8 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.67-1.76 (m, 2H), 2.20-2.32 (m, 2H), 2.40-2.53 (m, 2H), 2.56 (dd, J = 10.2, 12.0 Hz, 2H), 2.93 (dd, J = 4.2, 10.2 Hz, 2H), 3.79 (td, J = 6.0, 8.2 Hz, 2H), 3.97 (td, J = 6.0, 8.8 Hz, 2H), 4.45 (d, J = 4.5 Hz, 2H), 7.60 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 30.0 (CH₂), 35.3 (CH), 50.9 (CH₂), 65.1 (CH₂), 75.2 (CH), 79.1 (CH), 124.1 (C), 139.4 (C), 143.8 (C). IR (neat): 2928, 2871, 1587, 1489, 1448, 1292, 1051, 731. GC/MS m/z (abundance %): 383 (100, M⁺), 338 (83), 55 (19).

4.5.9. (3*bR*,6*aR*,9*aR*,12*aR*)-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline ((±)-5*T*).

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 3:2:1 v/v) afforded 52.6 mg of the title product in 41% yield as a yellow solid. Mp: 139.3 – 139.9 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.80-2.01 (m, 2H), 2.09-2.26 (m, 2H), 2.52-3.34 (m, 2H), 2.75-2.91 (m, 2H), 2.94-3.09 (m, 2H), 3.65-4.06 (m, 4H), 4.77 (d, J = 6.4 Hz, 2H), 6.80 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 7.4 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 29.5 (CH₂), 36.2 (CH₂), 51.4 (CH₂), 65.7 (CH₂), 75.5 (CH), 118.2 (C), 122.2 (CH), 130.6 (CH), 143.8 (C). IR (neat): 2927, 2856, 2821, 1487, 1446, 1292, 1047, 749. GC/MS m/z (abundance %): 257 (43, M⁺), 212 (100), 55 (53).

4.5.10. (3*bR*,6*aR*,9*aS*,12*aS*)-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline (5*C*)

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 3:2:1 v/v) afforded 46.2 mg of the title product in 36% yield as a yellow solid. Mp: 116.5 – 117.4 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.62-1.85 (m, 2H), 2.15-2.40 (m, 2H), 2.42-2.74 (m, 2H), 2.88-3.03 (2H), 3.72-4.08 (m, 4H), 4.55 (d, J = 4.4 Hz, 2H), 6.82 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 30.1 (CH₂), 35.3 (CH₂), 51.2 (CH₂), 65.0 (CH₂), 75.8 (CH), 118.0 (C), 121.5 (CH), 131.2 (CH), 144.0 (C). IR (neat): 2928, 2852, 2826, 1489, 1447, 1291, 1051, 753. GC/MS m/z (abundance %): 257 (49, M⁺), 212 (100), 55 (74).

4.5.11. butyl-(3*bR*,6*aR*,9*aR*,12*aR*)-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline-2-carboxylate ((±)-6*T*).

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 2:2:1 v/v) afforded 58.9 mg of the title product in 33% yield as a brown oil. ¹H NMR (300 MHz, CDCl₃): δ 0.94 (t, J = 7.5 Hz, 3H), 1.36-1.49 (m, 2H), 1.64-1.74 (m, 2H), 1.80-1.91 (m, 2H), 2.13-2.24 (m, 2H), 2.50-2.61 (m, 2H), 2.93 (dd, J = 8.1, 11.7 Hz, 2H), 3.08 (dd, J = 4.8, 11.7 Hz, 2H), 3.82 (td, J = 6.9, 8.4 Hz, 2H), 3.89 (td, J = 5.4, 8.4 Hz, 2H), 4.23 (t, J = 6.6 Hz, 2H), 4.72 (d, J = 6.0 Hz, 2H), 7.94 (s, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 13.7 (CH₃), 19.2 (CH₂), 29.4

(CH₂), 30.8 (CH₂), 35.5 (CH), 50.7 (CH₂), 64.1 (CH₂O), 65.5 (CH₂), 75.2 (CH), 119.2 (C), 120.8 (C), 132.6 (CH), 146.9 (C), 166.6 (C = O). IR (neat): 2957, 2933, 2872, 1701, 1610, 1296, 1195, 769, 733. GC/MS m/z (abundance %): 357 (63, M⁺), 312 (93), 55 (100).

4.5.12. *butyl-(3bR,6aR,9aS,12aS)-3b,5,6,6a,9a,10,11,12a-octahydro-7H,9H-furo[3,2-c]furo[2',3':4,5]pyrido[3,2,1-ij]quinoline-2-carboxylate (6C)*.

