

Hexafluoroisopropanol: a powerful solvent for the hydrogenation of indole derivatives. Selective access to tetrahydroindoles or *cis*-fused octahydroindoles†

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Pd/C in HFIP was used to hydrogenate indole derivatives under relatively mild conditions, leading to potential synthetic intermediates of bioactive compounds. Depending on their substitution, tetrahydroindoles or octahydroindoles could selectively be obtained.

Introduction

Hydrogenation of indole derivatives constitutes a powerful method to access cyclic N-containing skeletons.¹ Nevertheless, it is difficult, due to the highly resonance-stabilized aromatic nucleus and to the products themselves which could poison the metal catalyst. Moreover, the hydrogenation of the indole moiety may lead to three main classes of compounds, indolines, tetrahydroindoles or octahydroindoles and the control of the regioselectivity still remains a problem. In the course of our study on the hydrogenation of aromatic compounds,^{2,3} we have reported the solvent dependent hydrogenation of substituted quinolines using Rh/Al₂O₃ as a catalyst and either methanol or hexafluoroisopropanol (HFIP) as solvent to obtain either 1,2,3,4-tetrahydroquinolines or decahydroquinolines respectively. We thus decided to test our system on indole derivatives. The indoline skeleton is an ubiquitous structural motif in naturally occurring alkaloids and many biological active compounds such as Duocarmycins or Pentopril.⁴ Therefore, numerous transition metal catalytic systems have been developed to reduce selectively of the pyrrole ring.⁵ Other methods such as catalytic transfer hydrogenation in formic acid⁶ or the use of trimethylamine/borane mixture were also developed.⁷ Asymmetric versions were proposed too.⁸ As for the 4,5,6,7-tetrahydroindole derivatives, they are classically formed by multistep procedures such as microwave-assisted aminolysis of 4-oxo-4,5,6,7-tetrahydrobenzofuran with different primary amines,⁹ or from 1-(1-pyrrolidino)cyclohexene and chloropyruvates.¹⁰ Only few examples have been reported so far

by direct reduction of indoles. A two-step procedure including a regioselective Birch reduction followed by a catalytic hydrogenation was developed to obtain selectively the tetrahydroderivatives.¹¹ These products are generally formed as intermediates in the course of the total hydrogenation of indoles into octahydroindoles.¹² Nevertheless, tetrahydroindole derivatives constitute a class of compounds of growing interest as they were proved to be active for the treatment of neurodegenerative diseases¹³ and in some cases may have comparable activity as dopamine.¹⁴ As for octahydroindoles, this skeleton is present in numerous bioactive products such as aeruginosins¹⁵ or angiotensin converting enzyme (ACE) inhibitors.¹⁶ Octahydroindoles can also be used as ligands for catalytic asymmetric transformations¹⁷ or as reversible organic hydrogen storage liquids for hydrogen-powered fuel cells.¹⁸ Two main strategies can be proposed to obtain this skeleton: the direct hydrogenation of indole derivatives¹⁹ or the building of the core by successive chemical reactions, including asymmetric procedures.²⁰ If this last approach has been widely developed, only few examples are described in the case of hydrogenation of substituted indoles, which limits its application to organic synthesis.

In this paper we want to report our results on the hydrogenation of substituted indole derivatives. We will successively examine how the nature of the catalyst and of the solvent as well as the substitution of the different rings and of the nitrogen, may influence the selectivity of the reaction.

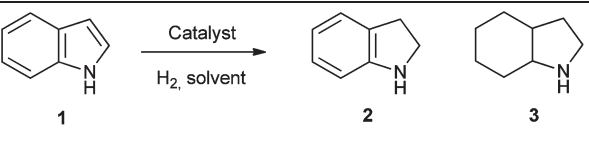
Results and discussion

We first chose to select our standard conditions by studying the hydrogenation of the unsubstituted indole. With the objective of delivering simple and selective methods useful for organic chemists, we used only commercially available heterogeneous catalysts. Classically, transition metal catalysts such as Pd, Ru, Rh or Pt are used, with different support and/or oxidation degree. Taking into account previous studies of this laboratory, we tested

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Table 1 Optimization of the reaction conditions


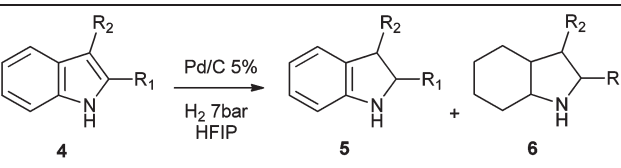
Entry	Catalyst	Solvent	<i>P</i> (bar)	<i>T</i> (°C)	<i>t</i> (h)	Yield ^a (%)	
						2	3
1	Pd/C	HFIP	7	11	22	17	77
2	Pd/C	HFIP	1	20	60	0	100
3	Pd/C	HFIP	7	20	22	0	100
4	Pd/C	HFIP	7	50	8	0	100
5	Pd/C	MeOH	7	20	50	22	0
6	Pd/C	MeOH	7	50	30	0	100
7	Pd/C	MeOH	7	50	8	21	67
8	Pd/C	TFE ^b	7	50	8	10	85
9	Pd/C	iPrOH	7	50	8	53	5
10	Pd/C	AcOH	1	20	60	22	57
11	PdO ₂	HFIP	7	50	8	72	14
12	PtO ₂	HFIP	7	50	8	0	100
13	RuO ₂	HFIP	7	50	8	0	0
14	Rh/Al ₂ O ₃	HFIP	7	50	8	0	100
15	Rh/Al ₂ O ₃	HFIP	1	20	22	33	51
16	Rh/Al ₂ O ₃	MeOH ^c	7	50	8	14	59

5% of metal; catalyst used, Pd/C (10% w/w), Rh/Al₂O₃ (5% w/w).
^a Estimated by ¹H NMR, missing product is starting material; standard conditions: indole 0.5 mmol, solvent 1 mL. ^b TFE: trifluoroethanol.
^c 14% of tetrahydroindole were detected.

more specifically HFIP as solvent, whose intrinsic properties turned out to be particularly interesting for the reduction of aromatic derivatives.^{2,3,21} Classical alcohols were also used as solvents. Moreover, catalytic hydrogenation usually requires forcing conditions, which could be diminished in the presence of acid, probably because of the formation of the iminium ion with disrupted aromaticity, which is then reduced more easily. We thus tried AcOH, frequently used for the hydrogenation of aromatic compounds. In a typical procedure, the indole derivative, the solvent and the catalyst were charged in an autoclave for the appropriate time under the requisite pressure. At the end of the reaction, the catalyst was filtered on Celite, the solvent evaporated and the reaction mixture analyzed by ¹H NMR. Results on the indole are summarized in Table 1.

