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Synthesis of supposed enone prodrugs of apomorphine and *N*-propyl-norapomorphine

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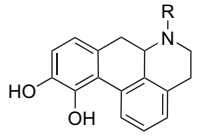
Abstract—We have previously demonstrated that the enone prodrug GMC-6650 acts as a highly efficient dopaminergic agonist. In vivo, this compound is bioactivated to its corresponding catecholamine, TL-334. The goal here was to investigate if this bioactivation also occurs for the supposed enone prodrug of apomorphine. We describe the 12-step synthesis of this supposed prodrug, 6-alkyl-5,6,6a,8,9,10-hexahydro-4*H*-dibenzo[*de*,*g*]quinolin-11(7*H*)-one (R=Me, *n*-Pr).

1. Introduction

Apomorphine (**1**) was first synthesized from morphine in 1869. In the past, it was used as an emetic compound[1] and it is now clinically used in Parkinson's disease (PD), in particular as a rescue compound at the 'off' state during the use of L-dopa.[2] Apomorphine is known as a dopamine D_1/D_2 agonist. *N*-Propyl-norapomorphine (NPA, **2**) is also a D_1/D_2 agonist with a more potent D_2 agonistic effect than apomorphine[3] (Fig. 1).



1 R=CH_3
2 R=$CH_2CH_2CH_3$

Figure 1. The structures of apomorphine (APO, **1**) and *N*-propyl-norapomorphine (NPA, **2**).

The catecholamine moiety of apomorphine and NPA oxidizes rapidly in vitro and in vivo, resulting in poor pharmacokinetic properties. Many efforts have been made to find new apomorphine structures and analogs that circumvent these bioavailability problems.[4–6] We have developed a new type of prodrug, which contains a cyclohexenone–ethylamine moiety as the basic structural element. In vivo, the enone structure can be bioactivated to the corresponding catecholamine.[7,8] Figure 2 shows a typical example of a dopamine agonist *S*-(−)-5,6-di-OH-DPAT (**3**) and its corresponding enone prodrug PD148903 (**4**). We found that **3** is formed in vivo after the administration of **4**. GMC-6650 (**5**) is a related enone prodrug and its corresponding catecholamine TL-334 (**6**) is an extremely potent dopamine D_1/D_2 agonist. The structural difference between apomorphine and TL-334 is only one aromatic ring. Due to the potent dopamine agonistic effects observed in vivo with these enone prodrugs, the corresponding enone derivatives (**21a** and **21b**, respectively) of apomorphine and NPA might be interesting prodrugs with clinical potential against PD. Here, we report the synthesis of enone compounds **21a**,**b**.

2. Results and discussion

In order to prepare this type of challenging compound, retrosynthetic analysis of the aporphines was done to design a synthetic route (Scheme 1).

In this strategy, an important transformation will be alkylation at the α-position of ketone (**14**). This tricyclic ring system (B, C and D rings) will be the key intermediate in the synthetic route, as the functional carbonyl group allows alkylation at the α-position. These benzo[*de*]quinolines can be prepared from 1-methyl-isoquinolines, starting from phenyl ethylamine.

The synthetic procedure followed is displayed in Schemes 2 and 3, starting from phenyl ethylamine **7**. Acetylation of **7** gave the acetamide **8**, which underwent a high temperature cyclization with polyphosphoric acid (PPA)[9] yielding **9** in

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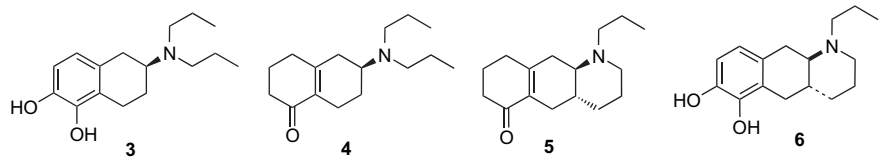
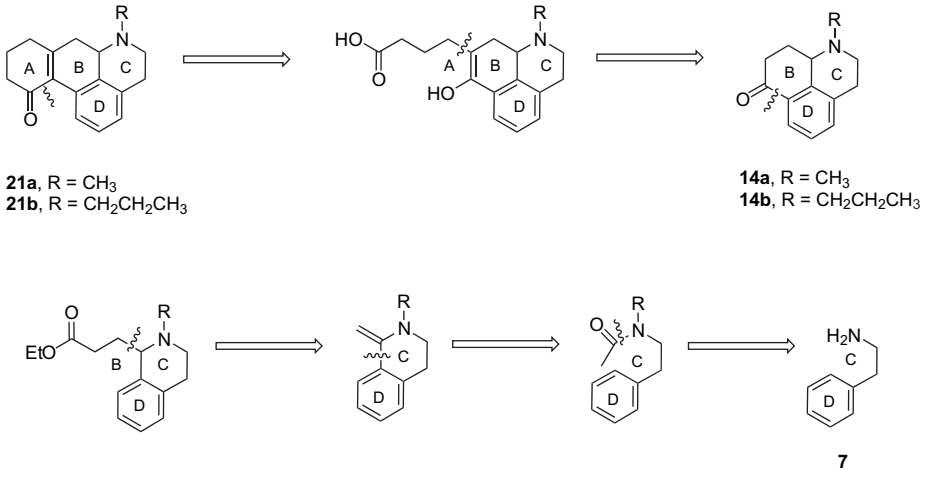
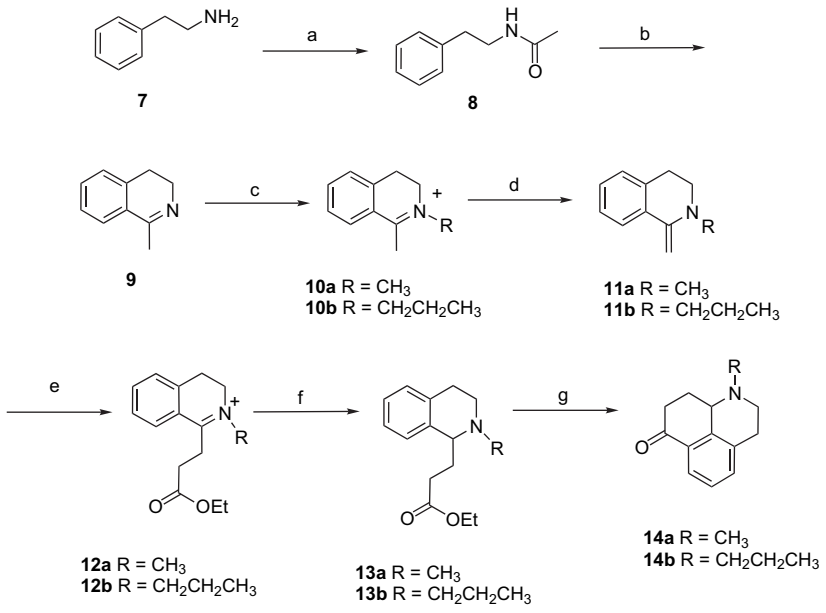


