Aluminum triflate catalyzed Povarov reaction for the synthesis of pyranotetrahydroquinolines

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Abstract

An efficient three component Povarov reaction is developed for the synthesis of pyrano[3,2-c]-tetrahydroquinolines using a catalytic amount of $\text{Al}(\text{OTf})_3$ as a Lewis acid catalyst, in good to excellent yields.

Keywords: $\text{Al}(\text{OTf})_3$, Povarov reaction, pyranotetrahydroquinolines

Introduction

Pyranotetrahydroquinolines are important structural motifs that are present as substructures in a number of natural products and interesting biologically active compounds that are reported to possess psychotropic, antiallergic, anti-inflammatory, and estrogenic activities.¹⁻⁵ Owing to their importance, a number of synthetic strategies have been developed for their synthesis.^{1,6-21} The reaction of an aromatic imine (in a two component reaction) or aniline (in a three component reaction) with benzaldehyde and electron rich dihydropyran (DHP) in the presence of an acid catalyst/promotor, known as the Povarov reaction,^{1,19-24} has been the common and convenient synthetic protocol for the preparation of such important compounds. Several acid catalysts/promoters, which include the following, have been reported in the literature: InCl_3 ,⁹ $\text{Sc}(\text{OTf})_3$,²⁵ I_2 ,¹⁷ Ferric sulfate,¹⁸ montmorillonite KSF,¹¹ lanthanide halides,¹³ $\text{BF}_3 \cdot \text{OEt}_2$,²² $\text{Sm}(\text{OTf})_3$,²⁶ ZrCl_4 ,²³ $\text{CF}_3\text{CO}_2\text{H}$,⁸ $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$,²⁸ polyaniline-*p*-toluenesulfonate salt,³ and cellulose sulfuric acid,¹⁵ VCl_3 ,²⁹ CAN ,³⁰ SmI_2 ,³¹ SelectfluorTM,³² Tritylium Cation,³³ and phosphoric acid.^{34,35} However, for the Lewis acid catalysed three-component Povarov reaction, the need for a stoichiometric amount of the catalyst, due to the decomposition or deactivation of the acid by the amines (both in the reactant and product) and the production of water during the intermediate imine formation, has been reported as the main limitation of the protocol.^{3,10,11}

Thus developing new Lewis acid catalysts that are stable under the reaction conditions and that can catalyse the reaction at a lower catalyst loading is desirable. Williams and Cullen reported that $\text{Al}(\text{OTf})_3$ was an effective recyclable catalyst (<10 mol% catalyst loading) for the ring opening of epoxides with amines to provide β -amino alcohols without the catalyst being deactivated by the nucleophile amine or hydroxyl amine product.³⁶ Inspired by this result and in continuation of our research into the application of $\text{Al}(\text{OTf})_3$ in a number of catalytic transformations such as in the synthesis of chiral O-heterocycles,³⁷ tetrahydropyranyl and tetrahydrofuranyl protection/deprotection of alcohols³⁸ and temperature-switched selective O-glycosylation,³⁹ we have evaluated its catalytic activity in the three component Povarov reaction and herein report its scope and limitations.

Results and Discussion

In our initial studies of the solvent-free $\text{Al}(\text{OTf})_3$ catalyzed three component Povarov reaction, we examined the reaction of aniline **1a** (1 equivalent), benzaldehyde **2a** (1 equivalent) and DHP (2 equivalents) in the presence of 5 mol% $\text{Al}(\text{OTf})_3$ at room temperature that gave the expected pyranotetrahydroquinolines **4a** and **5a** in 76% combined yield, in 25 min, as a 75:25 *cis*:*trans* ratio (Scheme 1). Encouraged by this result, the catalyst loading was reduced to 2 mol% to make it more economical and environmentally friendly. The outcome however was that the reaction became sluggish.

Scheme 1. 5 mol% $\text{Al}(\text{OTf})_3$, room temperature, 25 min, 76% (75:25 ratio).