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 2:2:1 v/v) afforded 44.6 mg of the title product in 25% yield as a brown oil. ¹H NMR (300 MHz, CDCl₃): δ 0.94 (t, J = 7.5 Hz, 3H), 1.43 (sext, J = 7.5 Hz, 2H), 1.65-1.77 (m, 4H), 2.21-2.34 (m, 2H), 2.42-2.52 (m, 2H), 2.72 (t, J = 11.5 Hz, 2H), 2.98 (dd, J = 5.4, 11.1 Hz, 2H), 3.83 (td, J = 6.3, 9.0 Hz, 2H), 3.96 (td, J = 6.3, 8.4 Hz, 2H), 4.24 (t, J = 6.6 Hz, 2H), 4.52 (d, J = 4.8 Hz, 2H), 7.98 (s, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 13.8 (CH₃), 19.2 (CH₂), 29.9 (CH₂), 30.9 (CH₂), 34.8 (CH), 50.4 (CH₂), 64.2 (CH₂O), 65.9 (CH₂), 75.6 (CH), 118.9 (C), 120.2 (C), 133.1 (CH), 147.5 (C), 166.5 (C = O). IR (neat): 2956, 2933, 2872, 1701, 1612, 1295, 1194, 768, 733. GC/MS m/z (abundance %): 357 (67, M⁺), 312 (88), 55 (100).

4.5.13. *(3bR,6aR,9aR,12aR)-2-(tert-butyl)-3b,5,6,6a,9a,10,11,12a-octahydro-7H,9H-furo[3,2-c]furo[2',3':4,5]pyrido[3,2,1-ij]quinoline ((±)-7T)*.

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 2:1:0.3 v/v) afforded 65.7 mg of the title product in 42% yield as a white solid. Mp: 120.7 – 121.4 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.29 (s, 9H), 1.88-1.99 (m, 2H), 2.11-2.22 (m, 2H), 2.57-2.69 (m, 2H), 2.81 (dd, J = 7.5, 11.2 Hz, 2H), 2.97 (dd, J = 4.2, 11.2 Hz, 2H), 3.80 (td, J = 7.2, 8.4 Hz, 2H), 3.91 (td, J = 5.1, 8.4 Hz, 2H), 4.76 (d, J = 6.6 Hz, 2H), 7.31 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 29.6 (CH₃), 31.4 (CH₂), 33.9 (C), 36.43 (CH), 51.8 (CH₂), 65.8 (CH₂), 75.8 (CH), 122.0 (C), 127.7 (CH), 141.6 (C), 145.18 (C). IR (neat): 2951, 2868, 2798, 1368, 874, 769. GC/MS m/z (abundance %): 313 (32, M⁺), 298 (100).

4.5.14. *(3bR,6aR,9aS,12aS)-2-(tert-butyl)-3b,5,6,6a,9a,10,11,12a-octahydro-7H,9H-furo[3,2-c]furo[2',3':4,5]pyrido[3,2,1-ij]quinoline (7C)*.

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 2:1:0.3 v/v) afforded 62.6 mg of the title product in 40% yield as a white solid. Mp: 93.6 – 94.2 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.29 (s, 9H), 1.88-1.99 (m, 2H), 2.11-2.22 (m, 2H), 2.57-2.69 (m, 2H), 2.81 (dd, J = 7.5, 11.2 Hz, 2H), 2.97 (dd, J = 4.2, 11.2 Hz, 2H), 3.80 (td, J = 7.2, 8.4 Hz, 2H), 3.91 (td, J = 5.1, 8.4 Hz, 2H), 4.76 (d, J = 6.6 Hz, 2H), 7.31 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 29.6 (CH₃), 31.4 (CH₂), 33.9 (C), 36.43 (CH), 51.8 (CH₂), 65.8 (CH₂), 75.8 (CH), 122.0 (C), 127.7 (CH), 141.6 (C), 145.18 (C). IR (neat): 2946, 2856, 2819, 1367, 874, 710. GC/MS m/z (abundance %): 313 (31, M⁺), 298 (100).

4.5.15. *(3bR,6aR,9aR,12aR)-2-methyl-3b,5,6,6a,9a,10,11,12a-octahydro-7H,9H-furo[3,2-c]furo[2',3':4,5]pyrido[3,2,1-ij]quinoline ((±)-8T)*.