Figure 2. Structures of enone prodrugs and their catecholamines: *S*-(−)-5,6-di-OH-DPAT (**3**) and PD148903 (**4**); GMC-6650 (**5**) and TL-334 (**6**).



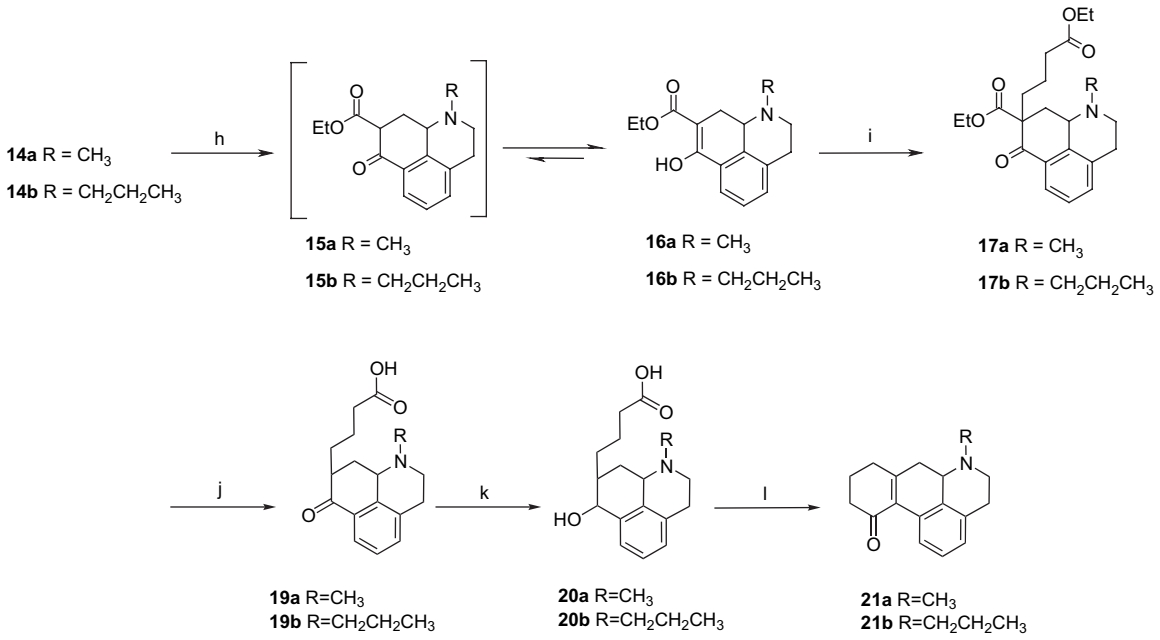
Scheme 1. Retro-synthetic analysis of **21a**,**b**.



Scheme 2. Reagents and conditions: (a) Ac_2O, pyridine, 90 °C, 2 h, 77%; (b) PPA, 130 °C, 30 min, 200 °C, 3 h, 53%; (c) R=CH_3: benzene, CH_3I, rt, overnight, 61%; R=$CH_2CH_2CH_3$: toluene, $CH_3CH_2CH_2I$, reflux, overnight, 85%; (d) 4 N NaOH, 0 °C; (e) toluene, $BrCH_2COOEt$; (f) $NaBH_4$, EtOH, rt, overnight, 71% (R=CH_3, over three steps), 69% (R=$CH_2CH_3CH_3$, over three steps); (g) PPA, 140 °C, 1 h, 54% (R=CH_3), 72% (R=$CH_2CH_3CH_3$).

moderate yield. The methylation and propylation of the *iso*-quinoline **9**[10] were performed under slightly different conditions due to the different reactivity of methyl iodide (rt in benzene) and propyl iodide[11] (reflux in toluene). In the presence of 4 M NaOH, the iodide salts of the imines (**10a** and **10b**) were converted to the enamines (**11a** and **11b**), which were next allowed to react with ethyl bromoacetate to yield the 1-*iso*-quinolinepropionate derivatives (**12a** and **12b**). After the reduction of these imines with $NaBH_4$, **13a** and **13b** were formed. The last step in the preparation of the key intermediate **14** was a ring closure with PPA.

