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Synthesis and study of a heterocyclic receptor designed for carboxylic acids

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Abstract—The synthesis of a tricyclic receptor having a bowl shape and three binding points for carboxylic acids has been achieved starting from readily available 1-tetralone derivatives according to two different methods. This host possesses a six-membered lactam moiety and a carboxamide at the end of a flexible arm. Association constant with benzoic acid and stoichiometry of the complex have been determined using ^{1}H NMR dilution experiments.

1. Introduction

In a previous paper,[1] we described the synthesis of a heterocyclic receptor for carboxylic acids. The design of this receptor is outlined in Figure 1. The three binding points are ensured by a five or a six-membered lactam and a remote carboxamide incorporated on the benzene ring of an heterocyclic structure having a bowl shape. In order to obtain this bowl shape, ring B must be saturated and a *cis*-fusion between rings B and C is required. In this preliminary communication, we gave only few details concerning the design and the synthetic pathway.

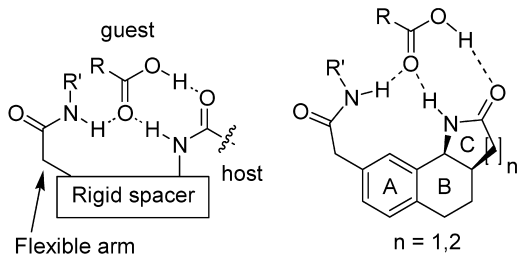

Figure 1. Cleft receptor design (left) and proposed receptor design (right).

The aim of this paper is to provide full details concerning both the design and the syntheses of this new kind of acids receptors.

2. Results and discussion

2.1. Design of the hosts

We performed first some molecular mechanic calculations (MM2 force field as implemented in PCMODEL® and CVFF force field as implemented in CERIUS[2]). We selected acetic acid as a model and tried the five and six-membered lactams **2a** and **2b** (Fig. 2).

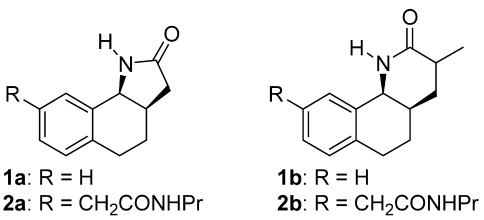

Figure 2. Selected five and six-membered lactams.

In these two cases, three hydrogen bonds can be obtained (structures depicted respectively in Figs. 3 and 4). We also performed some calculations at the PM3 level of theory on the six-membered lactam **2b**. Energy of the molecule was computed as a function of the dihedral angle θ between the benzene ring and the carboxamide group. As it can be seen in Figure 5, rotation about the flexible arm induces a maximum variation of 2 kcal mol^{-1}. As a consequence, it could be expected that the formation of a third hydrogen bond would be possible because the corresponding decreasing of the energy is larger than this variation.

In order to verify this hypothesis, it is necessary to compare the binding properties of receptors **1a**,**b** (two binding points)

Keywords: Molecular recognition; Carboxylic acids; Molecular modelling; Coupling reactions.
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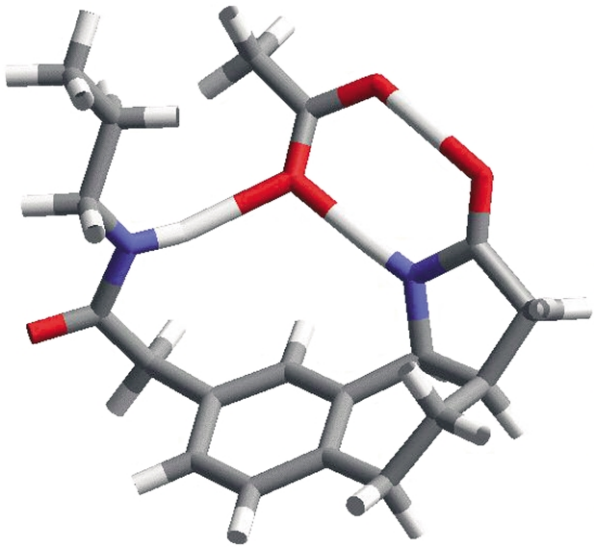


Figure 3. Molecular modelling of the five-membered lactam **2a** and its interactions with acetic acid.

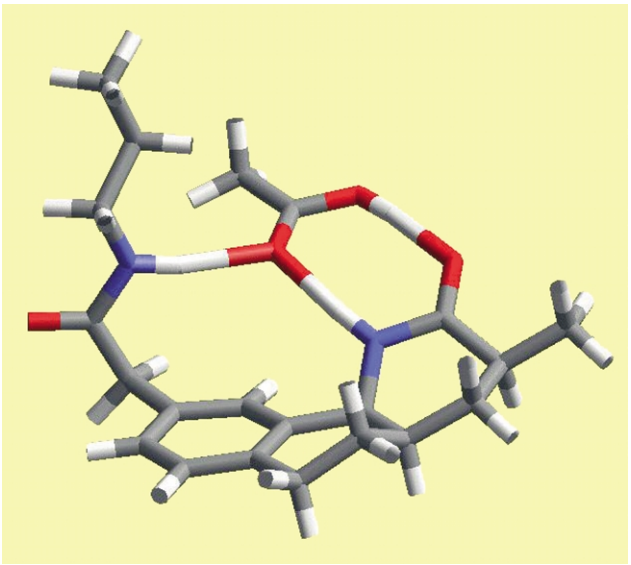


Figure 4. Molecular modelling of the six-membered lactam and its interactions with acetic acid.

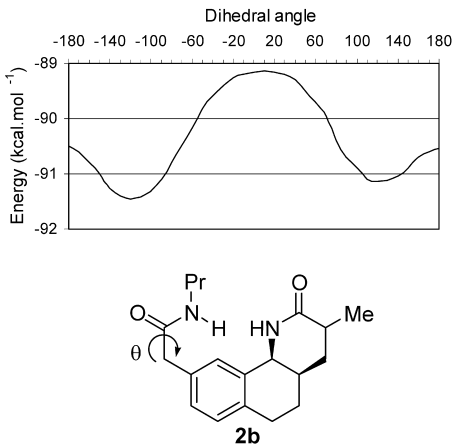


Figure 5. PM3 molecular modelling of host **2b** as a function of dihedral angle *θ*.

and receptors **2a**,**b** (three binding points). We decided first to synthesize the five-membered lactams.