HFIP turned out to be the best solvent. Using Pd/C under 7 bar of H₂ pressure at 50 °C in HFIP allowed to reduce totally the indole into octahydroindole in 8 h (entry 4). Whatever the solvent, indoline seemed to be the reaction intermediate (entries 1, 5, 8, 9 and 10) as no tetrahydroindole derivative was detected (except in the case of Rh/Al₂O₃ in MeOH, entry 16). In all cases, only the *cis* isomer of the octahydroindole was obtained. If there are numerous studies which claim access to *cis*-octahydroindole, to our knowledge, only Mokotoff and Hill have clearly assigned the two C1 and the C7a protons chemical shifts.²² Comparison with these reported data and NOESY experiments allowed us to confirm this stereochemistry (see ESI† part).

PtO₂ (entry 12) and Rh/Al₂O₃ (entry 14) revealed to be as efficient as Pd/C (entry 3) but for economical reason we chose Pd/C.

Table 2 Influence of the substitution of the pyrrole ring by electron donating groups on the hydrogenation of indole derivatives


Entry	R ₁ , R ₂	Comp. 4 (a-c)	<i>t</i> (h)	Yield ^a (%) 5(a-c)	6(a-c)
1 ²³	Me, H	a	8	0	100 (72 : 28) ^b
2	Me, H	a	1	82	Traces
3 ^c	Me, Me	b	22	10	50
4	Me, Me	b	8	0	100 (85) ^d (4 dia)
5	CH ₂ OH, H	c	48	0	100 (80 : 20) ^{b,e}
6	CH ₂ OH, H	c	8	40	40

^a Estimated by ¹H NMR, missing product is starting material; standard conditions: indole 0.5 mmol, HFIP 1 mL, 5% Pd/C, 50 °C, 7 bar H₂.
^b Diastereoisomeric ratio. ^c Performed at 20 °C. ^d Isolated yield. ^e 10% Pd/C.

We then tested indole derivatives bearing an electron donating group on the pyrrole ring (Table 2).

Once again, the intermediates are the indoline derivatives (Table 2, entries 2, 3, 6), which could explain why in the case of monosubstituted indoles two diastereoisomers of the octahydroindole derivatives were formed: the indolic compound was first adsorbed on the catalyst surface. Then, the pyrrole ring was reduced, leading to a racemic mixture of products. These two enantiomers were re-adsorbed on the catalyst surface, the benzene ring was hydrogenated in a *cis* manner, giving four compounds, enantiomers two to two, and thus two diastereoisomers, easily detectable by NMR. We assume that the adsorption of the indoline intermediate bearing the substituent which pointed towards the catalyst surface is more difficult which induces a difference in reactivity and thus justifies the diastereoselectivity. In the case of the tetrahydroindole intermediate, the pyrrole intermediate was also reduced in a *cis* way: a desorption-adsorption process may occur after the reduction of the first double bond and before the hydrogenation of the second one, which may explain the two diastereoisomers. Nevertheless, to a kinetic point of view, this is less favorable than a concomitant hydrogenation of the two aromatic bonds and thus in the case of the tetrahydroindole intermediate, the diastereoselectivity should be higher.

In the case of compound **6a**, a 72 : 28 ratio of two diastereoisomers was measured by ¹H NMR analysis, on protons 2 and 7a. Nevertheless, it was not possible to attribute the relative configuration of each center, despite all our efforts. In the case of compound **4c**, the intermediate **5c** is an amino alcohol which can act as a ligand for the palladium¹⁷ and thus reduce its activity, which can explain the results, 48 h *versus* 8 h for the reaction to go to completion (Table 2 entries 1 and 5). Two diastereoisomers in a 80 : 20 ratio were obtained (entry 5) but it was impossible to attribute the relative configuration of each center.

When an electron donating group was on the benzene ring, for example in the case of the 6-methoxy indole, a mixture of *cis* octahydroindole derivatives with a OMe, OH or H substituent on the 6 position was obtained.

We then examine the influence of an electron withdrawing group on the reactivity of indole derivatives (Table 3).

In these cases, the intermediates are the tetrahydroderivatives. This is in agreement with the hypothesis of the formation of the iminium salt intermediate: when an electron donating group is present on the pyrrole ring, it stabilizes the iminium which is then hydrogenated. In the case of an electron withdrawing group, this iminium is not stable, maybe not formed at all, and then the benzene ring is hydrogenated first. Moreover, when the ring is substituted on C2, contributing structures show a rupture of the benzene ring aromaticity *versus* a conservation of aromaticity when substituted on C3, which is in agreement with the easier formation of the tetrahydroindole intermediate in the first case. In the case of compound **4e**, the tetrahydroindole derivative **7e** was isolated exclusively (98% isolated yield, entry 1). This compound, intermediate in the synthesis of anti-inflammatory agents

and immunomodulators, has been obtained previously²⁴ by hydrogenation over Pd/C in iPrOH under 50 bar H₂ in 5 h at 110–140 °C which are considerably harder conditions than ours! When both the quantity of palladium and the reaction time increased, only minor quantities of the octahydroindole derivative **6e** were detected whereas Blankley *et al.*²⁵ reported the complete hydrogenation of the ethyl ester analog of **4e** in AcOH–EtOH using 10% Rh/C. When the ester is at position 3 (entries 2 and 3), the reduction was easier to perform, even though difficult and both the tetrahydro derivative **7f** and the octahydroindole **6f** can be isolated. A diastereoisomeric ratio of 73 : 27 was measured in favor of the (3*S**,3*aS**,7*aS**) isomer of **6f**. When the substituent is a carboxylic acid group (entry 4), in our standard conditions, decarboxylation occurs which has been already reported in the literature on indole derivatives with palladium.²⁶ Nevertheless, as no aromatic decarboxylated intermediates have been detected, we assume that this reaction occurred after total hydrogenation of the indole moiety. Using PtO₂ in acetic acid at atmospheric pressure of H₂ allowed this problem to be overcome, as described by Cativiela *et al.*²⁷ Changing HFIP for iPrOH allowed us to obtain selectively the tetrahydroderivative and also to avoid decarboxylation (entry 5).

With the access to natural products *via* the 2-carboxy-6-hydroxyoctahydroindole intermediate in mind, we thus examined the possibility to obtain them by hydrogenation of compounds of type **8**. In the literature, several methods have been published to build this skeleton by successive chemical reactions.²⁸ Nevertheless, to our knowledge, no direct hydrogenation of the disubstituted indole have been reported so far (Table 4).

As for compounds **8 (a,b)**, the intermediates were the tetrahydroindole derivatives **9 (a,b)**. Even with more catalyst and longer reaction time, it has not been possible for the reaction to go to completion (entries 1 and 2). Moreover, in the case of compound **9a**, a complex mixture of compound **10a** and demethylated or demethoxylated analogs was obtained. It has not been possible to isolate compound **10a** in its pure form. In the case of the 6-hydroxyderivative **8b**, compound **10b** was not observed as the hydrogenation stopped at the conjugated ketone derivative **11-(2*R**,3*aR**)** which could be easily isolated (entries 3 and 4).