Hoping to improve the diastereoisomeric ratio in favour of the kinetic product **4a**,³ the reaction was attempted at 0 °C using 5 mol% $\text{Al}(\text{OTf})_3$. Unfortunately the reaction mixture became too viscous and even at higher temperatures (40 °C, 60 °C and 80 °C) no improvement of selectivity in favour of the thermodynamic product³ **5a** took place. Next, we examined the role of the amount of DHP and it was found that 1.5 equivalents of the DHP (relative to aniline) were sufficient to provide the corresponding pyranotetrahydroquinolines **4a** and **5a** without significant effect on the yield and reaction time. The stereochemistries of the *cis* and *trans* isomers were established on the basis of the *J* value of H-5 in each isomer. The smaller $^3J_{\text{H-4a},\text{H-5}}$ value of 5.6

Hz indicates the cis relationship between H-4a and H-5 while the larger $^3J_{\text{H-4a,H-5}}$ value of 8.0 Hz suggests a trans relationship between these two protons.¹⁰

Having established the optimum reaction conditions, we then evaluated the scope of the reaction for various aniline and benzaldehyde derivatives. However, in most cases the reaction mixture solidified after the addition of the $\text{Al}(\text{OTf})_3$ without the formation of the expected pyranotetrahydroquinolines. This limitation led us to conduct re-optimization of the reaction in solvents which were previously reported to be suitable for the Povarov reaction.¹⁹⁻²¹ The solvents screened include acetonitrile, methylene chloride, THF, and toluene. Reactions were carried out by treating a solution of aniline, benzaldehyde and DHP in either THF or toluene with 5-20 mol% $\text{Al}(\text{OTf})_3$ but at room temperature or higher (60-80 °C) no formation of pyranotetrahydroquinolines **4a** and **5a** was observed. When reactions carried out in methylene chloride pyranotetrahydroquinolines **4a** and **5a** were obtained in 57% yield after 3.5 h with a 50:50 cis:trans selectivity at 50 °C. No product formation was detected at room temperature. Interestingly, employing acetonitrile and carrying out the reaction at room temperature the pyranotetrahydroquinolines **4a** and **5a** were obtained in 62% yield and 56:44 cis:trans ratio in 30 min. Since acetonitrile provided a better yield and shorter reaction time, it was identified as a suitable solvent for the $\text{Al}(\text{OTf})_3$ catalyzed Povarov reaction.

Having identified the best solvent and catalyst loading of the $\text{Al}(\text{OTf})_3$ which was 5 mol% (lower catalyst loading resulted in slower reaction rates), we then examined the effect of temperature on the selectivity of the reaction. While reactions at 0 °C resulted in formation of **4a** and **5a** in poor yield (48%) but better selectivity (70:30) in 3 h, reactions at 50 °C, the optimum temperature for the reaction, provided 70% of **4a** and **5a** in 48:52 ratio in 15 min. Below 50 °C reactions were slower whereas there was no change in yield and reaction rate for reactions > 50 °C.

Next, we examined the scope of the modified reaction using various aniline and benzaldehyde derivatives. Electron-donating and electron-withdrawing groups on the aryl ring of the benzaldehyde and aniline were compatible under the reaction conditions and the corresponding pyranotetrahydroquinolines **4a-i** and **5a-i** were obtained in reasonable to excellent yields with selectivities ranging from 50:50 to 22:78 in favour of the trans diastereoisomer except for **4b/5b** and **4f/5f**, which possess an electron donating group. The results are summarized in Table 1 with the products identified by ^1H and ^{13}C NMR. Moreover, the spectroscopic data were in agreement with the reported literature (Table 1).

For the lowest yielding reaction (Table 1, products **4f** and **5f**), microwave irradiation efficiently enhanced the reaction time and provided a better yield at the expense of poorer selectivity. The yield of the pyranotetrahydroquinolines **4f** and **5f** improved from 43% after stirring for 45 min to 81% in under 6 min reaction time with the selectivity going down from 60:40 to 50:50 cis:trans ratio. The enhancement of the reaction rate and yield upon microwave irradiation was also observed with other substrates as indicated in Table 1. In most cases the yields of the reactions improved, although the selectivity of the reactions was found to be unpredictable; however, the reaction rate increased in all cases (Table 1).