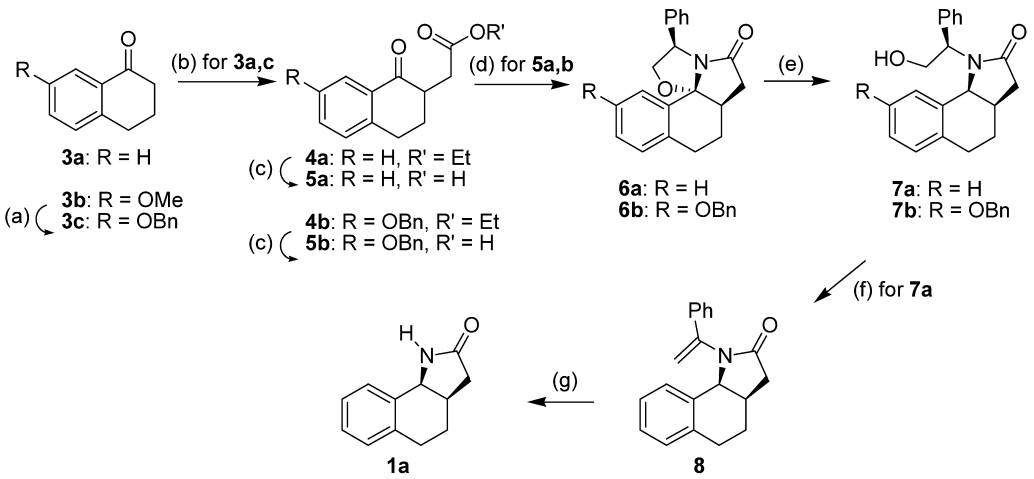
2.2. Towards the synthesis of the five-membered lactams

We selected the method used by Ennis et al.[2] in the β-tetralone series (Scheme 1). For this purpose, we needed an α-tetralone substituted at the 7-position by a group allowing further functional group interconversion leading to the carboxamide at the end of the flexible arm. The 7-benzyloxy-1-tetralone **3c** seemed to be a good choice since it could be obtained from the commercially available 7-methoxy-1-tetralone **3b**. Cleavage of the methoxy group of **3b** according to the procedure described by Chakrabotri et al.[3] and subsequent reaction with benzyl chloride under basic conditions afforded the required 7-substituted-1-tetralone **3c**. Tetralones **3a**,**c** where deprotonated with LDA and alkylated with ethyl bromoacetate in THF at −78 °C. While this work was in progress, Ennis and co-workers reported the same reaction on 1-tetralone **3a**.[4] The keto-esters **4a**,**b** thus obtained were then hydrolysed into the corresponding keto-acids **5a**,**b** and subsequent reaction with (*R*)-phenylglycinol led to the bis-lactams **6a**,**b**. As Ennis et al.[2] ring opening of bis-lactam **6a** proceeded smoothly but the same reaction on **6b** was more difficult and the yield was lower (67% for **6a** and 25% for **6b**). While dehydration of the alcohol **7a** led to the 7-unsubstituted lactam **8** in a 60% yield, only tarry material was obtained with the benzyloxy derivative. This first route being unsuccessful, we decided to focus our interest on the synthesis of the six-membered lactam.

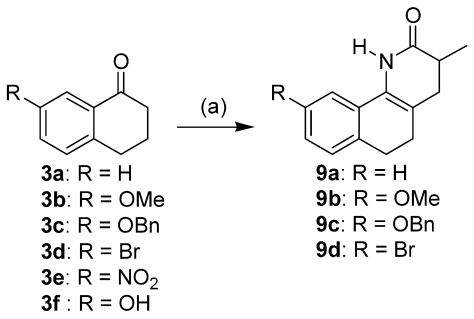
2.3. Synthesis of the six-membered lactam ring

The selected precursors were again 7-substituted-1-tetralones **3a**-**f**. They were reacted with methacrylamide under conditions published by Corriu's group[5] (Scheme 2). No reaction occurred with 7-nitro-1-tetralone **3e** and 7-hydroxy-1-tetralone **3f**, but benzo[*h*]quinolinones **9a**-**d** could be obtained in medium yields starting from tetralones **3a**-**d**. We tried to improve these yields by performing the reaction in various solvents but no significant improvement could be obtained. Having at hand the 7-substituted-1-tetralone **9d**, it was necessary to introduce the carboxamide group at the end of the flexible arm. We tried first the cuprous iodide catalysed reaction of the bromo derivative **9d** with diethyl malonate as described in our previous paper[1] (Scheme 3).

This method led to the targeted host **2b**. Careful examination of the ^{1}H NMR spectra of **2b** showed two signals corresponding to the N–H lactam and two signals for the methyl group at the 3-position. This fact could be explained by the epimerisation of the 3-position during the course of the synthesis. During the catalytic hydrogenation reaction of **13b** into **14**, the two hydrogen atoms attack the less hindered side of the molecule say *anti* to the methyl group leading to a racemic mixture of a single diastereoisomer. The ring junction is *cis* as showed by the small value of the coupling constant between the corresponding two hydrogen atoms (J=4 Hz). Moreover, a single signal is observed for the methyl group at the 3-position. However, epimerisation seems to occur during the decarboxylation



Scheme 1. Reagents, conditions and yields. (a) 1) PhSH, K_2CO_3, NMP, 30 min, 190 °C (80%). 2) K_2CO_3, Benzyl chloride, DMF, 4 h, 100 °C (90%); (b) 1) LDA, THF, 30 min, −78 °C. 2) Br–CH_2CO_2Et, 18 h, −78 °C→rt (40% for **4a**, 45% for **4b**); (c) KOH, EtOH, 2 h, reflux (85% for **5a** and **5b**); (d) (*R*)-phenylglycinol, toluene, 12 h, reflux (73% for **6a** and 72% for **6b**); (e) Et_3SiH, $TiCl_4$, CH_2Cl_2, 2 h, −78 °C (70% for **7a** and 25% for **7b**); (f) LiOH, H_2O, DMSO, 72 h, 100 °C (60%); (g) HCl, THF, H_2O, 8 h, reflux (40%).