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 3:2:1 v/v) afforded 56.9 mg of the title product in 42% yield as a yellow solid. Mp: 112.9 – 113.6 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.87-1.98 (m, 2H), 2.10-2.19 (m, 2H), 2.23 (s, 3H), 2.56-2.66 (m, 2H), 2.77 (dd, J = 7.8, 11.1 Hz, 2H), 2.94 (dd, J = 4.2, 11.1 Hz, 2H), 3.79 (td, J = 7.5, 8.4 Hz, 2H), 3.89 (td, J = 5.4, 8.4 Hz, 2H), 4.74 (d, J = 6.6 Hz, 2H), 7.09 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 29.5 (CH₃),

36.6 (CH₂), 52.0 (CH), 55.7 (CH₂), 66.0 (CH₂), 75.6 (CH), 116.1 (C), 123.8 (C), 138.3 (CH), 152.3 (C). IR (neat): 2927, 2863, 2824, 1495, 1888, 1051, 863, 700. GC/MS m/z (abundance %): 271 (66, M⁺), 226 (100), 55 (16).

4.5.16. *(3bR,6aR,9aS,12aS)-2-methyl-3b,5,6,6a,9a,10,11,12a-octahydro-7H,9H-furo[3,2-c]furo[2',3':4,5]pyrido[3,2,1-ij]quinoline (8C)*.

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 3:2:1 v/v) afforded 52.8 mg of the title product in 39% yield as a yellow solid. Mp: 91.6 – 92.1 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.67-1.76 (m, 2H), 2.17-2.33 (m, 2H), 2.24 (s, 3H), 2.46-2.58 (m, 2H), 2.53 (dd, J = 12.1, 6.0 Hz, 2H), 2.91 (dd, J = 12.1, 17.8 Hz, 2H), 3.81 (td, J = 6.0, 8.1 Hz, 2H), 3.96 (td, J = 6.0, 8.9 Hz, 2H), 4.51 (d, J = 3.3 Hz, 2H), 7.15 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 20.2 (CH₃), 30.2 (CH₂), 35.5 (CH), 51.5 (CH₂), 65.1 (CH₂), 75.8 (CH), 121.6 (C), 127.3 (C), 131.6 (CH), 141.9 (C). IR (neat): 2929, 2860, 2825, 1495, 1287, 1055, 825, 732. GC/MS m/z (abundance %): 271 (73, M⁺), 226 (100), 55 (15).

4.5.17. *(3bR,6aR,9aR,12aR)-3b,5,6,6a,9a,10,11,12a-octahydro-7H,9H-furo[3,2-c]furo[2',3':4,5]pyrido[3,2,1-ij]quinoline-2-carbonitrile ((±)-9T)*.

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 2:2:0.5 v/v) afforded 57.8 mg of the title product in 41% yield as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 1.79-1.90 (m, 2H), 2.12-2.25 (m, 2H), 2.49-2.60 (m, 2H), 2.95 (dd, J = 8.1, 12.0 Hz, 2H), 3.12 (dd, J = 4.8, 12.0 Hz, 2H), 3.82 (td, J = 6.9, 8.4 Hz, 2H), 3.89 (td, J = 5.4, 8.4 Hz, 2H), 4.65 (d, J = 6.0 Hz, 2H), 7.49 (s, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 29.2 (CH₂), 35.2 (CH), 50.3 (CH₂), 65.6 (CH₂), 74.5 (CH), 99.3 (C), 119.9 (CN), 121.9 (C), 134.5 (CH), 146.2 (C). IR (neat): 2933, 2872, 2839, 2209, 1609, 1510, 1292, 1054, 734. GC/MS m/z (abundance %): 282 (39, M⁺), 237 (100), 55 (30).

4.5.18. *(3bR,6aR,9aS,12aS)-3b,5,6,6a,9a,10,11,12a-octahydro-7H,9H-furo[3,2-c]furo[2',3':4,5]pyrido[3,2,1-ij]quinoline-2-carbonitrile (9C)*.

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 2:2:0.5 v/v) afforded 60.6 mg of the title product in 43% yield as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 1.69-1.78 (m, 2H), 2.21-2.34 (m, 2H), 2.41-2.52 (m, 2H), 2.72 (dd, J = 12.0, 11.4 Hz, 2H), 3.02 (dd, J = 5.1, 11.4 Hz, 2H), 3.82 (td, J = 5.7, 8.7 Hz, 2H), 3.95 (td, J = 6.2, 8.7 Hz, 2H), 4.45 (d, J = 6.0 Hz, 2H), 7.52 (s, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 29.7 (CH₂), 34.6 (CH), 50.2 (CH₂), 65.0 (CH₂), 74.9 (CH), 99.2 (C), 119.8 (CN), 121.4 (C), 135.0 (CH), 147.1 (C). IR (neat): 2940, 2868, 2847, 2211, 1612, 1508, 1295, 1054, 733. GC/MS m/z (abundance %): 282 (44, M⁺), 237 (100), 55 (30).