Table 3 Influence of the substitution of the pyrrole ring by an electron withdrawing group on the hydrogenation of indole derivatives

Entry	R ₁ , R ₂	Comp. 4 (e–h)	t (h)	Yield ^a (%)	
				7 (e–h)	6 (e–h)
1	COOMe, H	e	8	98 ^b	0
2	H, COOMe	f	86	48 (42) ^b	52 (44) ^b
3	H, COOMe	f	48 ^c	25 ^b	75 ^b (73 : 27) ^d
4	COOH, H	g	4	0	0 ^f
5 ^e	COOH, H	g	8	45 ^b	0
6	H, COOH	h	8	59	0 ^g

^a Estimated by ¹H NMR, missing product is starting material; standard conditions: indole 0.5 mmol, HFIP 1 mL, 5% Pd/C, 50 °C, 7 bar H₂.
^b Isolated yield. ^c Performed with 10% Pd/C. ^d Diastereoisomeric ratio.
^e In iPrOH. ^f 100% ^g 21% Starting material and 20%

Table 4 Hydrogenation of 2,6-disubstituted indole derivatives

Entry	R	Comp. 8 (a,b)	% Pd/C	t (h)	Yield ^a (%)		
					9 (a,b)	10 (a,b)	11
1	Me	a	5	8	66 ^b	34 ^c	0
2	Me	a	10	48	42	58 ^c	0
3	H	b	5	8	38	0	38
4	H	b	10	8	45 ^b (60)	0	28 ^b (40)
5	H	b	20	24	50	0	50

^a Estimated by ¹H NMR, missing product is starting material; standard conditions: indole 0.5 mmol, HFIP 1 mL, 50 °C, 7 bar H₂. ^b Isolated yield.
^c Complex mixture of product **10** and demethylated/demethoxylated products.

Table 5 Influence of the *N*-protection on the hydrogenation of indole derivatives

Entry	R, R ₁ , R ₂	Comp. 12 (a–g)	<i>t</i> (h)	13 (a–g)	Yield ^a (%)	
					14 (a–g)	15 (a–g)

1 ³²	Ac, H, H	a	8	100	0	0
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2 ³³	Boc, H, H	b	8	100 (99) ^b	0	0
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3	Tos, H, H	c	8	0	0	0
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4	Boc, H, OMe	d	8	53 (31) ^b	0	47
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5 ³⁴	Boc, COOMe, H	e	8	71 (47) ^b	20 (8) ^b	0
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6	Boc, COOMe, OMe	f	8	63	Trace	Trace
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7	Me, COOH, H	g	14	0	0	60 (48) ^b (2 <i>S</i> *, 3 <i>aS</i> *, 7 <i>aS</i> *)
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8 ^c	Me, COOH, H	g	24	20	0	25
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^a Estimated by ¹H NMR, missing product is starting material; standard conditions: indole 0.5 mmol, HFIP 1 mL, 5% Pd/C, 50 °C, 7 bar H₂. ^b Isolated yield. ^c 20 °C.

^a Estimated by ¹H NMR, missing product is starting material; standard conditions: indole 0.5 mmol, HFIP 1 mL, 5% Pd/C, 50 °C, 7 bar H₂. ^b Isolated yield. ^c 20 °C.

Forcing the reaction conditions has not a substantial effect on the reaction progress (entry 5). Nevertheless, intermediate **11** could be of interest as a careful choice of the reduction system might lead to the *trans* octahydroindol intermediate, the *trans* junction being present in some bioactive molecules such as Trandopril.²⁹ Formation of compound **11** starting from intermediate of type **9** was difficult to explain. Increasing both the catalyst loading and the reaction time did not significantly modify the **9**:**11** ratio (entries 4 and 5). Therefore we can assume that compound **11** did not come from compound **9**.

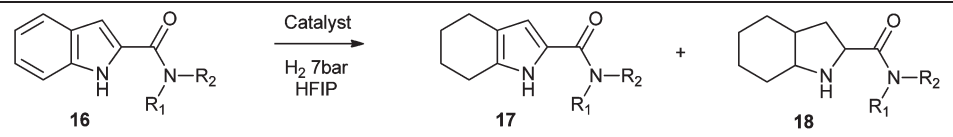

Substitution of the nitrogen group could also modify the reactivity of indole derivatives (Table 5). Among the different protecting groups, the *t*-butoxycarbonyl group (Boc), easy to introduce and easy to remove, was the most used. Thus Coulton *et al.*³⁰, with Rh/Al₂O₃ in EtOH–AcOH, selectively reduced various substituted indoles *N*-Boc protected into indolines. With PtO₂ in AcOH, Cativiela *et al.*³¹ obtained exclusively the octahydroindole derivative during the hydrogenation of indole-2-carboxymethyl ester *N*-Boc protected. With our system, introduction of the Boc group on the nitrogen slows down the reaction (compare Table 1 entry 4 and Table 5 entry 2) or even modifies the mechanism: for example, in the case of the indole-2-carboxymethyl ester **4e** only the tetrahydroindole derivative **7e** was isolated whereas for the *N*-Boc protected compound **12e**, the indoline intermediate **13e** was predominant (Table 3 entry 1 and Table 5 entry 5). The same tendency was observed for compound **8a** and its *N*-Boc-derivative **12f**. Considering the contributing structures, we assume that the introduction of the Boc group on the nitrogen, because of its electron withdrawing properties, diminishes the aromaticity of the pyrrole ring which is then easier to hydrogenate, leading to the indoline type intermediate, whereas in the case of electron withdrawing group on C2 or C3 positions, it is the aromaticity of the benzene ring which is decreased, leading to the tetrahydroindole intermediate.

The acyl group has the same effect on indole as the Boc one (entry 1). However, the *N*-sulfonyl indole **12c** failed to be reduced in our standard conditions (entry 3). This compound seems to be harder to reduce than the other *N*-substituted indoles as observed by Chandrasekhar *et al.*³⁵ In the case of an electron donating *N*-protecting group such as the methyl one, the reaction went slower (Table 3 entry 4 and Table 5 entry 7), the decarboxylation was limited but not suppressed.

As most of the natural products possessing the octahydroindole skeleton have an amide substituent at the 2-position,¹⁶ we thus decided to test the hydrogenation of these derivatives which would give a direct access to the desired octahydroindole compounds (Table 6).