Table 1. The Povarov reaction of various aniline and aldehyde derivatives using 5 mol% Al(OTf)₃, in CH₃CN at 50 °C/70 °C MW irradiation

Aniline	Aldehyde	Product	At 50 °C				MW irradiation			Ref.
			Time (min)	Cis:trans	Yield (%)	Time (min)	Cis:trans	Yield (%)		
1a R ¹ =R ² =H	2a R ³ =R ⁴ =H	4a and 5a	15	48:52	70	6	52:48	73	27	
1a R ¹ =R ² =H	2b R ³ =H, R ⁴ =OMe	4b and 5b	Over night	75:25	92	96	50:50	79	15	
1a R ¹ =R ² =H	2c R ³ =NO ₂ , R ⁴ =H	4c and 5c	40	50:50	56	18	36:64	68	40	
1a R ¹ =R ² =H	2d R ³ =H, R ⁴ =Cl	4d and 5d	15	50:50	59	6	62:38	73	27	
1b R ¹ = H, R ² =Cl	2a R ³ =R ⁴ =H	4e and 5e	15	45:55	71	6	78:22	78	15	
1c R ¹ = H, R ² =OMe	2a R ³ =R ⁴ =H	4f and 5f	45	60:40	43	6	50:50	81	27	
1d R ¹ =isopropyl, R ² =H	2a R ³ =R ⁴ =H	4g and 5g	45	22:78	88	24	28:72	71	8	
1d R ¹ =H, R ² =Cl	2b R ³ =H, R ⁴ =Cl	4h and 5h	20	47:53	62	6	74:26	65	18	
1d R ¹ =H, R ² =OMe	2c R ³ =H, R ⁴ =Cl	4i and 5i	20	48:52	64	6	76:24	76	41	

Comparison of $\text{Al}(\text{OTf})_3$ to other literature reported catalysts¹⁸ indicates that the current methodology is superior in terms of the reaction time and catalyst loading but comparable in selectivity and slightly inferior in yield, especially without microwave irradiation. (Table 2).

Table 2. Comparison of the current catalyst system to other reported systems¹⁸

Entry	Catalyst	Amount	Condition	Time	4d:5d	Yield %
1	FeCl_3	10 mol%	RT	6 h	50:50	82 ^a
2	Proline triflate	5 mol %	RT	5 h	25:75	85 ^a
3	4-Nitrophthalic acid	25 mol%	50 °C	3.5 h	39:61	90 ^a
4	I_2	30 mol%	RT	3 h	23:77	84 ^a
5	$\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$	10 mol%	Reflux	1.5 h	19:81	87 ^a
6	$\text{Al}(\text{OTf})_3$	5 mol%	50 °C	15 min	50:50	59^b
7	$\text{Al}(\text{OTf})_3$	5 mol%	MW	6 min	62:38	73^b

^a Comparative data extracted from reference 18. ^b Current study.

Conclusions

In conclusion, a procedure for the synthesis of pyranotetrahydroquinolines has been demonstrated using a catalytic amount of $\text{Al}(\text{OTf})_3$ as a catalyst in the three-component Povarov reaction. The high yields obtained, short reaction times and the need for only a catalytic amount (5 mol%) of $\text{Al}(\text{OTf})_3$ in the reactions are clear indications that, unlike many other Lewis acids, $\text{Al}(\text{OTf})_3$ is not deactivated by the amine and water present in the reaction. Thus, the latter can be considered a suitable catalyst for the Povarov reaction for the preparation of pyranotetrahydroquinolines.

Experimental Section

General. To a solution of aniline **1** (1.074 mmol), benzaldehyde **2** (1.074 mmol) and DHP **3** (2.147 mmol) in acetonitrile (4 mL) was added $\text{Al}(\text{OTf})_3$ (5 mol%, 0.054 mmol). The reaction mixture was stirred at 50 °C or under microwave irradiation at 70 °C until TLC analysis indicated completion of the reaction (refer to Table 1 for reaction times and yields). After completion of the reaction, the reaction mixture was allowed to cool down to room temperature and quenched by addition of saturated NaHCO_3 solution (5 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , concentrated *in vacuo* and purified by column chromatography on silica gel using a mixture of ethyl acetate:hexane (1:9) as eluent to provide the corresponding pyranotetrahydroquinolines.

All microwave irradiation experiments were carried out in a multimode Multiwave PRO microwave reactor at 70 °C and 600 W. This apparatus was used in the standard configuration as delivered. Reactions were carried out in sealed quartz glass vessels (using 8 mL of acetonitrile in an 80 mL vessel) and temperature control was done using external infrared sensor. The reaction mixture was continuously stirred until TLC analysis confirmed completion of the reaction (usually at 6 min interval). After the reaction is complete, the reaction vessel is cooled by forced-air cooling system to room temperature.