The next critical step was the alkylation at the α-position of the ketone **14**. Since the direct introduction of the ethyl butyrate group might be difficult to realize,[12] we have chosen a two-step procedure. First, we did an ethoxycarbonylation with diethyl carbonate using NaH as base to produce the anion, yielding **15a** and **15b**.[13] The procedure published in



Scheme 3. Reagents and conditions: (h) $CO(OC_2H_5)_2$, NaH, benzene, reflux, overnight, 62% (R=CH_3), 66% (R=$CH_2CH_3CH_3$); (i) $Br(CH_2)_3COOC_2H_5$, NaH, THF/DMF, reflux, overnight or NaH, DME, reflux, overnight; (j) concd HCl/CH_3COOH, reflux, 6 h, 75% (R=CH_3, over two steps), 75% (R=$CH_2CH_3CH_3$, over two steps); (k) $NaBH_4$, $NaHCO_3$, rt, overnight; (l) PPA, 65 °C, 1 h, 34% (R=CH_3, over two steps), 35% (R=$CH_2CH_3CH_3$, over two steps).

the literature (sodium ethoxide in ethanol) was not successful in our hands.[14] Compounds **15a** and **15b** existed in equilibrium between the keto and the enol form. The NMR spectroscopic experiments indicated that in solution, **15a** and **15b** existed as the enols **16a** and **16b**, respectively. It may be the case that in solution **15a** and **15b** are susceptible for ketone–enol tautomerism and the equilibrium shifts in solution to the enol form. The alkylation[15] of **15a** and **15b** with ethyl-4-bromobutyrate resulted in **17a** and **17b**, which existed as a mixture of diastereomers. Apparently, the keto form is more reactive because the reaction with ethyl-4-bromobutylate gave mainly the desired di-ester. Due to the presence of enol form of **16**, ether formation of **18a** and **18b** (see Fig. 3) were observed as by-products, which explained that after hydrolysis, **14a** and **14b** were regenerated from **18a** and **18b**.

Subsequent de-ethoxycarbonylation[16] of compounds **17a** and **17b** was performed in concd HCl and acetic acid (1:1). The ester group in **17a** and **17b** was hydrolyzed to the corresponding acids **19a** and **19b**. Although these two compounds have two stereogenic carbon atoms, due to the ketone–enol tautomerism, NMR spectroscopic data did not show the evidence of being diastereomers. After work-up, the crude acids **19a** and **19b** were purified by column chromatography. The reduction of **19a** and **19b** with $NaBH_4$ was performed in aq $NaHCO_3$ solution to yield **20a** and **20b**. After the solution was acidified to pH <2, the solution was evaporated. Without further purification, PPA was added and the mixture was heated to 65 °C for 1 h.[17]

After this cyclization, it was found that the ring-opened (ring C) by-product **22** was present in the final products (Fig. 4). Aromatization of the B-ring is probably the driving force for this ring opening. The cyclization of **20a**,**b** in PPA was crucial in this case. There seems to be an optimum between the formation of product and ring-opened by-product. Incomplete reaction was found with shorter reaction time (0.5 h), however, only ring-opened by-product was found with the extended reaction time (2 h). Therefore, 1 h reaction at 60 °C was found to be the optimal time for the balance of obtaining product and keeping a minimal amount of by-product.

The racemic mixtures of **21a** and **21b** were resolved into two enantiomers by preparative chiral HPLC with a Chiralpack AD column. Figure 5 shows the result of the single crystal X-ray analysis of (−)-**21b**. From the X-ray structure, the absolute configuration on the fused C-ring of this compound was shown to be (*R*)-(−). From the torsion angles data, C5–C6 has a torsion angle of 174.3° with C7–N; the torsion

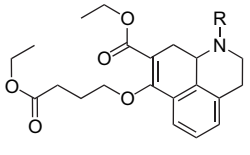


Figure 3. The structure of ether by-product **18** formed in step (i) in Scheme 2.

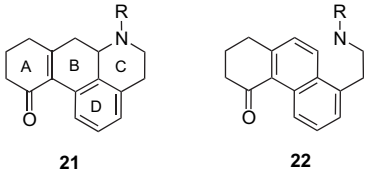


Figure 4. The structure of enone **21** and ring opening by-product **22**.

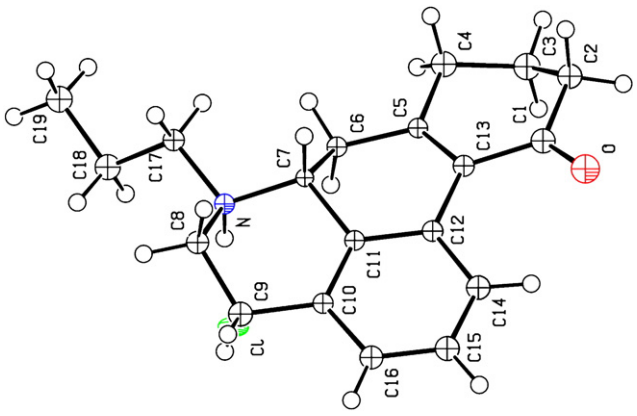


Figure 5. The structure of *R*-(−)-**21b**.

angle between N–C7 and C11–C12 is 160.3°; between C6–C7 and C11–C10 is 141.6°. The large torsion angles may be the reason for the instability of this type of compound, since the aromatization of the B-ring is the driving force to eliminate the large torsion.