Whatever the tested substrate, the intermediate was always the tetrahydroindole derivative **17** (a–e). In the case of unsubstituted nitrogen (entry 1), even harsher conditions (more palladium, longer reaction time) did not allow the reaction to go to completion. With only one hydrogen substituent on the nitrogen of the amide group, it has been possible to obtain with good isolated yields the octahydroindole derivative. When the substituent was the ethyl group (entry 2), a diastereoisomeric ratio of 88:12 in favor of the (2*S**, 3*aS**, 7*aS**) isomer was measured. When the substituent was a chiral substituent, no specific induction was observed as a mixture of 4 diastereoisomers in the same proportions as with the ethyl group was obtained (entry 6). In the case of disubstitution (entry 5), indole **16c** was totally hydrogenated and the octahydroindole derivative **18c** was isolated with an excellent diastereoisomeric ratio of 94:6 in favor of again the (2*S**, 3*aS**, 7*aS**) isomer. As for the Weinreb type amide (entry 7), the methoxy group was hydrogenolysed and the reactivity of the resulting compound could be compared to those of indole **16c**.

Table 6 Hydrogenation of 2-amido indole derivatives

					Yield ^a (%)	
Entry	R ₁ , R ₂	Comp. 16 (a–e)	t (h)	Catalyst	17 (a–e)	18 (a–e)
1	H, H	a	48	10% Pd/C	56	7
2	H, Et	b	48	10% Pd/C	9 ^b	91 ^b (88 : 12)
3	H, Et	b	5	5% Pd/C	52 ^b	0
4	Et, Et	c	3	5% Pd/C	62 ^b (65)	34 ^b (35)
5	Et, Et	c	48	5% Pd/C	0	93 ^b (100) (ratio 94 : 6)
6	H, 	d	48	10% Pd/C	8 ^b (10)	90 ^c
7	Me, OMe	e	24	5% Pd/C	5 ^b (10)	0
8 ^d	Me, OMe	e	39	5% Pd/C	56 ^b	0
9	Me, OMe	e	24	10% PtO ₂	25 ^b	0

^a Estimated by ¹H NMR, missing product is starting material; standard conditions: indole 0.5 mmol, HFIP 1 mL, 50 °C, 7 bar H₂. ^b Isolated yield.

^c Complex mixture of 4 diastereoisomers. ^d 20 °C.

Conclusions

In conclusion, a simple methodology to obtain tetrahydroindoles and/or octahydroindoles from indoles in a one pot reaction has been developed. Thus, the Pd/C-HFIP catalytic system has been demonstrated to be efficient for the hydrogenation of substituted indole derivatives, in mild conditions. Depending on the substituents, different compounds have been synthesized, and in particular various tetrahydroindoles have been isolated, which are valuable intermediates for the pharmaceutical industry. Moreover, octahydroindoles substituted by an amide group at C2 have been obtained with very good yield and diastereoselectivity, constituting an interesting class of synthesis intermediates.

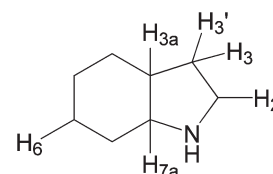
Experimental section

General remarks

NMR spectra were recorded on a Bruker AC300, 400 or a Bruker Advance III 500 MHz. HRMS Electron Impact (EI) or ElectroSpray (ESI) determinations were made using a Finigan-MAT 95 XL instrument. IR spectra (neat) were recorded on a Nicolet IS 100. Melting points were measured with a B-540 Büchi. *R_f* were calculated using TLC silicagel 60 F254 Merck.

General procedure for hydrogenation. The indole derivative (0.5 mmol) was added to a solution of catalyst in 1 mL of solvent and the solution was placed in an autoclave under hydrogen pressure at the requested temperature for a given time. The catalyst was then filtered through Celite and the product was

purified on silica gel.



(3aR*,7aR*)-Octahydro-1H-indole-HFIP 3. Yellow oil; *R_f* 0.25 (CH₂Cl₂–MeOH 85 : 15); H_{3a} H_{7a} Relation determined by NOESY; ¹H NMR: (400 MHz, CDCl₃) δ 7.68 (2H, br s), 4.26 (1H, sept, *J* = 6.5 Hz, H_{HFIP}), 3.21–3.07 (2H, m, H_{2,7a}), 2.97 (1H, ddd, *J* = 11.6, 9.6, 5.7 Hz, H_{2'}), 2.14–2.03 (1H, m, H_{3a}), 1.89–1.78 (2H, m, H₃), 1.72–1.21 (8H, m, H_{4–7}); ¹³C NMR: (100 MHz, CDCl₃) δ 69.9 (CH, sept, *J* = 33 Hz, C_{HFIP}), 57.6 (CH, C_{7a}), 43.3 (CH₂, C₂), 37.8 (CH, C_{3a}), 29.4 (CH₂, C₃), 26.5, 26.4, 22.7, 21.7 (4CH₂, C_{4–7}); ¹⁹F NMR: (282 MHz, CDCl₃) δ –76.15 (s); IR: ν 2925, 2854, 1448, 1374, 1284, 1180, 1099, 730 cm^{–1}; MS (ESI): calculated for C₁₁H₁₆N₂O [M + H]⁺: 126.1 found 126.1.

(2R*,3aS*,7aS*)-2-Methyloctahydro-1H-indole with (2S*,3aS*,7aS*)-2-methyloctahydro-1H-indole 6a. colorless oil; *R_f* 0.27 (CH₂Cl₂–MeOH 85 : 15); Mixture of diastereoisomers 72 : 28 A–B: ¹H NMR: (300 MHz, CDCl₃) δ 3.52–3.36 (0.7H, m, H_{2A}), 3.24–3.12 (1H, m, H_{2B,7aA}), 3.11–2.96 (1.3H, m, H_{1A,1B,7aB}), 2.09–1.90 (1.6H, m, H_{3B,3aA,3aB}), 1.77 (0.7H, ddd, *J* = 12.8, 8.0, 4.9 Hz, H_{3A}), 1.67–1.18 (9.6H, m, H_{3'A,4A,4B,5A,5B,6A,6B,7A,7B,8B}), 1.19–1.11 (2.4H, m, H_{8A}). ¹³C NMR: (75 MHz, CDCl₃) δ 58.0 (CH, C_{7aB}), 56.9 (CH, C_{7aA}), 53.2 (CH, C_{2B}), 51.1 (CH, C_{2A}),

39.4 (CH₂, C_{3B}), 39.1 (CH₂, C_{3A}), 38.9 (CH, C_{3aA}), 38.7 (CH, C_{3aB}), 28.8 (2CH₂, C_{4B,7B}), 27.9 (CH₂, C_{7A}), 26.9 (CH₂, C_{4A}), 23.8 (CH₂, C_{5B ou 6B}), 23.6 (CH₃, C_{8B}), 23.1 (CH₂, C_{5A ou 6A}), 23.0 (CH₃, C_{8B}), 21.7 (CH₂, C_{5B ou 6B}), 21.5 (CH₂, C_{5A ou 6A}).