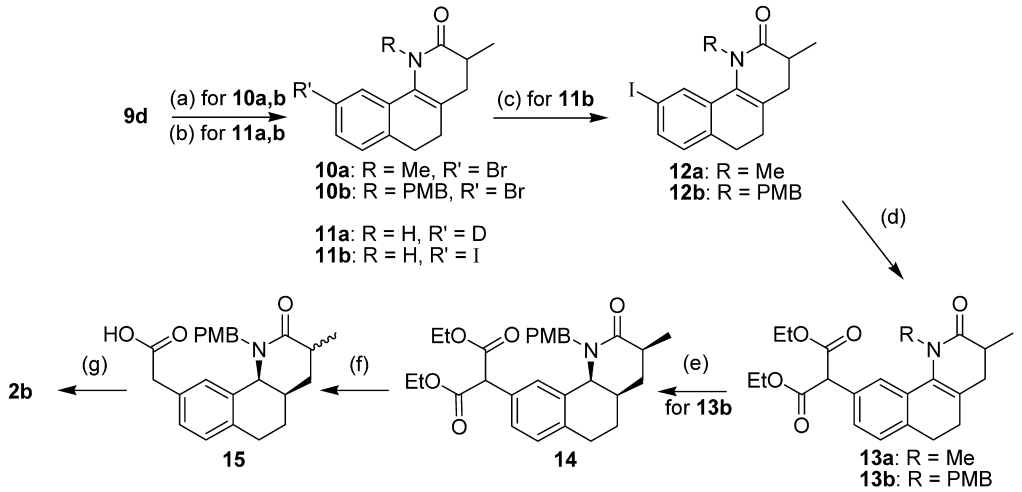


Scheme 2. Reagents, conditions and yields. (a) methacrylamide, $Si(OMe)_4$, CsF, 5 h, 80 °C (30–60%).

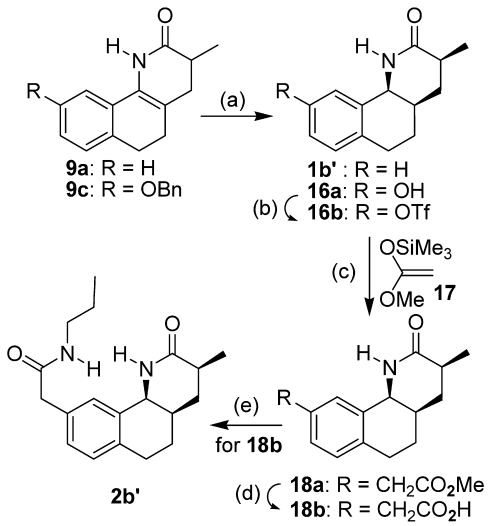
step which is carried out under basic conditions as shown by the duplication of the signal corresponding to the methyl group in the ^{1}H NMR spectrum of **15**. In order to avoid this troubleshooting decarboxylation step, we tried another synthesis involving the cross coupling reaction of the enoxysilane **17** with the triflate **16c** (Scheme 4). The required triflate **16b** was obtained within two steps starting from the benzyloxy derivative **9c**. Deprotection of the phenol and reduction of the C_{4a}–C_{10b} double bond of **9c** were achieved in the same pot via catalytic hydrogenation with 10% Pd–C and the phenol **16a** was converted into the triflate **16c** with ditriflimide under basic conditions. Cross coupling of the enoxysilane **17** with this triflate under conditions published by us[6] afforded ester **18a**. This ester was hydrolysed and the resulting intermediate carboxylic acid was converted into one of the stereoisomers **2b′** of the targeted host **2b**.

2.4. Binding properties of the hosts 1b′ and 2b′

We first performed some dilution experiments in order to study the self-association of the hosts **1b′** and **2b′**. They



Scheme 3. Reagents, conditions and yields. (a) CH_3I for **10a** and PMBCl for **10b**, KOH, DMSO, 30 min, rt (40% for **10a**, 60% for **10b**); (b) 1) *n*-BuLi, THF, 10 min, −78 °C. 2) *tert*-BuLi, 1 h, −78 °C. 3) MeOD for **11a** and I_2 for **11b**, 2 h, −78 °C (100% for **11a** by ^{1}H NMR, 70% for isolated **11b**); (c) same reagents and conditions as in a (40% for **12a** and 60% for **12b**); (d) EtOOC–CH_2–COOEt, NaH, CuI, dioxane, 5 h, reflux (40% for **13a**, 50% for **13b**); (e) H_2, Pd–C 10%, EtOH, 1 bar, 12 h, rt (45%); (f) 1) 3% NaOH, EtOH, 15 h, rt. 2) HCl, pH=2. 3) CuI, CH_3CN, 1 h, 60 °C (100% by ^{1}H NMR); (g) *n*-propylamine, EDCI, HOBt, MeCN, 72 h, rt (35%). 2) CAN, H_2O, MeCN, 5 h, rt (35%).



Scheme 4. Reagents, conditions and yields. (a) H_2, Pd–C 10%, EtOH, 1 bar, 12 h, rt (80% for **1b′** from **9a**, 85% for **16a** from **9c**); (b) Ditriflimide, DMF, NEt_3, 4 h 30, 0 °C→rt (40%); (c) $Pd(PPh_3)_4$, CH_3COOLi, THF, 21 h, reflux (40%); (d) 3% NaOH, EtOH, 15 h, rt (89%); (e) *n*-propylamine, EDCI, HOBt, MeCN, 72 h, rt (65%).

were dissolved in chloroform-*d* and on dilution, an upfield chemical shift of the lactam N–H proton could be observed. Classical Horman and Dreux[7] analysis of these shift values gave a Kd value (dimerisation constant) of about 20 M^{-1} for **2b′**. However, the method did not converge in the case of **1b′**. These two hosts were then titrated with benzoic acid. In order to specify the stoichiometry of the complexes formed, we first performed Job plots[8] (Fig. 6 for **1b′** and Fig. 8 for **2b′**). These plots clearly show the formation of 1/1 complexes (maximum value at x=0.5).

The association constants K_a were then determined assuming a 1/1 complexation process and neglecting the dimerisation process for **2b′**. K_a values of 80 and 200 M^{-1} were obtained for **1b′** and **2b′** respectively (Fig. 7 for **1b′** and Fig. 9 for **2b′**).

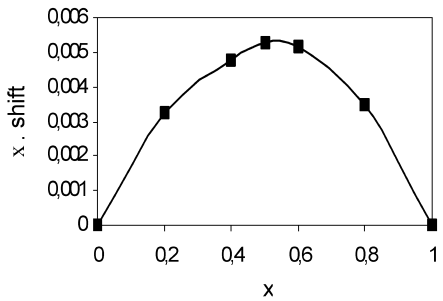


Figure 6. Job plot of host **1b′**. The sum of host and guest concentrations was constant (C_0=0.0135 mol L^{-1}, guest concentration=xC_0) and the chemical shift of the lactam proton was monitored.