(4aR,5R,10bR)-5-Phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolone (4a). White solid; mp 120-125 °C (Lit.³¹ 123-124 °C); δ_{H} (400 MHz, CDCl_3) 7.49-7.30 (m, 6H, Ar), 7.10 (t, J 7.4 Hz, 1H, Ar), 6.82 (t, J 7.4 Hz, 1H, Ar), 6.62 (d, J 8.0 Hz, 1H, Ar), 5.33 (d, J 5.6 Hz, 1H, H-5), 4.68 (d, J 2.0 Hz, 1H, H-10b), 3.88 (bs, 1H, NH), 3.59 (dd, J 1.6 Hz and 9.2 Hz, 1H, H-2a), 3.46 (td, J 11.6 Hz and 2.4 Hz, 1H, H-2b), 2.25-2.15 (m, 1H, H-4a), 1.65-1.25 (m, 4H, 2x CH_2), δ_{C} (100 MHz, CDCl_3) 145.1, 141.1, 128.3, 128.0, 127.6, 127.5, 126.8, 119.9, 118.2, 114.4, 72.7, 60.6, 59.3, 38.9, 25.4, 18.0.

(4aR,5S,10bR)-5-Phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolone (5a). Colorless oil; δ_{H} (400 MHz, CDCl_3) 7.50-7.31 (m, 5H, Ar), 7.25 (d, J 6.4 Hz, 1H, Ar), 7.11 (t, J 7.6 Hz, 1H, Ar), 6.73 (t, J 7.4 Hz, 1H, Ar), 6.42 (d, J 8.0 Hz, 1H, Ar), 4.73 (d, J 8.0 Hz, 1H, H-5), 4.41 (d, J 2.8 Hz, 1H, H-10b), 4.12 (dt, J 11.2 Hz and 2.0 Hz, 1H, H-2a), 3.76 (td, J 11.6 Hz and 2.4 Hz, 1H, H-2b), 2.17-1.35 (m, 4H, 2x CH_2); δ_{C} (100 MHz, CDCl_3) 144.8, 142.4, 130.9, 129.4, 128.7, 127.9, 127.8, 120.7, 117.5, 114.1, 68.6, 54.9, 38.9, 24.2, 22.1.

(4aR,5R,10bR)-5-(4-Methoxyphenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (4b). White solid; mp 153-157 °C (Lit.¹⁵ 120-123 °C); δ_{H} (400 MHz, CDCl_3) 7.41 (d, J 7.6 Hz, 1H, Ar), 7.32 (d, J 8.4 Hz, 2H, Ar), 7.08 (t, J 7.6 Hz, 1H, Ar), 6.90 (d, J 8.4 Hz, 2H, Ar), 6.77 (t, J 7.4 Hz, 1H, Ar), 6.58 (d, J 8.0 Hz, 1H, Ar), 5.30 (d, J 5.6 Hz, 1H, H-5), 4.63 (d, J 2.0 Hz, 1H, H-10b), 3.81 (bs, 4H, NH and OCH_3), 3.61-3.54 (m, 1H, H-2a), 3.46-3.35 (m, 1H, H-2b), 2.14-2.05 (m, 1H, H-4a), 1.55-1.28 (m, 4H, 2x CH_2); δ_{C} (100 MHz, CDCl_3) 158.9, 145.2, 133.1, 128.0, 127.9, 127.6, 119.9, 118.2, 114.4, 113.6, 72.7, 60.6, 58.7, 55.3, 39.0, 25.4, 18.0.

(4aR,5S,10bR)-5-(4-Methoxyphenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (5b). White solid; mp 115-117 °C (Lit.¹⁵ 100-103 °C); δ_{H} (400 MHz, CDCl₃) 7.32 (d, *J* 8.4 Hz, 2H, Ar), 7.21 (d, *J* 7.6 Hz, 1H, Ar), 7.10-7.00 (m, 1H, Ar), 6.90 (d, *J* 8.8 Hz, 2H, Ar), 6.68 (t, *J* 7.2 Hz, 1H, Ar), 6.50 (d, *J* 8.0 Hz, 1H, Ar), 4.66 (d, *J* 10.8 Hz, 1H, H-5), 4.38 (d, *J* 2.4 Hz, 1H, H-10b), 4.15-4.05 (m, 1H, H-2a), 3.81 (s, 3H, OCH₃), 3.71 (td, *J* 3.6 Hz and 2.0 Hz, 1H, H-2b), 2.10-2.00 (m, 1H, H-4a), 1.90-1.60 (m, 2H, CH₂), 1.53-1.25 (m, 2H, CH₂); δ_{C} (100 MHz, CDCl₃) 159.2, 130.9, 129.3, 129.0, 128.2, 126.0, 125.7, 125.2, 113.94, 68.7, 55.2, 54.1, 38.8, 24.1, 21.9.