For identification of the metabolites of **21a**,**b**, racemic apomorphine (**1**) and NPA (**2**) were used as standard. A multiple reaction monitoring (MRM) experiment was performed, which is accomplished by specifying the parent mass of the compound for MS/MS fragmentation and then specifically monitoring for a single fragmentation. The specific experiment is known as a 'transition', which can be written as parent mass→fragment mass. The MRM transition 268→219 was chosen to identify apomorphine. The retention time is 7.40 min. After the injection of brain and plasma samples of apoenone (**21a**) to LC/MS/MS system, there was no peak found at the retention time of 7.4 min with MRM transition 268→219. The multiple reaction monitoring (MRM) transition 296→219 was chosen to identify NPA (**2**) and the retention time is 7.96 min. After the injection of brain and plasma samples of NPA-enone (**21b**) to LC/MS/MS system, the MRM transition 296→219 was chosen and there was no peak found at the retention time of 7.96 min either. Therefore, in our preliminary experiments, apomorphine (**1**) or NPA (**2**) were found neither in blood nor in brain samples, which indicated that no conversion of these enone compounds occurred in vivo or probably the formation of the aromatized products are faster. Meanwhile, the apomorphine enone and the NPA-enone by-products (ring-opened, **22**) were found in blood as well as in brain samples.

3. Conclusion

We succeeded in synthesizing these challenging prodrugs of apomorphine and NPA (**21a** and **21b**) via a 12-steps route in an overall yield of 1%.

The result of identification of the metabolites of **21a**,**b** with the MRM experiment showed no conversion of these enone compounds occurred in vivo or probably the formation of the aromatized products are faster.

So far, the preliminary pharmacological results showed that the expected bioactivation mechanism, found for both PD148903 (**4**) and GMC-6650 (**5**), has not been observed for these apoenones. Therefore, it can be concluded that **21a** and **21b** are not suitable to become clinically effective dopaminergic agonists.

4. Experimental section

4.1. General

Melting points were determined in glass capillaries on an electro thermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Varian-VXR 300 spectrometer and ^{13}C NMR spectra were recorded at 50.3 MHz on a Varian Gemini 200 spectrometer. The chemical shifts are given in parts per million (ppm) relative to the solvent; the splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling constants are given in hertz (Hz). The spectra recorded were consistent with the proposed structures of intermediates and final compounds. Electronic ionization (EI) mass spectra were obtained on Shimadzu QP5000 GC/MS system equipped with a 17A GC, an AOC-20i auto-injector, and the GC–MS solution software 1.10 was used. Chemical ionization (CI) mass spectra were recorded by the Mass Spectrometry Unit of the University of Groningen. High-resolution mass spectrometry (HRMS) was analyzed on a JEOL MS route JMS-600H by the Department of Chemistry, University of Groningen.

4.1.1. 1-Methyl-3,4-dihydroisoquinoline (9). Phenyl ethylamine (**7**) (32.3 g, 0.27 mol) was dissolved in pyridine (25 mL, 0.30 mol) and acetic anhydride (29 mL, 0.31 mol) was added dropwise to the solution. The solution was heated at 90 °C for 2 h. After cooling to rt, the volatiles were removed in vacuo. The residue was partitioned between ethyl acetate (200 mL) and 4 M HCl (40 mL). The organic layer was washed with 1 M NaOH (3×40 mL), brine (3×20 mL), and dried over $MgSO_4$. The solvent was filtered and evaporated in vacuo. Crude *N*-phenethylacetamide **8** (34 g, 77% yield) was obtained as a light yellow solid, which was used for the next step without further purification.

PPA (180 g) was added to **8** (34 g, 0.21 mol) and the syrup was heated at 130 °C for 30 min, then 200 °C for 3 h. The reaction was cooled to 40 °C and water (900 mL) was added. The solution was adjusted to pH=9 with NH_3 (25% water solution) and extracted with CH_2Cl_2 (3×300 mL). The organic phase was washed with brine (3×50 mL) and dried over $MgSO_4$. After filtration and evaporation of the solvent, a black oil was obtained. Purification by column chromatography (silica, CH_2Cl_2/MeOH=30:1) afforded **9** as a light yellow oil (16 g, 53% yield). ^{1}H NMR ($CDCl_3$) δ 7.11–7.45 (m, 4H), 3.63 (m, 2H), 2.66 (m, 2H), 2.35 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 162.7, 135.8, 129.0, 128.0, 125.9, 125.3, 123.7, 45.4, 24.5, 21.8 ppm; MS (EI) *m*/*z* 145 (M^+).

4.1.2. 1-Methyl-3,4-dihydroisoquinoline (11a). The *iso*-quinoline **9** (10 g, 69.0 mmol) was dissolved in benzene (100 mL) and methyl iodide (30 g, 211.2 mmol) was introduced to the solution at rt under N_2. After addition, the solution turned to a suspension and was stirred overnight. After filtration, the solid was washed with benzene and then with ether;

10a iodide salt was obtained as a yellow solid, 12 g (61% yield). The analytic sample was re-crystallized from methanol/ether to yield light yellow needles, mp: 132–134 °C.

The *iso*-quinolinium salt **10a** (12 g, 41.8 mmol) was dissolved in H_2O (50 mL) and the solution was basified with 4 M NaOH at 0 °C. This solution was extracted with toluene (2×100 mL). The organic layer was washed with brine (3×50 mL) and dried over Na_2SO_4. After filtration, **11a** was used in toluene solution directly for the next step.