3. Conclusion

Our initial goal was to design a new kind of host for carboxylic acids. We selected a tricyclic structure with a bowl shape and a carboxamide moiety at the end of a flexible arm. We first checked this design with molecular and quantum mechanics calculations. Calculations were in good agreement with this design and showed that both a five

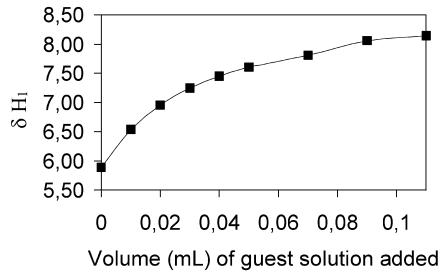


Figure 7. Titration of host **1b′** with benzoic acid. The initial guest concentration was 0.0204 mol L^{-1}. Aliquots of a guest solution (0.287 mol L^{-1}) were added and the chemical shift of the lactam proton was monitored.

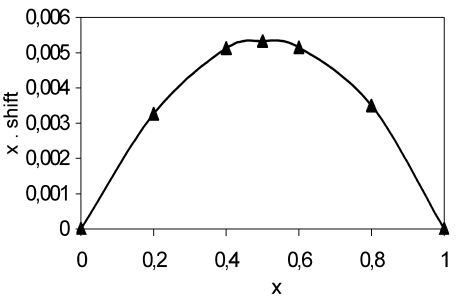


Figure 8. Job plot of host **2b′**. The sum of host and guest concentrations was constant (C_0=0.0135 mol L^{-1}, guest concentration=xC_0) and the chemical shift of the lactam proton was monitored.

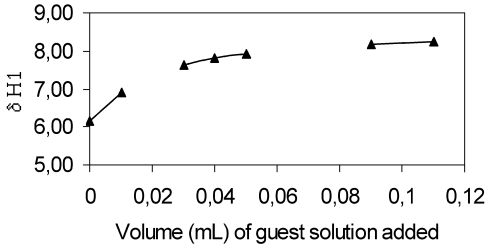


Figure 9. Titration of host **2b′** with benzoic acid. The initial guest concentration was 0.0193 mol L^{-1}. Aliquots of a guest solution (0.304 mol L^{-1}) were added and the chemical shift of the lactam proton was monitored. Owing to the complexity of spectra, some chemical shifts could not be measured.

or a six-membered lactam could be incorporated in the tricyclic part. Unfortunately the synthesis of the selected hosts was impossible in the case of a five membered lactam. However, it was possible to obtain the hosts **2b** and **2b′** with a six-membered lactam according to two different routes. A NMR study with monitoring of the lactam proton of **2b′** as a function of host and guest concentrations was then undertaken.

The lactam moiety of host **1b′** is able to bind with benzoic acid with an association constant of 80 M^{-1} in good agreement with a two binding points process. Addition of a third binding point (in **2b′**) ensures a significant increasing of the association constant and confirms that the flexible arm is really involved in the binding process.

We are now trying to incorporate an amine receptor in the flexible arm in order to obtain a receptor able to promote the

reaction between an acid and an amine via a supramolecular process.

4. Experimental

4.1. General details

The infra-red spectra were recorded on a Beckmann IR 4250 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a 200 or 300 MHz Bruker apparatus. Spectra were recorded in deuteriochloroform or in hexadeuteriodimethylsulfoxide (DMSO-d_6). Chemical shifts are given in ppm with TMS or HMDS as internal reference. Chemicals were purchased from Aldrich Co. and Janssen Co. and, unless otherwise stated, were used without further purification. Flash chromatography was performed with silica 60 (70–230 mesh from Merck) and monitored by thin layer chromatography (TLC) with silica plates (Merck, Kieselgel 60 F254).

4.1.1. Ethyl (7-benzyloxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (4b). To a cooled (−78 °C) solution of LDA (1.58 mmol, freshly prepared from diisopropylamine and *n*-butyllithium) in THF (1 mL), a solution of tetralone **3c** (400 mg, 1.58 mmol) in THF (1 mL) was slowly added. After 30 min stirring at −78 °C, a solution of ethyl bromoacetate (210 μL, 1.9 mmol) in THF (3.2 mL) was added. The resulting mixture was allowed to warm to rt and stirred for 18 h. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was successively washed with water, an aqueous solution of sodium hydrogencarbonate (5%) and an aqueous solution of hydrochloric acid (5%). After drying on magnesium sulfate, the solvent was removed under reduced pressure. Flash chromatography on silica gel (cyclohexane/dichloromethane 8/2, R_f=0.3) afforded 241 mg (45%) of compound **4b** as a pale yellow oil. IR (KBr) 1682, 1732 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H, *J*=7.2 Hz), 1.92 (m, 1H), 2.18 (m, 1H), 2.34 (m, 1H), 2.99 (m, 4H), 4.11 (q, 2H, *J*=7.2 Hz), 5.02 (s, 2H), 7.09 (m, 2H), 7.22–7.39 (m, 5H), 7.51 (d, 1H, *J*=1.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.7, 28.9, 29.9, 35.6, 45.1, 60.9, 70.5, 110.9, 122.8, 127.9, 128.4, 129.0, 130.4, 133.3, 137.0, 137.3, 151.9, 172.9, 198.7. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.41; H, 6.42.