(4aR,5R,10bR)-5-(2-Nitrophenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (4c). Yellow solid; mp 202-206 °C (Lit.²⁹ 203-204 °C); δ_{H} (400 MHz, CDCl₃) 7.95 (t, *J* 8.4 Hz, 2H, Ar), 7.63 (t, *J* 7.4 Hz, 1H, Ar), 7.49-7.40 (m, 2H, Ar), 7.08 (t, *J* 7.4 Hz, 1H, Ar), 6.82 (t, *J* 7.4 Hz, 1H, Ar), 6.59 (d, *J* 8.0 Hz, 1H, Ar), 5.32 (d, *J* 5.6 Hz, 1H, H-5), 5.14 (s, 1H, H-10b), 3.68 (s, 1H, NH), 3.55 (bd, *J* 10.4 Hz, 1H, H-2a), 3.41 (t, *J* 11.4 Hz, 1H, H-2b), 2.55-2.45 (m, 1H, H-4a), 1.69-1.26 (m, 4H, 2x CH₂); δ_{C} (100 MHz, CDCl₃) 148.8, 144.8, 135.7, 132.6, 129.4, 128.3, 128.1, 127.8, 120.4, 119.0, 114.9, 72.3, 60.5, 54.5, 36.2, 25.3, 18.5.

(4aR,5S,10bR)-5-(2-Nitrophenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (5c). Yellow solid; mp 211-214 °C; δ_{H} (400 MHz, CDCl₃) 7.80 (d, *J* 8.0 Hz, 1H, Ar), 7.65 (d, *J* 7.6 Hz, 1H, Ar), 7.60-7.50 (m, 1H, Ar), 7.45-7.35 (m, 1H, Ar), 7.25 (d, *J* 8.0 Hz, 1H, Ar), 7.15-7.05 (m, 1H, Ar), 6.74 (td, *J* 7.6 Hz and 0.8 Hz, 1H, Ar), 6.57 (d, *J* 8.0 Hz, 1H, Ar), 5.12 (d, *J* 8.0 Hz, 1H, H-5), 4.45 (d, *J* 3.6 Hz, 1H, H-10b), 4.24 (bs, 1H, NH), 3.90-3.81 (m, 1H, H-2a), 3.67-3.57 (m, 1H, H-2b), 2.25-2.15 (m, 1H, H-4a), 1.81-1.38 (m, 4H, 2 x CH₂); δ_{C} (100 MHz, CDCl₃) 149.9, 143.9, 132.8, 129.8, 129.3, 129.1, 128.4, 124.0, 119.8, 118.0, 114.0, 72.2, 66.0, 50.8, 37.7, 24.5, 23.1.

(4aR,5R,10bR)-5-(4-chlorophenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (4d). White solid mp 170-173 °C (Lit.¹⁸ 170 °C); δ_{H} (400 MHz, CDCl₃) 7.41 (d, *J* 7.6 Hz, 1H, Ar), 7.34 (s, 4H, Ar), 7.13-7.00 (m, 1H, Ar), 6.80 (t, *J* 7.6 Hz, 1H, Ar), 6.54 (d, *J* 8.0 Hz, 1H, Ar), 5.30 (d, *J* 5.2 Hz, 1H, H-5), 4.65 (d, *J* 2.4 Hz, 1H, H-10b), 3.82 (bs, 1H, NH), 3.57 (dd, *J* 10.0 Hz and 8.0 Hz, 1H, H-2a), 3.45-3.35 (m, 1H, H-2b), 2.15-2.05 (m, 1H, H-4a), 1.60-1.20 (m, 4H, 2 x CH₂); δ_{C} (100 MHz, CDCl₃) 144.9, 139.6, 133.1, 128.5, 128.1, 127.6, 119.1, 118.6, 114.5, 72.6, 60.6, 58.8, 38.9, 25.3, 17.9.