2,3-Dimethyloctahydro-1H-indole-HFIP 6b. Colorless oil; mixture of 4 diastereoisomers; *R*_f 0.35 (CH₂Cl₂–MeOH: 85 : 15); ¹H NMR: (400 MHz, CDCl₃) δ 6.02 (2H, br s), 4.25 (1H, sept, *J* = 6.5 Hz, H_{HFIP}), 3.72–3.56 (0.6H, m), 3.48–3.39 (0.2H, m, H), 3.38–3.27 (0.4H, m, H), 3.24–3.15 (0.4H, m), 3.14–3.04 (0.2H, m), 2.81–2.71 (0.2H, m), 2.43–2.27 (0.5H, m), 2.17–1.97 (0.5H, m), 1.96–1.48 (5H, m), 1.47–0.81 (10H, m); ¹³C NMR: (100 MHz, CDCl₃) δ 122.6 (CF₃, q, *J* = 284 Hz, C_{HFIP}), 69.4 (CH, sept., *J* = 34 Hz, C_{HFIP}), 63.1, 61.5, 57.0, 56.4, 55.4, 54.5, 51.8, 45.7, 44.9, 42.8, 40.4, 39.4, 36.9, 30.8, 30.0, 28.7, 27.8, 26.4, 25.7, 25.4, 25.2, 25.1, 24.8, 23.5, 23.1, 23.0, 21.8, 21.2, 20.5, 20.4, 18.3, 17.0, 16.6, 16.3, 13.7, 12.8, 10.5. MS (ESI): calculated for C₁₀H₂₀N [M + H]⁺: 154.2 found 154.2.

(Octahydro-1H-indol-2-yl)methanol-HFIP 6c. Yellow oil; *R*_f 0.49 (CH₂Cl₂–MeOH 80 : 20); Mixture of two diastereoisomères 80 : 20; ¹H NMR (only one isomer can be clearly described): (400 MHz, CDCl₃) δ 5.96 (3H, s, H_{1,OH,11}), 4.33 (1H, sept., *J* = 6.5 Hz, H_{HFIP}), 3.71 (0.2H, dd, *J* = 11.5, 3.5 Hz, H_B), 3.57–3.31 (3H, m, HCH₂OH₂), 3.14 (1H, q, *J* = 5.3 Hz, H_{7a}), 2.18–1.96 (1H, m, H_{3a}), 1.76–1.13 (10H, m, H_{4,7}); ¹³C NMR (the two isomers can be described): (100 MHz, CDCl₃) δ 122.8 (CF₃, q, *J* = 284 Hz, C_{HFIP}), 69.9 (CH, sept., *J* = 32 Hz, C_{HFIP}), 65.2 (CH₂, C CH₂OH_A), 64.1 (CH₂, CCH₂OH_B), 59.9, 58.0 (2CH, C_{2B,7aB}), 58.4, 57.5 (2CH, C_{2A,7aA}), 38.4 (CH, C_{3aA}), 38.1 (CH, C_{3aB}), 32.8 (CH₂, C_{3A}), 32.2 (CH₂, C_{3B}), 28.3, 27.6, 23.0, 22.6 (4CH₂, C_{4-7B}) 27.0, 27.0, 23.2, 21.6 (CH₂, C_{4-7A}); HRMS (ESI): calculated for C₉H₁₈NO [M + H]⁺: 156.1383 found 156.1387.

Methyl octahydro-1H-indole-3-carboxylate 6f

(3S*,3aS*,7aS*)-6f. Colorless oil; *R*_f 0.53 (CH₂Cl₂–MeOH 80 : 20); H₃, H_{3a}, H_{7a} Relation determined by NOESY: ¹H NMR: (500 MHz, CDCl₃) δ 6.44 (1H, br s, H₁), 3.70 (3H, s, H_{MeO}), 3.65–3.37 (3H, m, H_{2,7a}), 2.94–2.85 (1H, m, H₃), 2.44 (1H, s, H_{3a}), 1.88–1.47 (6H, m), 1.44–1.31 (2H, m); ¹³C NMR: (125 MHz, CDCl₃) δ 173.9 (C, C_{CO}), 58.3 (CH, C_{7a}), 52.4 (CH₃, C_{MeO}), 46.3 (CH₂, C₂), 46.3 (CH, C₃), 42.5 (CH, C_{3a}), 26.1, 26.1, 22.4, 21.7 (CH₂, C₄₋₇); IR: ν 3303, 2925, 2857, 1730, 1173, 914 cm⁻¹. HRMS (ESI): calculated for C₁₀H₁₈NO₂ [M + H]⁺: 184.1332 found 184.1328.

(3R*,3aS*,7aS*)-6f. Colorless oil; *R*_f 0.49 (CH₂Cl₂–MeOH 80 : 20); H₃, H_{3a}, H_{7a} Relation determined by NOESY: ¹H NMR: (500 MHz, CDCl₃) δ 3.66 (3H, s, H_{MeO}), 3.53–3.40 (1H, m, H₂), 3.20 (1H, br s, H_{7a}), 3.14–3.07 (2H, m, H_{2',3}), 2.24–2.11 (2H, m, H_{1,3a}), 1.85 (1H, dd, *J* = 14.4, 2.0 Hz, H₇), 1.71–1.56 (2H, m, H_{5,7}), 1.52–1.44 (1H, m, H₆), 1.40–1.28 (2H, m, H_{4,6}), 1.19–1.11 (2H, m, H_{4',5}); ¹³C NMR: (125 MHz, CDCl₃) δ 173.5 (C, C_{CO}), 58.6 (CH, C_{7a}), 51.6 (CH₃, C_{Me}), 49.2 (CH, C₃), 46.2 (CH₂, C₂), 41.5 (CH, C_{3a}), 27.2 (CH₂, C₇), 24.7 (CH₂, C₅), 22.8 (CH₂, C₄), 20.1 (CH₂, C₆); IR: 3250, 2927, 2853, 1729, 1434, 1194, 1171, 922 cm⁻¹; HRMS (ESI): calculated for C₁₀H₁₈NO₂ [M + H]⁺: 184.1332 found 184.1324.