4.1.2. 7-Benzyloxy-11-phenyl-2,2a,3,4,10,11-hexahydro-9-oxa-11a-aza-pentaleno[6a,1-a]naphthalen-1-one (6b). To a solution of ester **4b** (250 mg, 0.74 mmol) in ethanol (2.1 mL), potassium hydroxide (45.4 mg, 0.8 mmol) in ethanol (0.4 mL) was added and the resulting mixture was heated to reflux for 2 h. After cooling to rt, the solution was extracted with dichloromethane and the aqueous layer was acidified with diluted hydrochloric acid. Extraction with dichloromethane followed by drying on magnesium sulfate and removal of solvents under reduced pressure afforded 195 mg (85%) of crude (7-benzyloxy-1-oxo-1,2,3,4-tetrahydronaphth-2-yl)acetic acid **5b** as a white solid. IR (KBr) 1680, 1712, 3082 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.92 (m, 1H), 2.18 (m, 1H), 2.34 (m, 1H), 2.99 (m, 4H), 5.02 (s, 2H), 7.09 (m, 2H), 7.22–7.39 (m, 5H), 7.51 (d, 1H, *J*=1.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.9, 29.9, 35.5, 44.9, 70.5, 110.9, 123.0, 127.9, 128.5, 129.0, 130.5, 133.1, 137.0, 137.3, 157.9, 178.4, 198.8. A solution of the above ketoacid **5b** (200 mg, 0.64 mmol) and (*R*)-phenylglycinol (172 mg, 1.28 mmol) in toluene (3.2 mL) was heated to reflux for 12 h in a flask fitted with a Dean Stark trap. After cooling to rt, the toluene was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2, R_f=0.4) to afford 190 mg (72%) of compound **6b** as a brown oil. IR (KBr) 1497, 1714 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (m, 1H), 2.25 (m, 1H), 2.41 (m, 1H), 2.70 (m, 3H), 2.70 (m, 1H), 3.89 (d, 1H, *J*=16.1 Hz), 4.10 (d, 1H, *J*=16.1 Hz), 4.08 (dd, 1H, *J*=8.7, 8.7 Hz), 4.59 (dd, 1H, *J*=8.7, 8.7 Hz), 5.25 (t, 1H, *J*=8.7 Hz), 6.42 (d, 1H, *J*=1.5 Hz), 6.75 (dd, 1H, *J*=6.5, 1.5 Hz), 6.98–7.36 (m, 11H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 27.5, 28.9, 41.2, 44.1, 58.8, 69.4, 71.5, 111.7, 117.4, 127.0, 127.8, 128.0, 128.2, 128.8, 129.3, 139.9, 179.6. Anal. Calcd for $C_{27}H_{25}NO_3$: C, 78.81; H, 6.12; N, 3.40. Found: C, 78.95; H, 6.2; N, 3.45.

4.1.3. 8-Benzyloxy-1-(3-hydroxy-1-phenylpropyl)-1,3,3a,4,5,9b-hexahydro-benz[*g*]indol-2-one (7b). To a cooled (−78 °C) solution of bis-lactam **6b** (194 mg, 0.47 mmol) in dichloromethane (2 mL), triethylsilane (335 μL, 2.07 mmol) was added. The mixture was stirred at −78 °C for 15 min and titanium tetrachloride (228 μL, 2.07 mmol) was slowly added. The solution was stirred −78 °C for 2 h, allowed to warm to rt and hydrolized with a saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with dichloromethane. The organic layer was washed with water, dried on magnesium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 2/8, R_f=0.4) to afford 50 mg (25%) of compound **7b** as an amorphous solid. IR (KBr) 1659, 3266 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65 (m, 2H), 2.30 (dd, 1H, *J*=18.0, 3.6 Hz), 2.49–2.82 (m, 3H), 2.85 (dd, 1H, *J*=18.0, 8.9 Hz), 3.75 (m, 2H), 4.10 (m, 1H), 4.52 (m, 1H), 4.31 (d, 1H, *J*=9.1 Hz), 5.05 (m, 2H), 6.40 (m, 1H), 6.61 (m, 1H), 6.92 (m, 2H), 7.11–7.25 (m, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.6, 29.9, 31.3, 60.9, 62.0, 62.5, 64.9, 116.0, 117.3, 127.3, 127.8, 128.1, 128.2, 129.1, 129.3, 130.1, 132.1, 133.4, 137.3, 154.9, 177.0. Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.61; H, 6.44; N, 3.31.

4.2. General procedure for the Corriu's reaction of 1-tetralones with methacrylamide

Cesium fluoride must be dried on phosphoric anhydride, under vacuum at 100 °C. Under a stream of nitrogen, cesium fluoride, 7-substituted-1-tetralone, methacrylamide and tetramethoxysilane were introduced into a flask. The resulting mixture was heated at 80 °C for 5 h. The mixture was then cooled to rt, triturated with ethyl acetate and filtered on a celite pad. The solution was washed with water, dried on magnesium sulfate and the solvent was removed under reduced pressure. The final product was recrystallized or chromatographed on silica gel.

4.2.1. 3-Methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (9a). According to the general procedure, 1-tetralone **3a** (3.2 g, 22 mmol), cesium fluoride (5.35 g, 35 mmol),

methacrylamide (1.9 g, 22 mmol) and tetramethoxysilane (5.15 mL, 35 mmol) afforded 1.8 g (40%) of **9a** after recrystallization from ethyl acetate. Mp 174 °C (lit.[5] 173 °C). IR (KBr) 1660, 3245 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (d, 3H, J=7.2 Hz), 2.15–2.61 (m, 5H), 2.69–2.77 (m, 2H), 7.02 (m, 4H), 7.39 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.9, 27.0, 28.6, 34.6, 35.4, 114.4, 119.2, 127.1, 127.7, 128.4, 129.7, 136.1, 174.8. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.8; H, 7.1; N, 6.6.

4.2.2. 9-Methoxy-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (9b). According to the general procedure, 7-methoxy-1-tetralone **3b** (0.39 g, 2.2 mmol), cesium fluoride (2.68 g, 17.5 mmol), methacrylamide (0.95 g, 2.2 mmol) and tetramethoxysilane (2.58 mL, 17.5 mmol) afforded 0.146 g (60%) of **9b** after recrystallization from ethyl acetate. Mp 114 °C. IR (KBr) 1672, 3220 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20 (d, 3H, J=7.5 Hz), 2.10–2.60 (m, 7H), 3.60 (s, 3H), 6.60 (d, 1H, J=1.5 Hz), 6.75 (dd, 1H, J=7.0, 1.5 Hz), 6.95 (d, 1H, J=7.0 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.15, 29.62, 29.96, 36.96, 37.70, 58.18, 107.88, 114.98, 116.51, 129.10, 130.21, 131.47, 132.57, 160.95, 176.01. HRMS. Calcd for $C_{15}H_{17}NO_2$: 243.1259. Found: 243.1250.

4.2.3. 9-Benzyloxy-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (9c). According to the general procedure, 7-benzyloxy-1-tetralone **3c** (0.555 g, 2.2 mmol), cesium fluoride (2.68 g, 17.5 mmol), methacrylamide (0.95 g, 2.2 mmol) and tetramethoxysilane (2.58 mL, 17.5 mmol) afforded 0.282 g (40%) of **9c** after flash chromatography on silica gel (cyclohexane/dichloromethane 3/7, R_f=0.4). Mp 159 °C (ethyl acetate). IR (KBr) 1660, 3240 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20 (d, 3H, J=7.4 Hz), 2.10–2.70 (m, 7H), 5.00 (s, 2H), 6.70 (m, 2H), 6.95 (d, 1H, J=8.1 Hz), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.9, 27.3, 27.7, 34.6, 35.4, 70.6, 106.7, 113.5, 115.3, 127.8, 128.4, 128.9, 129.1, 130.8, 137.1, 137.3, 158.2, 174.8. Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 79.05; H, 6.7; N, 4.3.