(4aR,5S,10bR)-5-(4-Chlorophenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (5d). White solid; mp 125-130 °C (Lit.¹⁸ 124 °C); δ_{H} (400 MHz, CDCl₃) 7.34 (bs, 4H, Ar), 7.21 (d, *J* 7.6 Hz, 1H, Ar), 7.09 (t, *J* 7.6 Hz, 1H, Ar), 6.71 (t, *J* 7.4 Hz, 1H, Ar), 6.52 (d, *J* 8.0 Hz, 1H, Ar), 4.68 (d, *J* 10.8 Hz, 1H, H-5), 4.37 (d, *J* 2.4 Hz, 1H, H-10b), 4.12-3.95 (m, 2H, NH and H-2a), 3.71 (td, *J* 11.6 Hz and 2.4 Hz, 1H, H-2b), 2.10-2.00 (m, 1H, H-4a), 1.87-1.55 (m, 2H, CH₂), 1.50-1.38 (m, 2H, CH₂); δ_{C} (100 MHz, CDCl₃) 144.5, 140.9, 133.5, 130.9, 129.4, 129.1, 128.8, 120.7, 117.7, 114.2, 74.3, 68.5, 54.3, 38.9, 24.0, 22.0.

(4aR,5R,10bR)-9-Chloro-5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (4e). White solid; mp 168-172 °C (Lit.¹⁵ 170-175 °C); δ_{H} (400 MHz, CDCl₃) 7.40-7.35 (m, 6H, Ar), 7.05-6.95 (m, 1H, Ar), 6.51 (d, *J* 8.4 Hz, 1H, Ar), 5.25 (d, *J* 5.6 Hz, 1H, H-5), 4.64 (d, *J* 2.4

Hz, 1H, H-10b), 3.88 (s, 1H, NH), 3.65-3.55 (m, 1H, H-2a), 3.45-3.36 (m, 1H, H-2b), 2.20-2.10 (m, 1H, H-4a), 1.55-1.35 (m, 4H, 2 x CH₂); δ_c (100 MHz, CDCl₃) 143.7, 140.6, 128.4, 128.0, 127.7, 127.6, 126.7, 123.0, 121.6, 115.6, 72.4, 60.8, 59.3, 38.5, 25.3, 18.0.

(4aR,5S,10bR)-9-Chloro-5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline

(5e). Colorless oil; δ_H (400 MHz, CDCl₃) 7.45-7.30 (m, 5H, Ar), 7.20 (d, *J* 2.4 Hz, 1H, Ar), 7.02 (dd, *J* 8.4 Hz and 2.4 Hz, 1H, Ar), 6.44 (d, *J* 8.4 Hz, 1H, Ar), 4.66 (d, *J* 10.4 Hz, 1H, H-5), 4.33 (d, *J* 2.4 Hz, 1H, H-10b), 4.15-4.03 (m, 2H, H-2a and NH), 3.70 (td, *J* 11.2 Hz and 2.4 Hz, 1H, H-2b), 2.10-2.00 (m, 1H, H-4a), 1.90-1.40 (m, 4H, 2 x CH₂); δ_c (100 MHz, CDCl₃) 143.3, 141.9, 130.3, 129.2, 127.98, 127.6, 121.8, 121.7, 115.3, 73.9, 68.4, 54.9, 38.6, 23.9, 22.0.

(4aR,5R,10bR)-9-Methoxy-5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline

(4f). White solid; mp 144-147 °C (Lit.¹⁸ 144 °C); δ_H (400 MHz, CDCl₃) 7.40-7.25 (m, 5H, Ar), 7.02 (d, *J* 2.8 Hz, 1H, Ar), 6.71 (dd, *J* 8.4 Hz and 2.8 Hz, 1H, Ar), 6.56 (d, *J* 8.8 Hz, 1H, Ar), 5.30 (d, *J* 5.2 Hz, 1H, H-5), 4.61 (d, *J* 2.0 Hz, 1H, H-10b), 3.77 (s, 3H, OCH₃), 3.70-3.55 (m, 2H, NH and H-2a), 3.42 (dt, *J* 11.6 Hz and 2.4 Hz, 1H, H-2b), 2.22-2.08 (m, 1H, H-4a), 1.60-1.20 (m, 4H, 2 x CH₂); δ_c (100 MHz, CDCl₃) 152.8, 141.3, 139.1, 128.3, 127.4, 126.8, 121.1, 115.7, 115.0, 111.8, 72.9, 60.8, 59.6, 55.8, 39.0, 25.3, 17.9.

