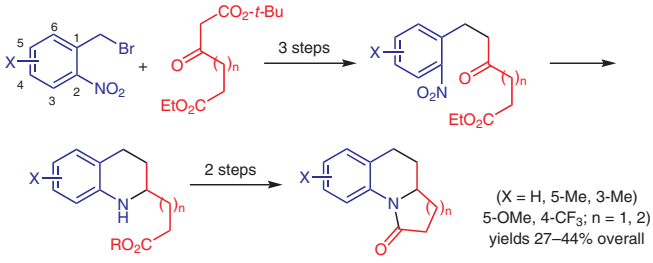
Synthesis F. M. Watts, R. A. Bunce Paper

Synthesis of Aryl-Substituted 3,3a,4,5-Tetrahydropyrrolo[1,2-*a*]quinolin-1(2*H*)-ones and 2,3,4,4a,5,6-Hexahydro-1*H*-pyrido[1,2-*a*]quinolin-1-ones

Field M. Watts
Richard A. Bunce*

Department of Chemistry, Oklahoma State University, 107 Physical Sciences, Stillwater, OK, 74078, USA
rab@okstate.edu



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Abstract A new route to the title benzo-fused angular tricyclic amides 3,3a,4,5-tetrahydropyrrolo- and 2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolin-1-ones is reported from 1-(*tert*-butyl) 6-ethyl 3-oxohexanedioate and 1-(*tert*-butyl) 7-ethyl 3-oxoheptanedioate. Alkylation of these β-keto diesters with a series of 2-nitrobenzyl bromides followed by acid hydrolysis and decarboxylation gives ethyl 6-(2-nitrophenyl)-4-oxohexanoates and ethyl 7-(2-nitrophenyl)-5-oxoheptanoates, respectively. Reductive amination under hydrogenation conditions followed by ester hydrolysis and condensative ring closure affords the final lactam products. The reactions proceed cleanly and only two chromatographic purifications are required.

Key words benzo-fused lactams, alkylation–decarboxylation, β-keto diesters, reductive amination, ester hydrolysis, lactamization

Fused polycyclic heterocycles are ubiquitous in natural product and drug chemistry. As a result of the basicity and H-bonding ability of the nitrogen, many of these compounds can bind to receptors that are important to animal and plant functions. Two compounds that have received relatively little attention are the benzo-fused angular tricyclic amides 3,3a,4,5-tetrahydropyrrolo[1,2-*a*]-quinolin-1(2*H*)-one (6-6-5 lactam, **1**) and 2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolin-1-one (6-6-6 lactam, **2**) (Figure 1). While these molecular architectures are not specifically found in many natural products or drugs, their reduction products, 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (commonly known as benzoindolizidine) and 2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinoline, (commonly known as benzoquinolizidine) constitute a large family of compounds that have shown significant biological activity.[1,2] Thus, considerable effort has been devoted to the development of synthetic approaches to these systems.[3–7]