4.2.4. 9-Bromo-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo-[*h*]quinolin-2-one (9d). According to the general procedure, 7-bromo-1-tetralone **3d** (5 g, 22 mmol), cesium fluoride (5.35 g, 35 mmol), methacrylamide (1.9 g, 22 mmol) and tetramethoxysilane (5.15 mL, 35 mmol) afforded 1.9 g (30%) of **9d** after recrystallization from ethyl acetate. Mp 212 °C. IR (KBr) 1670, 3230 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, 3H, J=7.4 Hz), 2.27–2.80 (m, 7H), 7.00 (d, 1H, J=8.1 Hz), 7.29 (d, 1H, J=8.1 Hz), 7.46 (s, 1H), 8.45 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.3, 26.3, 27.4, 34.0, 34.7, 115.4, 120.2, 122.5, 127.5, 129.2, 129.7, 131.2, 134.3, 174.5. Anal. Calcd for $C_{14}H_{14}BrNO$: C, 57.55; H, 4.83; N, 4.79. Found: C, 57.4; H, 4.9; N, 4.6.

4.3. General procedure for the halogen–lithium exchange reaction on 9-bromo-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (9d)

In a flask flushed with nitrogen, the bromo derivative (0.292 g, 1 mmol) was dissolved in THF (6 mL) and the solution was cooled at −78 °C. Then, *n*-butyllithium (0.96 mL, 2.2 mmol) was added and the solution was stirred for 10 min at −78 °C. *tert*-Butyllithium (1 M solution, 3.4 mL, 3.4 mmol) was then added and the appropriate electrophile was added after 1 h stirring at −78 °C.

4.3.1. 9-Deutero-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (11a). The electrophile was methanol-*d* (1 mL, 2.4 mmol). After 2 h stirring at −78 °C, hydrolysis was carried out with a saturated aqueous solution of NH_4Cl. The solution was allowed to warm at rt and extracted with dichloromethane. The combined extracts were dried on magnesium sulfate and concentrated under reduced pressure to afford 0.214 mg of crude product **11a** which was not further purified. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30 (d, 3H, J=6.5 Hz), 2.4–2.8 (m, 7H), 7.30 (s, 3H), 7.90 (s, 1H).

4.3.2. 9-Iodo-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]-quinolin-2-one (11b). The electrophile was a solution of iodine (0.86 g, 3.4 mmol) in THF (8.6 mL). After 2 h stirring at −78 °C, hydrolysis was carried out with a saturated aqueous solution of sodium thiosulfate until disappearance of the red colour. The solution was allowed to warm at rt and extracted with dichloromethane. The combined extracts were dried on magnesium sulfate and concentrated under reduced pressure to afford 0.237 mg (70%) of **11b** after recrystallization from ethyl acetate. Mp 225 °C. IR (KBr) 1670, 3240 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 (d, 3H, J=6.5 Hz), 2.35–2.80 (m, 7H), 6.92 (d, 1H, J=6.5 Hz), 7.47 (d, 1H, J=6.5 Hz), 7.52 (s, 1H), 7.79 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.9, 26.8, 28.1, 34.6, 35.3, 91.9, 115.9, 127.7, 128.6, 130.0, 131.9, 135.5, 136.4, 174.8. Anal. Calcd for $C_{14}H_{14}INO$: C, 49.58; H, 4.16; N, 4.13. Found: C, 49.6; H, 4.2; N, 4.2.

4.4. General procedure for the protection of the N–H lactam

Potassium hydroxide (0.224 g, 4 mmol, previously dried under vacuum) was dissolved in freshly distilled DMSO (3 mL). The lactam and the alkylation reagent were then added. The mixture was stirred at rt for 30 min. Water was then added and the resulting solution was extracted with dichloromethane. The extracts were washed with water, dried and concentrated under reduced pressure.

4.4.1. 9-Bromo-1,3-dimethyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (10a). According to the general procedure, compound **9d** (0.292 g, 1 mmol) and methyl iodide (0.25 mL, 4 mmol) afforded 0.123 g (40%) of N-protected compound **10a** as a yellow solid after purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 7/3, R_f=0.3). Mp (ethyl acetate) 124 °C. IR (KBr) 1670 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, 3H, J=7.4 Hz), 2.27–2.80 (m, 7H), 3.12 (s, 3H), 7.0 (d, 1H, J=8.1 Hz), 7.29 (d, 1H, J=8.1 Hz), 7.46 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.3, 26.3, 27.4, 34.0, 34.7, 36.1, 115.4, 120.2, 122.5, 127.5, 129.2, 129.7, 131.2, 134.3, 174.5. Anal. Calcd for $C_{15}H_{16}BrNO$: C, 58.84; H, 5.27; N, 4.57. Found: C, 58.9; H, 5.45; N, 4.6.

4.4.2. 9-Iodo-1,3-dimethyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (12a). According to the general

procedure, compound **11b** (0.339 g, 1 mmol) and methyl iodide (0.25 mL, 4 mmol) afforded 0.142 g (40%) of N-protected compound **12a** as a pale yellow solid after purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 7/3, R_f=0.3). Mp (ethyl acetate) 136 °C. IR (KBr) 1670 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, 3H, J=7.2 Hz), 2.10–2.60 (m, 7H), 3.12 (s, 3H), 6.80 (d, 1H, J=7.0 Hz), 7.28 (d, 1H, J=1.5 Hz), 7.41 (dd, 1H, J=7.0, 1.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.4, 28.2, 28.3, 33.4, 34.5, 35.9, 91.5, 125.3, 129.8, 131.7, 132.9, 134.4, 135.7, 136.3, 175.7. Anal. Calcd for $C_{15}H_{16}INO$: C, 51.01; H, 4.57; N, 3.97. Found: C, 51.1; H, 4.7; N, 4.0.