(4aR,5S,10bR)-9-Methoxy-5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline

(5f). Colorless oil; δ_H (400 MHz, CDCl₃) 7.45-7.26 (m, 5H, Ar), 6.81 (d, *J* 2.8 Hz, 1H, Ar), 6.74 (dd, *J* 8.4 Hz and 2.8 Hz, 1H, Ar), 6.49 (d, *J* 8.4 Hz, 1H, Ar), 4.65 (d, *J* 10.4 Hz, 1H, H-5), 4.36 (d, *J* 2.4 Hz, 1H, H-10b), 4.13-4.04 (m, 1H, H-2a), 3.88 (bs, 1H, NH), 3.80-3.65 (m, 4H, OCH₃ and H-2b), 2.13-2.04 (m, 1H, H-4a), 1.90-1.27 (m, 4H, 2 x CH₂); δ_c (100 MHz, CDCl₃) 152.0, 142.4, 139.0, 128.5, 127.8, 121.3, 116.8, 115.5, 114.9, 74.5, 68.5, 55.9, 55.2, 39.0, 24.1, 22.1.

(4aR,5R,10bR)-7-Isopropyl-5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline

(4g). Colorless oil; δ_H (400 MHz, CDCl₃) 7.49-7.30 (m, 6H, Ar), 7.08 (d, *J* 7.2 Hz, 1H, Ar), 6.80 (t, *J* 7.6 Hz, 1H, Ar), 5.36 (d, *J* 5.6 Hz, 1H, H-5), 4.69 (d, *J* 2.0 Hz, 1H, H-10b), 3.86 (bs, 1H, NH), 3.60-3.51 (m, 1H, H-2a), 3.50-3.38 (m, 1H, H-2b), 2.87-2.75 (m, 1H, (CH₃)₂CH), 2.20-2.10 (m, 1H, H-4a), 1.60-1.35 (m, 4H, 2 x CH₂), 1.30 (d, *J* 6.8 Hz, 3H, CH₃), 1.25 (d, *J* 6.8 Hz, 3H, CH₃); δ_c (100 MHz, CDCl₃) 141.7, 141.5, 131.8, 128.4, 127.5, 126.8, 125.1, 124.0, 119.8, 118.0, 60.6, 59.2, 38.6, 27.5, 25.4, 22.4, 22.1, 18.0.

(4aR,5S,10bR)-7-Isopropyl-5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline

(5g). Colorless oil; δ_H (400 MHz, CDCl₃) 7.50-7.32 (m, 5H, Ar), 7.13 (t, *J* 6.8 Hz, 2H, Ar), 6.76 (t, *J* 7.6 Hz, 1H, Ar), 4.79 (d, *J* 11.2 Hz, 1H, H-5), 4.43 (d, *J* 2.4 Hz, 1H, H-10b), 4.20-4.05 (m, 2H, NH and H-2a), 3.75 (td, *J* 12.0 Hz and 2.4 Hz, H-2b), 2.82-2.69 (m, 1H, (CH₃)₂CH), 2.15-2.05 (m, 1H, H-4a), 1.97-1.82 (m, 1H, H-3a), 1.73-1.60 (m, 1H, H-3b), 1.53-1.30 (m, 2H, CH₂), 1.21 (d, *J* 6.8 Hz, 3 H, CH₃), 1.18 (d, *J* 6.8 Hz, 3H, CH₃); δ_c (100 MHz, CDCl₃) 142.8, 141.1, 131.2, 128.6, 127.8, 127.8, 125.2, 120.3, 117.1, 68.7, 54.8, 38.7, 27.0, 24.0, 22.3, 22.0, 21.9.

(4aR,5R,10bR)-9-Chloro-5-(4-chlorophenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (4h).

White solid; mp 188-192 °C (Lit.¹⁸ 188 °C); δ_H (400 MHz, CDCl₃) 7.41 (d, *J* 7.6 Hz, 1H, Ar), 7.34 (bs, 3H, Ar), 7.15-7.05 (m, 1H, Ar), 6.80-6.70 (m, 1H, Ar), 6.59 (d, *J* 7.6 Hz, 1H, Ar), 5.30 (d, *J* 5.6 Hz, 1H, H-5), 4.65 (d, *J* 2.4 Hz, 1H, H-10b), 3.81 (bs, 1H, NH), 3.63-

3.53 (m, 1H, H-2a), 3.41 (td, *J* 11.6 Hz and 2.4 Hz, 1H, H-2b), 2.16-2.06 (m, 1H, H-4a), 1.58-1.02 (m, 4H, 2 x CH₂); δ_C (100 MHz, CDCl₃) 143.1, 140.5, 130.4, 129.3, 129.0, 128.9, 122.1, 121.9, 115.4, 68.5, 54.4, 38.7, 23.9, 22.0.