4.5.19. *(3bR,6aR,9aR,12aR)-2-(trifluoromethyl)-3b,5,6,6a,9a,10,11,12a-octahydro-7H,9H-furo[3,2-c]furo[2',3':4,5]pyrido[3,2,1-ij]quinoline ((±)-10T)*.

Column chromatography on silica gel (dichloromethane/ethyl acetate = 3:0.05 v/v) afforded 68.2 mg of the title product in 42% yield as a white solid. Mp: 126.8 – 127.6 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.83-1.99 (m, 2H), 2.24-2.25 (m, 2H), 2.53-2.64 (m, 2H), 2.91 (dd, J = 8.1, 11.7 Hz, 2H), 3.08 (dd, J = 4.8, 11.7 Hz, 2H), 3.82 (td, J = 6.9, 8.4 Hz, 2H), 3.89 (td, J = 5.4, 8.4 Hz, 2H), 4.72 (d, J = 6.0 Hz, 2H), 7.50 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 29.3 (CH₂), 35.7 (CH), 50.7 (CH₂), 65.7 (CH₂), 75.0 (CH), 119.4 (q, J_{C-F} = 32.6 Hz, CH), 122.8 (C), 124.6 (q, J_{C-F} = 278.9 Hz, CF₃), 127.7 (q, J_{C-F} = 3.8 Hz, C), 145.7 (C). IR (neat):

2947, 2864, 1622, 1510, 1322, 1103, 733. GC/MS m/z (abundance %): 325 (41, M⁺), 280 (100), 55 (37).

4.5.20. (3*bR*,6*aR*,9*aS*,12*aS*)-2-(trifluoromethyl)-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline (**10C**).

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 3:0.05 v/v) afforded 65.0 mg of the title product in 40% yield as a white solid. Mp: 104.5 – 105.6 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.70-1.79 (m, 2H), 2.23-2.35 (m, 2H), 2.44-2.54 (m, 2H), 2.68 (dd, J = 10.8, 11.7 Hz, 2H), 2.99 (dd, J = 5.1, 10.8 Hz, 2H), 3.83 (td, J = 6.3, 8.7 Hz, 2H), 3.97 (td, J = 6.3, 8.7 Hz, 2H), 4.51 (d, J = 4.8 Hz, 2H), 7.55 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 29.9 (CH₂), 34.9 (CH), 50.6 (CH₂), 65.0 (CH₂), 75.4 (CH), 119.1 (q, J_{C-F} = 32.7 Hz, CH), 122.7 (C), 124.6 (q, J_{C-F} = 269.2 Hz, CF₃), 128.2 (q, J_{C-F} = 3.8 Hz, C), 146.4 (C). IR (neat): 2968, 2856, 1620, 1514, 1322, 1059, 737. GC/MS m/z (abundance %): 325 (42, M⁺), 280 (100), 55 (40).

4.5.21. (3*bR*,6*aR*,9*aR*,12*aR*)-2-phenyl-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline ((±)-**11T**).

Column chromatography on silica gel (dichloromethane/ethyl acetate = 3:0.1 v/v) afforded 48.2 mg of the title product in 29% yield as a yellow solid. Mp: 113.2 – 113.8 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.87-1.98 (m, 2H), 2.12-2.23 (m, 2H), 2.56-2.66 (m, 2H), 2.86 (dd, J = 7.6, 11.4 Hz, 2H), 3.01 (dd, J = 4.5, 11.4 Hz, 2H), 3.81 (td, J = 7.5, 8.4 Hz, 2H); 3.92 (td, J = 5.4, 8.4 Hz, 2H), 4.80 (d, J = 6.0 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.54 (s, 2H), 7.57 (d, J = 7.5 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 29.5 (CH₂), 36.2 (CH), 51.3 (CH₂), 65.8 (CH₂), 75.6 (CH), 122.5 (C), 126.1 (CH), 126.4 (CH), 128.5 (CH), 129.2 (CH), 130.9 (C), 140.7 (C), 143.1 (C). IR (neat): 2930, 2869, 2829, 1614, 1487, 1453, 1048, 731, 697. GC/MS m/z (abundance %): 333 (100, M⁺), 288 (89), 55 (13).