4.4.3. 9-Iodo-1-(4-methoxybenzyl)-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (12b). According to the general procedure, compound **11b** (0.339 g, 1 mmol) and 4-methoxybenzyl chloride (0.205 mL, 1.5 mmol) afforded 0.176 g (60%) of N-protected compound **12b** as a brown solid after purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 85/15, R_f=0.3). Mp (ethyl acetate) 102 °C. IR (KBr) 1667 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, 3H, J=7.1 Hz), 2.01–2.48 (m, 7H), 3.68 (s, 3H), 4.52 (d, 1H, J=11.8 Hz), 5.13 (d, 1H, J=11.8 Hz), 6.61 (m, 2H), 6.83 (m, 3H), 7.29 (d, 1H, J=1.5 Hz), 7.41 (dd, 1H, J=8.0, 1.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.3, 28.1, 28.3, 33.3, 36.4, 47.4, 55.6, 91.4, 113.9, 127.9, 129.7, 129.8, 130.5, 131.7, 133.0, 133.3, 135.7, 136.4, 159.0, 175.8. Anal. Calcd for $C_{22}H_{22}INO_2$: C, 57.53; H, 4.83; N, 3.05. Found: C, 57.40; H, 4.78. N, 2.99.

4.5. General procedure for the copper catalysed coupling reactions with diethyl malonate

To a suspension of sodium hydride (55% dispersion in mineral oil) in dry dioxane freshly distilled diethyl malonate was added under nitrogen. Cuprous iodide and the iodo derivative were then added and the mixture was heated to reflux for 5 h. After hydrolysis with a small amount of ice-water, the solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. After filtration, the organic extract was washed with a saturated aqueous solution of sodium thiosulfate. After drying on magnesium sulfate, the solvent was removed under reduced pressure.

4.5.1. 2-(1,3-Dimethyl-2-oxo-1,2,3,4,5,6-hexahydro-benzo[*h*]quinolin-9-yl)-malonic acid diethyl ester (13a). According to the general procedure, reaction of sodium hydride (0.088 g, 2 mmol) in dioxane (1.2 mL) with diethyl malonate (0.34 mL, 2 mmol), cuprous iodide (0.38 g, 2 mmol) and lactam **12a** (0.353 g, 1 mmol) afforded 0.154 g (40%) of **13a** as a brown oil after flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2, R_f=0.3). IR (KBr) 1674, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (m, 9H), 2.15–2.61 (m, 7H), 3.06 (s, 3H), 4.13 (m, 4H), 4.53 (s, 1H), 6.85 (d, 1H, J=6.5 Hz), 7.30 (s, 1H), 7.40 (d, 1H, J=6.5 Hz). Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.45; H, 6.99; N, 3.70.

4.5.2. 2-[1-(4-Methoxybenzyl)-3-methyl-2-oxo-1,2,3,4,5,6-hexahydrobenzo[*h*]quinolin-9-yl]malonic acid diethyl ester (13b). According to the general procedure, reaction of sodium hydride (0.088 g, 2 mmol) in dioxane (1.2 mL) with diethyl malonate (0.34 mL, 2 mmol), cuprous iodide (0.38 g, 2 mmol) and lactam **12b** (0.46 g, 1 mmol) afforded 0.246 g (50%) of **13b** as a pale brown oil after flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2, R_f=0.3). IR (KBr) 1674, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, 3H, J=7.0 Hz), 1.24 (m, 6H), 2.02–2.55 (m, 7H), 3.65 (s, 3H), 4.15 (m, 4H), 4.46 (s, 1H), 4.57 (d, 1H, J=16.0 Hz), 5.20 (d, 1H, J=16.0 Hz), 6.63 (d, 2H, J=11.0 Hz), 6.83 (d, 2H, J=11.0 Hz), 7.18 (m, 3H). Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.86; H, 6.77; N, 2.85. Found: C, 70.95; H, 6.8; N, 2.9.

4.6. General procedure for the catalytic hydrogenation reaction of benzo[*h*]quinolin-2-ones

The compound to reduce was dissolved in ethanol in a pressure vessel and palladium on carbon (10%) was added under nitrogen. The vessel was flushed with hydrogen and the mixture was stirred for 12 h at 1 bar. The mixture was filtered on a celite pad and the solvent was removed under reduced pressure.

4.6.1. 2-[1-(4-Methoxybenzyl)-3-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-benzo[*h*] quinolin-9-yl]-malonic acid diethyl ester (14). According to the general procedure, compound **13b** (0.49 g, 1 mmol) in ethanol (50 mL) containing 10% Pd–C (0.245 g) afforded 0.22 g (45%) of crude **14** as a yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (m, 9H), 1.26 (m, 1H), 1.65 (m, 1H), 1.85 (m, 1H), 1.96 (m, 1H), 2.29 (m, 1H), 2.42 (m, 1H), 2.6–2.8 (m, 2H), 3.65 (s, 3H), 4.11 (m, 4H), 4.21 (m, 1H), 4.45 (s, 1H), 5.65 (m, 2H), 6.68 (m, 2H), 7.05 (m, 5H).

4.6.2. 3-Methyl-3,4,4a,5,6,10b-hexahydro-1*H*-benzo[*h*]-quinolin-2-one (1b′). According to the general procedure, compound **9a** (0.64 g, 3 mmol) in ethanol (65 mL) containing 10% Pd–C (0.48 g) afforded 0.52 g (80%) of **1b′** as a yellow solid after recrystallization from ethyl acetate. Mp 122 °C. IR (KBr) 1670, 3240 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (d, 3H, J=5.0 Hz), 1.26 (m, 1H), 1.65 (m, 1H), 1.85 (m, 1H), 1.96 (m, 1H), 2.29 (m, 1H), 2.42 (m, 1H), 2.6–2.8 (m, 2H), 4.45 (dd, 1H, J=5.2, 3.2 Hz), 6.45 (m, 1H), 7.05–7.23 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.7, 27.1, 27.6, 32.9, 33.6, 35.6, 53.0, 126.9, 127.8, 128.3, 129.2, 136.3, 136.9, 176.2. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.0; H, 8.0; N, 6.55.

4.6.3. 9-Hydroxy-3methyl-3,4,4a,5,6,10b-hexahydro-1*H*-benzo[*h*]quinolin-2-one (16a). According to the general procedure, compound **9c** (0.16 g, 0.5 mmol) in ethanol (10 mL) containing 10% Pd–C (0.08 g) afforded 0.098 g (85%) of crude **16a** as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.02 (d, 3H, J=7.2 Hz), 1.18 (m, 1H), 1.61 (m, 1H), 1.84 (m, 1H), 1.96 (m, 1H), 2.29 (m, 1H), 2.52 (m, 1H), 2.65 (m, 2H), 4.35 (d, 1H, J=3.2 Hz), 6.51–6.68 (m, 2H), 6.82 (d, 1H, J=8.7 Hz).