Methyl 4,5,6,7-tetrahydro-1H-indole-3-carboxylate 7f. White solid; *R*_f 0.33 (ethyl acetate–petroleum ether 30 : 70); mp: 123–125 °C; ¹H NMR: (400 MHz, CDCl₃) δ 8.37 (1H, br s), 7.25 (1H, s), 3.78 (3H, s), 2.73 (2H, t, *J* = 5.8 Hz), 2.54 (2H, t, *J* = 5.8 Hz), 1.86–1.69 (4H, m); ¹³C NMR: (100 MHz, CDCl₃) δ 166.3, 128.6, 122.4, 118.6, 113.7, 50.8, 23.4, 23.0, 22.8, 22.7; IR: ν 3300, 2924, 2851, 1671, 1437, 1326, 1144 cm⁻¹; HRMS (ESI): calculated for C₁₀H₁₃NO₂Na [M + Na]⁺: 202.0838 found 202.0848.

4,5,6,7-Tetrahydro-1H-indole-2-carboxylic acid 7g. White solid; *R*_f 0.20 (ethyl acetate–petroleum ether 30 : 70); mp: 158–159 °C; ¹H NMR: (400 MHz, CDCl₃) δ 6.66 (1H, d, *J* = 2.6 Hz), 3.94 (2H, br s), 2.56 (2H, t, *J* = 5.6 Hz), 2.45 (2H, t, *J* = 5.3 Hz), 1.85–1.57 (4H, m); ¹³C NMR: (100 MHz, CDCl₃) δ 165.8, 135.0, 120.6, 119.5, 116.5, 23.5, 23.1, 23.0, 22.8; IR: ν 3315, 2923, 2852, 1658, 1456, 1180, 761 cm⁻¹; HRMS (ESI): calculated for C₉H₁₀NO₂ [M – H]⁻: 164.0717 found 164.0722.

Methyl 6-methoxy-4,5,6,7-tetrahydro-1H-indole-2-carboxylate

9a. Yellow oil; *R*_f 0.51 (ethyl acetate–petroleum ether 60 : 40); ¹H NMR: (300 MHz, CDCl₃) δ 9.20 (1H, br s), 6.63 (1H, d, *J* = 2.3 Hz), 3.81 (3H, s), 3.74–3.62 (1H, m), 3.41 (3H, s), 2.96 (1H, dd, *J* = 16.0, 5.2 Hz), 2.71–2.56 (2H, m), 2.56–2.42 (1H, m), 2.12–1.94 (1H, m), 1.88–1.73 (1H, m); ¹³C NMR: (75 MHz, CDCl₃) δ 162.1, 131.3, 121.2, 119.0, 114.1, 76.2, 56.3, 51.4, 29.3, 28.2, 19.9; IR: ν 3300, 2927, 1674, 1471, 1292, 1222, 1090 cm⁻¹; HRMS (ESI): calculated for C₁₁H₁₅NO₃Na [M + Na]⁺: 2320.944 found 2320.944.

Methyl 6-hydroxy-4,5,6,7-tetrahydro-1H-indole-2-carboxylate

9b. White solid; *R*_f 0.62 (CH₂Cl₂–MeOH 90 : 10); mp: 146–148 °C; ¹H NMR: (400 MHz, MeOD–CDCl₃ 8 : 2) δ 6.60 (1H, s), 4.15–3.99 (1H, m), 3.77 (3H, s), 2.92 (1H, dd, *J* = 15.9, 4.8 Hz), 2.71–2.44 (3H, m), 1.95 (1H, d, *J* = 9.4 Hz), 1.83–1.67 (1H, m). ¹³C NMR: (100 MHz, MeOD–CDCl₃ 8 : 2) δ 163.1, 132.7, 121.5, 119.0, 115.0, 67.8, 51.4, 32.4, 20.6. IR: ν 3370, 3297, 2948, 2925, 2850, 1675, 1500, 1462, 1220, 1201, 1038 cm⁻¹; HRMS (ESI): calculated for C₁₀H₁₃NO₃Na [M + Na]⁺: 218.0788 found 218.0786.

(2S*,3aS*)-Methyl 6-oxo-2,3,3a,4,5,6-hexahydro-1H-indole-2-carboxylate 11. White solid; *R*_f 0.48 (CH₂Cl₂–MeOH 90 : 10); mp: 146–148 °C; H₂ H_{3a} relation determined by NOESY ¹H NMR: (300 MHz, CDCl₃) δ 6.13 (1H, br s, H₁), 5.24 (1H, s, H₇), 4.43 (1H, dd, *J* = 10.4, 6.5 Hz, H₂), 3.78 (3H, s, H_{MeO}), 3.03–2.85 (1H, m, H_{3a}), 2.60 (1H, dt, *J* = 12.3, 6.5 Hz, H₃), 2.47–2.25 (2H, m, H₅), 2.23–2.09 (1H, m, H₄), 1.83–1.58 (2H, m, H_{3',4'}); ¹³C NMR: (100 MHz, CDCl₃) δ 197.2 (C, C₆), 171.7, 171.0 (2C, C_{7a,CO}), 94.9 (CH, C₇), 60.0 (CH₃, C₂), 52.8 (CH, C_{MeO}), 40.7 (CH, C_{3a}), 36.1 (CH₂, C₅), 34.3 (CH₂, C₃), 27.9 (CH₂, C₄); IR: ν 3294, 3158, 3032, 2918, 2850, 1730, 1619, 1542, 1199 cm⁻¹; HRMS (ESI): calculated for C₁₀H₁₄NO₃ [M + H]⁺: 196.0968 found 196.0968.

***t*-Butyl 6-methoxyindoline-1-carboxylate 13d.** Yellow oil; *R*_f 0.60 (ethyl acetate–petroleum ether 30 : 70); Rotamer mixture; ¹H NMR: (400 MHz, CDCl₃) δ 7.53 (0.5H, br s), 7.28–7.06 (0.5H, br s), 7.00 (1H, d, *J* = 8.1 Hz), 6.47 (1H, dd, *J* = 8.1, 2.4 Hz), 4.10–3.87 (2H, m), 3.79 (3H, s), 3.00 (2H, t, *J* = 8.7 Hz), 1.69–1.44 (9H, m, H₁₁); ¹³C NMR: (100 MHz, CDCl₃) δ 159.9,

152.9, 144.6, 125.2, 124.0, 122.9, 109.0, 107.5, 101.6, 101.0, 81.8, 80.8, 56.8, 55.9, 48.2, 47.4, 32.4, 30.2, 30.1, 30.0, 29.0, 29.1, 28.9, 26.9, 26.7, 26.3, 25.3, 24.1, 21.4; IR: ν 3005, 2975, 2932, 2836, 1697, 1612, 1499, 1388, 1367, 1162, 852, 763 cm^{-1} ; HRMS (ESI): calculated for $\text{C}_{14}\text{H}_{19}\text{NO}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 272.1257 found 272.1258.