(4a*R*,5*S*,10*bR*)-9-Chloro-5-(4-chlorophenyl)-3,4,4a,5,6,10*b*-hexahydro-2*H*-pyrano[3,2-*c*]quinoline (5h). White solid; mp 154-156 °C (Lit.¹⁸ 152 °C); δ_H (400 MHz, CDCl₃) 7.34 (s, 4H, Ar), 7.21 (dd, *J* 7.6 Hz and 1.2 Hz, 1H, Ar), 7.08 (td, *J* 8.0 Hz and 1.6 Hz, 1H, Ar), 6.71 (td, *J* 7.6 Hz and 0.8 Hz, 1H, Ar), 6.52 (d, *J* 8.0 Hz, 1H, Ar), 4.68 (d, *J* 10.8 Hz, 1H, H-5), 4.37 (d, *J* 2.8 Hz, 1H, H-10*b*), 4.12-3.97 (m, 2H, NH and H-2a), 3.71 (td, *J* 11.2 Hz and 2.4 Hz, H-2b), 2.07-2.0 (m, H, H-4a), 1.90-1.60 (m, 2H, CH₂), 1.50-1.30 (m, 2H, CH₂); δ_C (100 MHz, CDCl₃) 144.9, 139.6, 133.1, 128.5, 128.4, 128.1, 127.6, 119.9, 118.6, 114.5, 72.6, 60.6, 58.8, 38.9, 25.3, 17.9.

(4a*R*,5*R*,10*bR*)-5-(4-Chlorophenyl)-9-methoxy-3,4,4a,5,6,10*b*-hexahydro-2*H*-pyrano[3,2-*c*]quinoline (4i). White solid; mp 158-164 °C; δ_H (400 MHz, CDCl₃) 7.40-7.30 (m, 4H, Ar), 7.01 (d, *J* 2.4 Hz, 1H, Ar), 6.71 (dd, *J* 8.4 Hz and 2.4 Hz, Ar), 6.56 (d, *J* 8.8 Hz, 1H, Ar), 5.27 (d, *J* 5.6 Hz, 1H, H-5), 4.58 (d, *J* 1.6 Hz, 1H, H-10*b*), 3.76 (s, 3H, OCH₃), 3.65-3.55 (m, 2H, NH and H-2a), 3.50-3.30 (m, 1H, H-2b), 2.15-2.05 (m, 1H, H-4a), 1.60-1.15 (m, 4H, 2 x CH₂); δ_C (100 MHz, CDCl₃) 153.6, 140.0, 138.9, 133.1, 128.5, 128.3, 121.3, 116.0, 115.2, 111.9, 72.9, 60.9, 39.2, 25.4, 17.8.

(4a*R*,5*S*,10*bR*)-5-(4-Chlorophenyl)-9-methoxy-3,4,4a,5,6,10*b*-hexahydro-2*H*-pyrano[3,2-*c*]quinoline (5i). Light green oil; δ_H (400 MHz, CDCl₃) 7.38-7.30 (m, 4H, Ar), 6.79 (d, *J* 2.4 Hz, 1H, Ar), 6.73 (dd, *J* 8.8 Hz and 2.8 Hz, 1H, Ar), 6.49 (d, *J* 8.4 Hz, 1H, Ar), 4.62 (d, *J* 10.8 Hz, 1H, H-5), 4.34 (d, *J* 2.4 Hz, 1H, H-10*b*), 4.07 (bd, *J* 11.2 Hz, 1H, H-2a), 3.83 (s, 1H, NH), 3.75-3.67 (m, 4H, O-CH₃ and H-2b), 2.09-1.97 (m, 1H, H-4a), 1.86-1.65 (m, 2H, CH₂), 1.48-1.27 (m, 2H, CH₂); δ_C (100 MHz, CDCl₃) 152.2, 141.0, 138.5, 129.2, 128.8, 121.4, 117.0, 115.7, 114.8, 68.6, 56.0, 39.1; 24.2; 22.1.

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