4.5.22. (3*bR*,6*aR*,9*aS*,12*aS*)-2-phenyl-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline (**11C**).

Column chromatography on silica gel (dichloromethane/ethyl acetate = 3:0.1 v/v) afforded 54.9 mg of the title product in 33% yield as a yellow solid. Mp: 94.7 – 95.6 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.70-1.79 (m, 2H), 2.24-2.36 (m, 2H), 2.49-2.61 (m, 2H), 2.64 (dd, J = 10.5, 12.0 Hz, 2H), 2.97 (dd, J = 4.5, 10.5 Hz, 2H), 3.85 (td, J = 6.3, 8.7 Hz, 2H), 3.99 (td, J = 6.3, 8.1 Hz, 2H), 4.60 (d, J = 4.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.59 (d, J = 7.5 Hz, 1H), 7.61 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 30.1 (CH₂), 35.4 (CH), 51.1 (CH₂), 65.1 (CH₂), 75.9 (CH), 121.8 (C), 126.1 (CH), 126.3 (CH), 128.5 (CH), 129.7 (CH), 130.7 (C), 140.6 (C), 143.5 (C). IR (neat): 2926, 2862, 2822, 1616, 1485, 1451, 1056, 772, 703. GC/MS m/z (abundance %): 333 (100, M⁺), 288 (95), 55 (13).

4.5.23. (3*bR*,6*aR*,9*aR*,12*aR*)-2-phenoxy-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline ((±)-**12T**).

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 4:2:1 v/v) afforded 59.3 mg of the title product in 34% yield as a brown oil. ¹H NMR (300 MHz, CDCl₃): δ 1.88-1.99 (m, 2H), 2.11-2.22 (m, 2H), 2.57-2.68 (m, 2H), 2.82 (dd, J = 7.6 e 11.3 Hz, 2H), 2.98 (dd, J = 4.4, 11.3 Hz, 2H), 3.77 (td, J = 7.2, 8.4 Hz, 2H), 3.89 (td, J = 5.4, 8.4 Hz, 2H), 4.69 (d, J = 6.6 Hz, 2H), 7.00 (s, 2H), 6.95-7.03 (m, 1H), 7.23-7.29 (m, 4H). ¹³C NMR (75 MHz; CDCl₃): δ 30.2 (CH₂), 35.6 (CH), 51.6 (CH₂), 65.3 (CH₂), 75.8 (CH), 117.8 (CH), 122.2

(CH), 122.7 (C), 123.1 (CH), 129.5(CH), 140.8 (C), 148.2 (C), 158.5 (C). IR (neat): 2939, 2868, 2819, 1790, 1592, 1486, 1217, 1036, 872. GC/MS m/z (abundance %): 349 (100, M⁺), 304 (76), 55 (15).

4.5.24. (3*bR*,6*aR*,9*aS*,12*aS*)-2-phenoxy-3*b*,5,6,6*a*,9*a*,10,11,12*a*-octahydro-7*H*,9*H*-furo[3,2-*c*]furo[2',3':4,5]pyrido[3,2,1-*ij*]quinoline (**12C**).

Column chromatography on silica gel (hexane/dichloromethane/ethyl acetate = 4:2:1 v/v) afforded 55.8 mg of the title product in 32% yield as a brown oil. ¹H NMR (300 MHz, CDCl₃): δ 1.68-1.77 (m, 2H), 2.21-2.33 (m, 2H), 2.46-2.53 (m, 4H), 2.87 (dd, J = 3.0, 9.0 Hz, 2H), 3.71 (td, J = 6.1, 9.0 Hz, 2H), 3.89 (td, J = 6.1, 8.4 Hz, 2H), 4.40 (d, J = 3.6 Hz, 2H), 6.91 (s, 2H), 6.99 (m, 1H), 7.17-7.20 (m, 4H). ¹³C NMR (75 MHz; CDCl₃): δ 29.7 (CH₂), 30.2 (CH), 51.6 (CH₂), 65.3 (CH₂), 75.8 (CH), 117.8 (CH), 122.2 (CH), 122.7 (C), 123.1 (CH), 129.5 (CH), 140.8 (C), 148.2 (C), 158.5 (C). IR (neat): 2937, 2868, 2820, 2790, 1591, 1485, 1216, 1049, 875. GC/MS m/z (abundance %): 349 (100, M⁺), 304 (74), 55 (13).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at <https://doi.org/xxxx>.

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