1-*t*-Butyl 2-methyl 6-methoxyindoline-1,2-dicarboxylate 13f. Colorless oil; R_f 0.50 (ethyl acetate–petroleum ether 30 : 70); ^1H NMR: (400 MHz, CDCl_3) δ 7.57 (1H, br s), 6.97 (1H, d, J = 8.2 Hz), 6.50 (1H, dd, J = 8.2, 2.1 Hz), 4.87 (1H, br s), 3.85–3.71 (6H, m), 3.43 (1H, dd, J = 15.9, 11.7 Hz), 3.03 (1H, dd, J = 15.9, 4.4 Hz), 1.79–1.33 (9H, m); ^{13}C NMR: (100 MHz, CDCl_3) δ 172.7, 160.1, 151.7, 143.9, 124.7, 119.7, 109.3, 100.6, 81.5, 61.4, 55.7, 52.4, 32.1, 28.4; IR: ν 3002, 2976, 2935, 2867, 1734, 1702, 1609, 1498, 1255, 1151, 1019, 912, 850, 763 cm^{-1} ; HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_5\text{Na}$ $[\text{M} + \text{Na}]^+$: 330.1312 found 330.1303.

(2*S,3*aS**,7*aS**)-1-Methyloctahydro-1*H*-indole-2-carboxylic acid 15g.** White solid; R_f 0.25 (CH_2Cl_2 –MeOH: 85 : 15); mp: 157–159 °C; H_2 , H_{3a} , H_{7a} Relation determined by NOESY: ^1H NMR: (300 MHz, CDCl_3) δ 7.95 (1H, br s), 3.64 (1H, dd, J = 10.2, 5.6 Hz, H_2), 3.21 (1H, q, J = 5.4 Hz, H_{7a}), 2.83 (3H, s, H_{Me}), 2.55–2.27 (2H, m, $\text{H}_{3a,3}$), 2.24–2.00 (1H, m, H_3), 1.96–1.83 (2H, m, H_7), 1.81–1.18 (6H, m, $\text{H}_{4,5,6}$); ^1H NMR: (500 MHz, C_6D_6) δ 4.09 (1H, br s), 3.48 (1H, dd, J = 10.2, 6.2 Hz, H_2), 2.56 (1H, q, J = 5.8 Hz, H_{7a}), 2.29 (3H, s, H_{Me}), 2.14 (1H, ddd, J = 13.0, 10.2, 6.5 Hz, H_3), 1.94 (1H, dt, J = 6.2, 13.0 Hz, H_3), 1.74–1.62 (1H, m, H_{3a}), 1.50–1.42 (1H, m), 1.38 (1H, ddd, J = 14.2, 9.2, 4.5 Hz), 1.34–1.24 (1H, m), 1.24–1.13 (3H, m), 1.10–1.00 (1H, m), 0.95–0.81 (1H, m); ^{13}C NMR: (75 MHz, CDCl_3) δ 171.1 (C, C_{CO}), 71.4 (CH, C_2), 68.5 (CH, C_{7a}), 42.0 (CH_3 , C_{Me}), 37.0 (CH, C_{3a}), 33.3 (CH_2 , C_3), 26.3, 24.3, 22.2, 21.2 (4CH_2 , C_{4-7}); IR: ν 3056, 2954, 2927, 2889, 2849, 2255, 1623, 1372, 1019 cm^{-1} ; HRMS (ESI): calculated for $\text{C}_{10}\text{H}_{17}\text{NO}_2\text{Na}$ $[\text{M} + \text{Na}]^+$: 206.1151 found 206.1152.

***N*-Ethyl-4,5,6,7-tetrahydro-1*H*-indole-2-carboxamide 17b.** Yellow oil; R_f 0.62 (CH_2Cl_2 –MeOH 90 : 10); ^1H NMR: (300 MHz, CDCl_3) δ 9.51 (1H, br s), 6.34 (1H, d, J = 2.4 Hz), 6.05 (1H, s), 3.43 (2H, q, J = 7.2 Hz), 2.59 (2H, t, J = 6.0 Hz), 2.48 (2H, t, J = 5.7 Hz), 1.88–1.63 (4H, m), 1.20 (3H, t, J = 7.2 Hz); ^{13}C NMR: (100 MHz, CDCl_3) δ 161.5, 131.7, 123.9, 118.9, 107.6, 34.3, 23.7, 23.2, 22.9, 22.8, 15.3; IR: ν 3256, 2926, 2852, 1676, 1545, 1246, 842 cm^{-1} ; HRMS (ESI): calculated for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$: 193.1335 found 193.1338.

***N,N*-Diethyl-4,5,6,7-tetrahydro-1*H*-indole-2-carboxamide 17c.** White solid; R_f 0.53 (ethyl acetate–petroleum ether 50 : 50); mp: 106–109 °C; ^1H NMR: (300 MHz, CDCl_3) δ 9.57 (1H, br s), 6.30 (1H, d, J = 2.1 Hz), 3.60 (4H, q, J = 7.0 Hz), 2.63 (2H, t, J = 5.8 Hz), 2.53 (2H, t, J = 5.7 Hz), 1.91–1.65 (4H, m), 1.27 (6H, t, J = 7.0 Hz); ^{13}C NMR: (75 MHz, CDCl_3) δ 161.8, 131.0, 122.8, 118.9, 110.8, 42.1, 23.8, 23.2, 22.9, 22.7, 13.7; IR: ν 3250, 2974, 2923, 2850, 1579, 1463, 1263, 1144, 828 cm^{-1} ; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{ONa}$ $[\text{M} + \text{Na}]^+$: 243.1468 found 243.1465.

***N*-Methoxy-*N*-methyl-4,5,6,7-tetrahydro-1*H*-indole-2-carboxamide 17e.** White solid; R_f 0.76 (CH_2Cl_2 –MeOH 90 : 10); mp:

146–148 °C; ^1H NMR: (400 MHz, CDCl_3) δ 9.88 (1H, br s), 6.66 (1H, d, J = 2.3 Hz), 3.77 (3H, s), 3.34 (3H, s), 2.63 (2H, t, J = 6.1 Hz), 2.53 (2H, t, J = 5.9 Hz), 1.88–1.64 (4H, m); ^{13}C NMR: (100 MHz, CDCl_3) δ 162.0, 132.6, 121.3, 119.6, 114.0, 61.0, 33.2, 23.7, 23.1, 22.9, 22.8; IR: ν 3250, 2934, 2850, 1594, 1235, 1129, 958 cm^{-1} ; HRMS (ESI): calculated for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2\text{Na}$ $[\text{M} + \text{Na}]^+$: 231.1104 found 231.1093.