4.1.3. 1-Propyl-3,4-dihydroisoquinoline (11b). To a stirred solution of 1-methyl-3,4-dihydroisoquinoline **9** (13 g, 89.7 mmol) in toluene (30 mL) was added propyl iodide (14.2 mL, 145.0 mmol) at rt. The mixture was heated at 90 °C for 18 h. After the suspension was filtrated, the formed solid was washed with CH_2Cl_2/ether (1:2) to yield **10b** as a yellow solid, 24 g (85% yield). The analytic sample was crystallized from methanol/ether as light yellow crystals, mp: 194–197 °C.

The *iso*-quinolinium salt **10b** (24 g, 76.4 mmol) was dissolved in H_2O (100 mL) and 4 M NaOH was added to the solution at 0 °C. The solution was extracted with toluene (2×150 mL) and the combined organic layers were dried over Na_2SO_4. Filtration and evaporation of the solvent yielded **11b** as a red oil (9.9 g, 70% yield). ^{1}H NMR ($CDCl_3$) δ 7.74 (m, 1H), 7.15 (m, 3H), 4.48 (s, 1H), 3.86 (s, 1H), 3.24 (m, 4H), 2.89 (t, 2H, J=5.8 Hz), 1.69 (q, 2H, J=7.3 Hz), 0.97 (t, 3H, J=7.3 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 145.0, 133.3, 131.3, 126.5, 125.8, 124.7, 123.4, 75.4, 52.7, 46.2, 29.1, 17.3, 10.3 ppm; MS (EI) m/z 187 (M^+).

4.1.4. Ethyl 3-[2-methyl-3,4-dihydro-1(2*H*)-isoquinolinylidene]propanoate (12a). A solution of ethyl bromoacetate (6 mL, 53.0 mmol) in toluene (20 mL) was added slowly at rt to a stirred solution of **11a** (from 12 g **10a** salt) in toluene under N_2 at rt in 45 min. The reaction was stirred as such overnight. A red syrup **12a** was formed during the reaction. The toluene was removed and the red syrup was washed with toluene (4×30 mL). Ethanol (100 mL) was added to the syrup and this solution was used without further purification in the next step.

4.1.5. Ethyl 3-[2-propyl-3,4-dihydro-1(2*H*)-isoquinolinylidene]propanoate (12b). Ethyl bromoacetate (35 mL, 315.0 mmol) was added slowly to the red oil **11b** (9.9 g, 52.9 mmol) while stirring. A red syrup was formed after the addition. The reaction was heated at 60 °C for 1.5 h. The extra ethyl bromoacetate was removed and the red syrup was washed with toluene (4×50 mL). Ethanol (80 mL) was added to the red syrup and this solution was used for the next step.

4.1.6. Ethyl 3-(2-methyl-1,2,3,4-tetrahydro-1-isoquinolinyl)propanoate (13a). To the stirred ethanol solution of **12a** (from **10a** salt, 12 g, 41.8 mmol) was added $NaBH_4$ (3.1 g, 81.6 mmol) in small portions at 0 °C. The mixture was allowed to reach to rt and continued to stir overnight. After removal of the solvent in vacuo, water (50 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (3×100 mL). The organic layer was washed with brine (3×30 mL), dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was obtained, which was purified by column chromatography (silica treated with NH_3, CH_2Cl_2/MeOH=40:1) yielding **13a** as a yellow oil (7.3 g, 71% yield over two steps). ^{1}H NMR ($CDCl_3$) δ 7.12 (m, 4H), 4.09 (q, 2H, J=7.1 Hz), 3.53 (m, 1H), 3.05 (m, 1H), 2.48–2.82 (m, 3H), 2.44 (s, 3H), 2.20–2.42 (m, 1H), 2.10 (m, 3H), 1.23 (t, 3H, J=7.1 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 172.7, 135.9, 133.8, 127.1, 125.5, 124.4, 124.3, 61.3, 58.6, 47.3, 41.6, 28.5, 28.2, 25.3, 12.7 ppm; MS (EI) m/z 202 (M−45).

4.1.7. Ethyl 3-(2-propyl-1,2,3,4-tetrahydro-1-isoquinolinyl)propyl ether (13b). This compound was prepared from **12b** (from **11b**, 9.9 g, 52.9 mmol) using the same procedure as described for **13a**. After purification, **13b** was obtained as a yellow oil (10 g, 36.3 mmol, 69% yield over two steps). ^{1}H NMR ($CDCl_3$) δ 7.03–7.26 (m, 4H), 4.11 (dd, 2H, J=7.1, 7.3 Hz), 3.59 (m, 1H), 3.17 (m, 1H), 2.69–2.95 (m, 2H), 2.27–2.60 (m, 5H), 1.21 (m, 2H), 1.41–1.56 (dd, 2H, J=7.1, 7.3 Hz), 1.26 (t, 3H, J=7.3 Hz), 0.90 (t, 3H, J=7.3 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 172.7, 136.8, 133.6, 127.3, 126.3, 124.3, 124.2, 58.7, 58.6, 54.1, 42.3, 29.6, 23.0, 19.6, 12.7, 10.3 ppm; MS (EI) m/z 230 (M−45).