4.6.4. Trifluoromethanesulfonic acid 3-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-benzo[*h*]quinolin-9-yl ester (16b). To a cooled solution (0 °C) of the crude phenol **16a** (0.76 g, 3.28 mmol) in freshly distilled DMF (22 mL)

containing triethylamine (1.15 mL, 8.2 mmol), ditriflimide (2.6 g, 7.22 mmol) was added. The mixture was stirred at 0 °C for 30 min and then at rt for 4 h. The solvent was removed under reduced pressure (1 mm Hg) and the residue was dissolved in diethyl ether. The solution was washed with water and the organic layer was dried on magnesium sulfate. The solvent was removed and the excess of ditriflimide was removed by recrystallization in cyclohexane. The ditriflimide was carefully washed with cyclohexane and the resulting organic layer was washed with water and dried on magnesium sulfate. After removing of the solvent, the residue was recystallized in cyclohexane to afford 0.48 g (40%) of triflate **16b** as a white solid. Mp 171 °C. IR (KBr) 1418, 1443, 1668, 3074, 3226 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (d, 3H, J=7.4 Hz), 1.22 (m, 1H), 1.69 (m, 1H), 1.89 (m, 1H), 1.91 (m, 1H), 2.29 (m, 1H), 2.42 (m, 1H), 2.61–2.88 (m, 2H), 4.47 (d, 1H, J=3.2 Hz), 6.61 (s, 1H), 7.19 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.8, 26.7, 26.8, 32.4, 33.1, 35.9, 53.0, 120.7, 120.9, 130.9, 133.6, 137.3, 139.2, 148.5, 176.1. ^{19}F ($CDCl_3$, 282.4 MHz) δ 73.3. Anal. Calcd for $C_{15}H_{16}F_3NO_4S$: C, 49.58; H, 4.44; N, 3.85. Found: C, 49.65; H, 4.51; N, 3.78.

4.6.5. (3-Methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]quinolin-9-yl)-acetic acid methyl ester (18a). Enoxysilane **17**[6] (0.366 g, 2.5 mmol corresponding to the *O*-silylated product) was added to a solution of triflate **16c** (0.363 g, 1 mmol), lithium acetate (0.2 g, 3 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.15 mmol) in THF (20 mL) under a nitrogen atmosphere. The mixture was heated to reflux for 16 h. After cooling at rt, an other amount of catalyst was added (0.023 g, 0.02 mmol) and the mixture was heated to reflux for 5 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate, R_f=0.3). After removal of the eluent, the residue was dissolved in dichloromethane, washed with water, dried on magnesium sulfate. Removal of the solvent followed by recrystallization in ethyl acetate afforded 0.115 g (40%) of compound **18a** as a white solid. Mp 114 °C. IR (KBr) 1652, 1742, 3190 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, 3H, J=5.0 Hz), 1.22 (m, 1H), 1.63 (m, 1H), 1.82 (m, 1H), 1.99 (m, 1H), 2.30 (m, 1H), 2.43 (m, 1H), 2.59–2.81 (m, 2H), 3.53 (s, 2H), 3.62 (s, 3H), 4.42 (m, 1H), 6.04 (m, 1H), 7.00–7.11 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.6, 27.1, 27.4, 32.9, 33.7, 35.5, 41.1, 52.5, 52.9, 128.9, 129.2, 129.6, 132.7, 135.9, 136.3, 172.4, 176.0. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.1; H, 7.4; N, 4.7.

4.6.6. 3-Methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]quinolin-9-yl acetic acid (18b). To a solution of ester **18a** (93 mg, 0.32 mmol) in ethanol (1 mL), sodium hydroxide (38.8 mg, 0.97 mmol) in ethanol (0.25 mL) was added and the resulting mixture was stirred at rt for 15 h. The solution was acidified to pH=2 with diluted hydrochloric acid and ethanol was evaporated. The solution was filtered and the solid was collected to afford 79 mg (89%) of crude **18b** as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (d, 3H, J=6.8 Hz), 1.18 (m, 1H), 1.37 (m, 1H), 1.65–1.73 (m, 2H), 1.91 (m, 1H), 2.30–2.43 (m, 2H), 2.53–2.72 (m, 2H), 3.52 (d, 1H, J=16.0 Hz), 3.63 (d, 1H, J=16.0 Hz), 4.47 (m, 1H), 6.97 (s, 2H), 7.36 (s, 1H), 9.28 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.9, 25.7, 27.1, 31.5, 32.2, 36.0, 41.4, 53.4, 128.9, 129.0, 129.2, 133.1, 134.5, 136.7, 176.9, 178.3.

4.6.7. 2-(3-Methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]quinolin-9-yl)-*N*-propyl-acetamide (2b′). A solution of acid **18b** (0.039 g, 0.14 mmol), *n*-propylamine (0.012 mL, 0.14 mmol), HOBT (0.019 g, 0.14 mmol) and EDCI (0.027 g, 0.14 mmol) in acetonitrile (5 mL) was stirred at rt for 72 h. The mixture was diluted with ethyl acetate, washed with a 2M aqueous solution of HCl and then with a 2M aqueous solution of NaOH. After drying on magnesium sulfate, the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel (ethyl acetate/methanol 9/1, R_f=0.5) to afford 0.029 g (65%) of compound **2b′** as a pale yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (t, 3H, J=7.3 Hz), 1.09 (d, 3H, J=7.2 Hz), 1.18–1.28 (m, 1H), 1.37 (qt, 2H, J=7.3, 6.9 Hz), 1.60–171 (m, 1H), 1.76–1.95 (m, 2H), 2.10 (s, 1H), 2.25–2.46 (m, 1H), 2.56–2.79 (m, 2H), 3,07 (t, 2H, J=6.9 Hz), 3.42 (s, 2H), 4.44 (m, 1H), 5.71 (m, 1H), 6.80 (m, 1H), 7.03 (m, 2H), 7.17 (m, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 11.7, 16.8, 23.1, 27.0, 27.1, 32.7, 33.2, 35.7, 41.7, 43.9, 53.0, 128.7, 129.3, 129.8, 133.9, 135.6, 136.9, 171.3, 176.2. Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.7, H, 8.45; N, 8.95.

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