***N*-Methyl-4,5,6,7-tetrahydro-1*H*-indole-2-carboxamide 17f.** White solid; R_f 0.55 (CH_2Cl_2 –MeOH 90 : 10); mp: 184–187 °C; ^1H NMR: (400 MHz, MeOD) δ 6.42 (1H, s), 2.82 (3H, s), 2.55 (2H, t, J = 6.1 Hz), 2.44 (2H, t, J = 5.9 Hz), 1.84–1.64 (4H, m); ^{13}C NMR: (100 MHz, MeOD) δ 164.8, 132.8, 124.6, 119.5, 110.6, 26.2, 24.9, 24.3, 23.8, 23.6; IR: ν 3356, 3165, 3086, 1574, 1497, 1248, 976 cm^{-1} ; HRMS (ESI): calculated for $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$: 179.1179 found 179.1182.

(2*R,3*aR**,7*aR**)-*N*-Ethyloctahydro-1*H*-indole-2-carboxamide 18b.** Yellow oil; R_f 0.20 (CH_2Cl_2 –MeOH 90 : 10); H_2 , H_{3a} , H_{7a} Relation determined by NOESY: ^1H NMR: (400 MHz, CDCl_3) δ 7.98 (1H, br s), 3.92 (1H, dd, J = 10.3, 5.6 Hz, H_2), 3.58 (1H, br s), 3.41–3.16 (3H, m, $\text{H}_{7a,\text{NCH}_2\text{CH}_3}$), 2.35 (1H, ddd, J = 12.9, 10.3, 7.0 Hz, H_3), 2.15–1.98 (1H, m, H_{3a}), 1.79 (1H, dt, J = 12.9, 5.6 Hz, H_3), 1.67–1.19 (8H, m, H_{4-7}), 1.14 (3H, t, J = 7.3 Hz, H_{Me}); ^{13}C NMR: (100 MHz, CDCl_3) δ 174.4 (C, C_{CO}), 58.9 (CH, C_2), 57.9 (CH, C_{7a}), 38.1 (CH, C_{3a}), 35.3 (CH_2 , C_3), 34.1 (CH_2 , $\text{C}_{\text{NCH}_2\text{CH}_3}$), 28.6, 27.2, 23.3, 22.0 (4CH_2 , C_{4-7}), 14.9 (CH_3 , C_{Me}); IR: ν 3300, 3073, 2928, 2856, 1660, 1563, 1379, 1276, 1081 cm^{-1} ; HRMS (ESI): calculated for $\text{C}_{11}\text{H}_{21}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$: 197.1648 found 197.1650.

(2*S,3*aR**,7*aR**)-*N*-Ethyloctahydro-1*H*-indole-2-carboxamide (2*R**,3*aR**,7*aR**)-*N*-ethyloctahydro-1*H*-indole-2-carboxamide 18b.** Yellow oil; R_f 0.20 (CH_2Cl_2 –MeOH 90 : 10); Mixture of diastereoisomers 88 : 12 A–B; ^1H NMR: (300 MHz, CDCl_3) δ 7.78 (0.85H, br s, H_{1A}), 3.84 (0.15H, dd, J = 9.1, 6.6 Hz, H_{2B}), 3.76 (0.85H, dd, J = 10.5, 5.2 Hz, H_{2A}), 3.42–3.16 (2.85H, m, H_{7aA} , NCH_2CH_3A , NCH_2CH_3B), 3.09 (0.15H, q, J = 5.0 Hz, H_{7aB}), 2.41–1.90 (3.15H, m, $\text{H}_{3A,3aA,9A,1B,3B,3aB,\text{NHB}}$), 1.87–1.70 (1H, m, $\text{H}_{3'A,3'B}$), 1.67–1.05 (11H, m, $\text{H}_{4-7A,4-7B,\text{CH}_3A,\text{CH}_3B}$); ^{13}C NMR: (125 MHz, CDCl_3) δ 175.4 (C, C_{COA}), 175.3 (C, C_{COB}), 58.9 (CH, C_{2A}), 58.8 (CH, C_{2B}), 57.7 (CH, C_{7aA}), 57.4 (CH, C_{7aB}), 38.1 (CH, C_{3aA}), 38.0 (CH, C_{3aB}), 35.8 (CH_2 , C_{3B}), 35.4 (CH_2 , C_{3a}), 33.6 (CH_2 , $\text{C}_{\text{NCH}_2\text{CH}_3A}$), 33.6 (CH_2 , $\text{C}_{\text{NCH}_2\text{CH}_3B}$), 29.1, 27.8, 27.4, 26.3, 23.5, 23.1, 21.8, 21.2 (8CH_2 , $\text{C}_{4-7A,4-7B}$), 14.9 (CH_3 , $\text{C}_{\text{NCH}_2\text{CH}_3B}$), 14.8 (CH_3 , $\text{C}_{\text{NCH}_2\text{CH}_3A}$). HRMS (ESI): calculated for $\text{C}_{11}\text{H}_{21}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$: 197.1648 found 197.1650.

(2*R,3*aR**,7*aR**)-*N,N*-Diethyloctahydro-1*H*-indole-2-carboxamide 18c.** Yellow solid; R_f 0.55 (CH_2Cl_2 –MeOH 85 : 15); mp: 152–154 °C; mixture of diastereoisomers 94/6; H_2 , H_{3a} , H_{7a} Relation determined by NOESY: ^1H NMR: (500 MHz, MeOD) δ 4.20 (0.07 H, dd, J = 10.3, 3.3 Hz, $\text{H}_{2\text{minor}}$), 4.12 (1H, dd, J = 10.0, 6.3 Hz, H_2), 3.60–3.39 (2H, m, $\text{H}_{\text{NCH}_2\text{CH}_3}$), 3.39–3.26 (3H, m, H_{7a} , NCH_2CH_3), 2.42 (1H, ddd, J = 12.7, 10.0, 7.0 Hz, H_3), 2.23–2.14 (1H, m, H_{3a}), 1.92–1.76 (2H, m, H_7), 1.62–1.46 (5H, m, $\text{H}_{3',4',5',6}$), 1.41–1.26 (2H, m, $\text{H}_{4,5}$), 1.22 (3H, t, J = 7.1 Hz, H_{Me}), 1.14 (3H, t, J = 7.1 Hz, H_{Me}); ^{13}C NMR: (125 MHz, MeOD) δ 172.9 (C, C_{CO}), 59.6 (CH, C_{7a}), 58.1

(CH, C₂), 42.5 (CH₂, C_{NCH₂CH₃}), 41.6 (CH₂, C_{NCH₂CH₃}), 39.5 (CH, C_{3a}), 37.3 (CH₂, C₃), 28.0 (CH₂, C₄), 27.1 (CH₂, C₇), 24.5 (CH₂, C₅), 22.3 (CH₂, C₆), 14.3 (CH₃, C_{Me}), 13.0 (CH₃, C_{Me}); IR: ν 3050, 2925, 2855, 1641, 1549, 1285, 1089, 732 cm⁻¹; HRMS (ESI) calculated for C₁₃H₂₅N₂O [M + H]⁺: 225.1961 found 225.1961.

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