4.1.8. 1-Methyl-1,2,3,8,9,9a-hexahydro-7*H*-benzo[*de*]-quinolin-7-one (14a). A mixture of **13a** (5 g, 20.2 mmol) and PPA (100 g) was stirred at 140 °C for 1 h. After cooling to 60 °C, the mixture was poured into water (800 mL), and the solution was adjusted to pH=9 by the addition of NH_3 (25% water solution). The solution was extracted with CH_2Cl_2 (4×150 mL). The combined organic layers were washed with H_2O (3×100 mL) and brine (3×50 mL), and dried over Na_2SO_4. After filtration and evaporation of the solvent, a black oil was obtained, which was purified by column chromatography (silica treated with NH_3, CH_2Cl_2/MeOH=50:1). Compound **14a** was obtained as a yellow oil (2.2 g, 54% yield). ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 1H), 7.27 (m, 2H), 3.05–3.35 (m, 3H), 2.49–2.86 (m, 4H), 2.49 (s, 3H), 1.77–1.95 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 196.2, 139.0, 132.6, 132.5, 129.4, 125.3, 123.8, 61.2, 52.3, 41.5, 36.1, 26.9, 26.6 ppm; MS (EI) m/z 201 (M^+). HRMS 201.1166 (obsd). Calcd for $C_{13}H_{15}NO$ 201.1154.

4.1.9. 1-Propyl-1,2,3,8,9,9a-hexahydro-7*H*-benzo[*de*]quinolin-7-one (14b). This compound was prepared from **13b** (10 g, 36.4 mmol) using the same procedure as described for **14a**. Purification of the residue resulted in **14b** as a yellow oil (6 g, 72% yield). ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 1H), 7.27 (m, 2H), 3.56 (m, 1H), 3.02–3.28 (m, 2H), 2.81 (m, 3H), 2.40–2.69 (m, 4H), 1.86 (m, 1H), 1.52–1.74 (m, 2H), 0.93 (t, 3H, J=7.3 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 196.4, 139.8, 133.0, 132.5, 129.5, 125.2, 123.8, 58.9, 53.5, 48.2, 36.3, 27.1, 26.7, 17.7, 10.5 ppm; MS (EI) m/z 229 (M^+). HRMS 229.1471 (obsd). Calcd for $C_{15}H_{19}NO$ 229.1467.

4.1.10. 1-Ethyl-7-hydroxy-1-methyl-2,3,9,9a-tetrahydro-1*H*-benzo[*de*]quinoline-8-carboxylate (16a). To a suspension of NaH (60%, 250 mg, 6.2 mmol) in benzene (5 mL) was added dropwise a solution of diethyl carbonate (353 mg, 3.0 mmol) in benzene (5 mL), followed by the dropwise addition of **14a** (500 mg, 2.5 mmol) in benzene (5 mL). The reaction was heated at reflux overnight. After cooling, the mixture was poured into ice. The water layer was extracted with ether (3×30 mL). The combined organic

layers were washed with brine (3×10 mL), dried over Na_2SO_4. After filtration and evaporation, the obtained residue was purified by column chromatography (silica treated with NH_3, CH_2Cl_2/MeOH=60:1) and yielded **16a** as a yellow oil (420 mg, 62% yield). ^{1}H NMR ($CDCl_3$) δ 12.46 (s, 1H), 7.64 (m, 1H), 7.23 (m, 2H), 4.30 (q, 2H, J=7.1 Hz), 3.00–3.27 (m, 4H), 2.56–2.77 (m, 2H), 2.51 (s, 3H), 2.45 (m, 1H), 1.36 (t, 3H, J=7.1 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 171.0, 163.2, 133.8, 131.9, 129.7, 127.2, 125.0, 120.8, 94.0, 59.7, 59.2, 52.0, 42.3, 27.3, 24.2, 12.9 ppm; MS (CI) m/z 274 (M^++1).

4.1.11. Ethyl 7-hydroxy-1-propyl-2,3,9,9a-tetrahydro-1*H*-benzo[*de*]quinoline-8-carboxylate (16b). This compound was prepared from **14b** (1 g, 4.4 mmol) with diethyl carbonate (620 mg, 5.2 mmol) using the same procedure as described for **16a**. After work-up, **16b** was obtained as a yellow oil (870 mg, 66% yield). ^{1}H NMR ($CDCl_3$) δ 12.38 (s, 1H), 7.57 (m, 1H), 7.17 (m, 2H), 4.26 (q, 2H, J=7.3 Hz), 3.43 (m, 1H), 2.96–3.16 (m, 3H), 2.64–2.88 (m, 2H), 2.39 (m, 2H), 2.10 (t, 1H, J=4.6 Hz), 1.53 (m, 2H), 1.31 (t, 3H, J=7.3 Hz), 0.91 (t, 3H, J=7.3 Hz) ppm; ^{13}C NMR ($CDCl_3$), δ 171.1, 163.2, 134.6, 132.3, 129.7, 127.5, 125.5, 124.8, 120.7, 94.2, 59.2, 57.1, 54.4, 47.7, 27.4, 24.1, 17.6, 12.9, 10.5 ppm; MS (EI) m/z 228 (M−73).

4.1.12. Ethyl 8-(4-ethoxy-4-oxobutyl)-1-methyl-7-oxo-2,3,7,8,9, 9a-hexahydro-1*H*-benzo[*de*]quinoline-8-carboxylate (17a). To a suspension of NaH (60%, 79 mg, 1.98 mmol) in THF (10 mL) and DMF (1 mL) was added a solution of **16a** (430 mg, 1.57 mmol) in THF (10 mL) at 0 °C. After stirring at rt for 2 h, a solution of ethyl-4-bromobutylate (480 mg, 2.46 mmol) in THF (10 mL) was added dropwise, and the resulting mixture was heated under reflux for 20 h. After cooling, the solvent was evaporated and followed by the addition of H_2O (3 mL), extracted with ether (3×30 mL), washed with brine (3×10 mL), and dried over Na_2SO_4. Purification by column chromatography (silica, ethyl acetate) yielded **17a** as a light yellow oil (220 mg). NMR and GC indicated the mixture of diastereomers of the product, also the by-product **18a** was involved, which is 20% of the total amount according to GC. The mixture was used directly in the next step.

4.1.13. Ethyl 8-(4-ethoxy-4-oxobutyl)-1-propyl-7-oxo-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinoline-8-carboxylate (17b). This compound was prepared from **16b** (870 mg, 2.9 mmol) in ethylene glycol dimethyl ether (DME) (15 mL) using the same procedure as described for **17a**. Purification by column chromatography (silica, hexane/ethyl acetate, 3:1) resulted in **17b** as a light yellow oil (630 mg). It was clearly shown that the product existed as a mixture of diastereomers based on NMR and GC, also the by-product **18b** was involved, which is 20% of the total amount according to GC. The mixture was used directly in the next step.

4.1.14. 4-(1-Methyl-7-oxo-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-8-yl)butanoic acid (19a). The compound **17a** (300 mg, 0.78 mmol) was dissolved in concd HCl and acetic acid (3 mL: 3 mL), and the solution was heated under reflux for 6 h under N_2. After cooling to rt, the solvent was evaporated in vacuo. The obtained residue was purified by column chromatography (silica, CH_2Cl_2/MeOH=15:1), yielding **19a** as a white solid (205 mg, 75% yield). ^{1}H NMR (CD_3OD) δ 7.93 (d, 1H, J=7.1 Hz), 7.50 (m, 2H), 3.24–3.86 (m, 8H), 3.06 (s, 3H), 2.75 (m, 2H), 2.11–2.35 (m, 2H), 1.73 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 195.7, 168.1, 132.4, 132.1, 129.9, 129.6, 127.2, 124.8, 59.5, 50.8, 36.5, 32.7, 29.3, 27.4, 22.8, 20.4, 15.5 ppm; MS (CI) m/z 288.2 (M+1). HRMS 287.1550 (obsd). Calcd for $C_{17}H_{21}NO_3$ 287.1521.

4.1.15. 4-(1-Propyl-7-oxo-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-8-yl)butanoic acid (19b). This compound was prepared from **17b** (300 mg, 0.72 mmol) using the same procedure as described for **19a**. After work-up, **19b** was obtained as a white solid (170 mg, 75% yield). ^{1}H NMR (CD_3OD) δ 7.77 (d, 1H, J=6.9 Hz), 7.31 (m, 2H), 4.34 (d, 1H, J=9.5 Hz), 3.57 (d, 1H, J=7.6 Hz), 2.82–3.20 (m, 7H), 2.56 (dd, 1H, J=3.3 Hz), 2.21 (m, 2H), 1.43–1.98 (m, 6H), 0.92 (t, 3H, J=7.3 Hz) ppm; ^{13}C NMR (CD_3OD) δ 196.5, 175.5, 134.7, 132.2, 130.8, 129.9, 126.4, 124.3, 58.4, 51.1, 47.2, 46.4, 32.9, 30.0, 27.5, 23.7, 20.5, 16.0, 8.7 ppm; MS (CI) m/z 316.2 (M+1). HRMS 315.1834 (obsd). Calcd for $C_{19}H_{25}NO_3$ 315.1834.

4.1.16. 4-(7-Hydroxy-1-methyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-8-yl)butanoic acid (20a). Compound **19a** (170 mg, 0.59 mmol) was dissolved in water (3 mL) containing $NaHCO_3$ (110 mg, 1.31 mmol) at rt. $NaBH_4$ (33 mg, 0.87 mmol) was added to this solution portionwise and the mixture was stirred at rt overnight. The solution was adjusted with 4 N HCl to pH=2 and the volatiles were removed in vacuo. The residue **20a** was used in the next step without further purification.

4.1.17. 4-(7-Hydroxy-1-methyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-8-yl)butanoic acid (20b). This compound was prepared from **19b** (170 mg, 0.54 mmol) using the same procedure described for **20a** and the obtained **20b** was used in the next step without further purification.

4.1.18. 6-Methyl-5,6,6a,8,9,10-hexahydro-4*H*-dibenzo-[*de*,*g*]quinolin-11(7*H*)-one (21a). To PPA (3.7 g) was added **20a** (from 0.59 mmol **19a**) in one pot and the syrup was stirred for 1 h at 65 °C. The resulting dark syrup was cooled to 40 °C, followed by the addition of water (30 mL). The solution was adjusted to pH=9 with NH_3 (25% water solution). The solution was extracted with CH_2Cl_2 (3×10 mL), washed with water (3×10 mL) and brine (3×10 mL), and dried over Na_2SO_4. After filtration and evaporation of the solvent, a dark syrup was obtained, which was purified by column chromatography (silica treated with NH_3, CH_2Cl_2/MeOH=60:1), yielded **21a** (50 mg, 34% yield over two steps). ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1H, J=7.8 Hz), 7.20 (m, 1H), 7.01 (d, 1H, J=7.6 Hz), 2.97–3.20 (m, 3H), 2.25–2.75 (m, 11H), 2.04 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 195.3, 155.8, 130.9, 130.8, 129.1, 128.2, 126.1, 124.7, 123.4, 58.8, 51.8, 42.6, 37.7, 34.1, 30.7, 27.5, 20.2 ppm; MS (CI) m/z 254.2 (M+1).

The ring opening by-product is **22a** (40 mg, 27%). ^{1}H NMR ($CDCl_3$) δ 9.27 (d, 1H, J=8.8 Hz), 8.20 (d, 1H, J=8.8 Hz), 7.26–7.55 (m, 3H), 3.44 (s, 1H), 3.29 (t, 2H, J=7.3 Hz), 3.07 (t, 2H, J=6.1 Hz), 2.95 (m, 2H), 2.76 (m, 2H), 2.46 (s, 3H), 2.16 (p, 2H, J=6.6, 6.1 Hz) ppm; ^{13}C NMR

($CDCl_3$) δ 199.0, 144.7, 134.1, 130.4, 129.7, 127.9, 126.8, 126.5, 125.5, 125.3, 124.0, 51.0, 39.6, 34.4, 31.6, 29.9, 21.4 ppm; MS (CI) *m*/*z* 254.2 (M+1).

4.1.19. 6-Propyl-5,6,6a,8,9,10-hexahydro-4*H*-dibenzo-[*de*,*g*]quinolin-11(7*H*)-one (21b). This compound was prepared from **20b** (from 0.54 mmol **19b**) using the same procedure as described for **21a**. Purification of the residue yielded **21b** (60 mg, 35% yield over two steps). ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 1H, *J*=7.7 Hz), 7.11 (t, 1H, *J*=7.7, 8.1 Hz), 6.95 (d, 1H, *J*=7.7 Hz), 3.34 (m, 1H), 2.95–3.13 (m, 2H), 2.22–2.80 (m, 10H), 1.90–2.14 (m, 2H), 1.46–1.63 (m, 2H), 0.91 (t, 3H, *J*=7.3 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 195.3, 156.1, 131.5, 131.3, 129.2, 128.5, 126.0, 124.5, 123.3, 56.2, 54.9, 47.6, 37.7, 34.2, 30.7, 27.6, 20.3, 17.9, 10.6 ppm; MS (CI) *m*/*z* 282 (M+1).

The ring-opened product is **22b** (60 mg, 35%). ^{1}H NMR ($CDCl_3$) δ 9.27 (d, 1H, *J*=8.5 Hz), 8.20 (d, 1H, *J*=8.8 Hz), 7.53 (m, 1H), 7.31 (m, 2H), 3.27 (t, 2H, *J*=7.3 Hz), 3.09 (dd, 2H, *J*=6.1, 5.9 Hz), 2.96 (dd, 2H, *J*=6.3, 7.1 Hz), 2.77 (dd, 2H, *J*=6.1, 7.1 Hz), 2.60 (t, 2H, *J*=7.3 Hz), 2.16 (m, 2H), 1.80 (s, 1H), 1.51 (dd, 2H, *J*=7.1, 7.3 Hz), 0.89 (t, 3H, *J*=7.3 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 199.0, 144.6, 134.6, 130.4, 129.7, 128.1, 126.8, 126.5, 125.3, 125.2, 123.8, 50.3, 49.3, 39.6, 32.3, 29.9, 21.6, 21.4, 10.3 ppm; MS (CI) *m*/*z* 282 (M+1).

4.2. General procedure for chiral separation of 21a

A 30 mg/mL solution of racemic **21a** in 2-propanol was injected into a HPLC system using a Water 510 HPLC pump with a Chiralpack AD preparative column (250×10 mm). Mobile phase was a mixture produced by an ISCO Model 2360 gradient programmer and consisted of 93% *n*-hexane [containing 0.1% (w/w) triethyl amine] and 7% 2-propanol/*n*-hexane [1/1 (w/w) containing 0.1% triethyl amine]. Flow of the mobile phase was 4.0 mL/min. The peaks were detected by a Water 486 Millipore tunable absorbance detector (λ=254 nm, AUFS=2.0) and were recorded on paper using a Kipp & Zonen flatbed recorder (chart speed 5 mm/min). After evaporation of the mobile phase, the optical rotation of the two fractions was determined using a Perkin–Elmer 241 polarimeter. First fraction: $[\alpha]_D^{23}$ −316 (*c* 0.65, methanol), second fraction: $[\alpha]_D^{23}$ +312 (*c* 0.55, methanol). Both enantiomers (ee >95%) were analyzed for their purity using analytical HPLC (Chiralpack AD column, 250×4.6 mm).

4.3. Procedure for chiral separation of 21b

Similar as for **21a**, the solution of racemic compound was 20 mg/mL, and the mobile phase consisted of 95% *n*-hexane [containing 0.1% (w/w) triethyl amine] and 5% 2-propanol/*n*-hexane [1/1(w/w), containing 0.1% triethyl amine]. First fraction: $[\alpha]_D^{23}$ −254 (*c* 0.365, methanol), second fraction: $[\alpha]_D^{23}$ +235 (*c* 0.405, methanol). Both enantiomers (ee >95%) were analyzed for their purity using analytical HPLC (Chiralpack AD column, 250×4.6 mm).

4.4. X-ray crystallographic data of 21b

Compound (−)-**21b** (10 mg, as its HCl salt) was dissolved in abs EtOH (0.5 mL) at rt. Ether was gently added on top of ethanol until a diffuse cloud formed in the border formed by the two phases. The two layers were kept standing overnight, and platelet, colorless crystals were formed. The crystallographic data for the structure **21b** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 281494. Copies of the data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or form the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk].

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Supplementary data

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