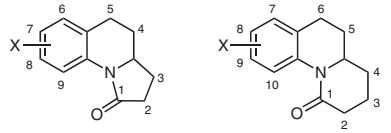


Figure 1 Target molecules of the study

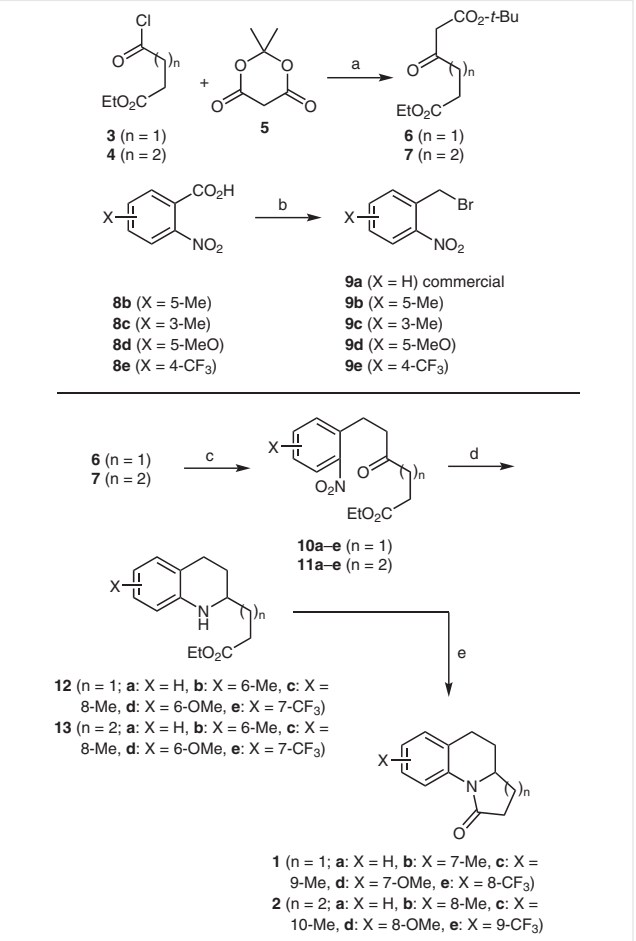
There are several previous routes that have been used to access these tricyclic lactams. One group[8] reported the low pressure (1 atm) hydrogenation of (*E*)-3-(quinolin-2-yl)acrylic acid over W-2 Raney nickel, which reduced the pyridine ring and gave the unsubstituted 6-6-5 lactam directly in 33% yield. Double bond reduction of the corresponding acrylic ester was also reported,[9] followed by base hydrolysis and ring closure to give the tricyclic target in 42% yield. In a similar approach,[10] diethyl 2-[2-(quinolin-2-yl)ethyl]malonate was hydrogenated over Raney nickel at 130 atm to initially form the substituted 1,2,3,4-tetrahydroquinoline, which then closed the 6-6-6 lactam in 29% overall yield. One final reductive route utilized sodium in 1-butanol with (*E*)-3-(quinolin-2-yl)acrylic acid to directly generate a 45% yield of the 6-6-5 lactam.[11] The modest yield in each of these earlier procedures was accompanied by various side products that had to be removed. More recently, two papers described the formation of the 6-6-5 lactam framework from *ortho*-substituted aromatic systems. In the first,[12] *N*-[2-(but-3-en-1-yl)phenyl]-2-iodoacetamide was treated with bis(tributyltin) and boron trifluoride diethyl etherate in dichloromethane (DCM) under sunlamp irradiation. The second[13] involved treatment of the analogous chloroacetamide derivative with 10 mol% palladium acetate, sodium carbonate and 4 Å molecular sieves in acetonitrile. The yields were 95% and 90%, respectively, though several steps were required to prepare the cyclization sub-

strates and the final products were likely contaminated with traces of the metals employed. Finally, Wang and co-workers[14] were able to generate the 6-6-5 lactam in 55% yield by an intramolecular Diels–Alder cycloaddition of *o*-quinodimethane imine generated in situ by passing a dilute tetrahydrofuran (THF) solution of 1-(2,2-dioxidobenzo[*c*]isothiazol-1(3*H*)-yl)pent-4-en-1-one at 100 bar of pressure through a 300 °C flow reactor (residence time = 4 s). The disadvantages of this method were the specialized apparatus required and the low throughput allowed by the reactor.

The current method assembled the cyclization substrates from easily accessible β-keto diesters **6** and **7**. Acylation of Meldrum's acid (**5**)[15] with ethyl succinyl chloride (**3**) and ethyl glutaryl chloride (**4**) according to the method of Yonemitsu and co-workers,[16,17] followed by refluxing in *tert*-butyl alcohol afforded 1-(*tert*-butyl) 6-ethyl 3-oxohexanedioate (**6**) (82%) and 1-(*tert*-butyl) 7-ethyl 3-oxoheptanedioate (**7**) (84%), respectively, after distillation. In addition to commercial 2-nitrobenzyl bromide (**9a**), substituted 2-nitrobenzyl bromides **9b–e** were prepared in two steps from the available 2-nitrobenzoic acids **8b–e** by reduction with borane–tetrahydrofuran[18] and treatment with phosphorus tribromide[19] in 75–77% overall yields. Deprotonation of β-keto diesters **6** and **7** with sodium hydride in THF and addition of bromides **9** afforded the alkylated products. Subsequent treatment with trifluoroacetic acid/triethylsilane followed by heating at 130 °C for 5 minutes cleaved the *tert*-butyl ester and decarboxylated the acid[20,21] to give ethyl 6-(2-nitroaryl)-4-oxohexanoates **10a–e** and ethyl 7-(2-nitroaryl)-5-oxoheptanoates **11a–e** in 60–65% yields from **6** and **7** after chromatographic purification.

Hydrogenation of **10** and **11** in THF over 5% Pd/C afforded the tetrahydroquinoline derivatives **12** and **13**, respectively, which were hydrolyzed with lithium hydroxide in aqueous THF[22] and ring closed using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl) and 4-(dimethylamino)pyridine (DMAP) in DCM.[21] Final chromatographic purification afforded the lactam products **1** and **2** in 60–70% yield from **10** and **11**, respectively. The entire synthetic approach is outlined in Scheme 1.

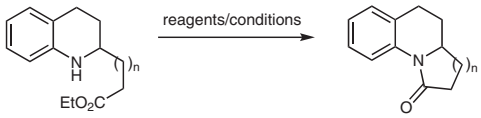
All intermediates and products were characterized by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy; the final compounds were further analyzed by elemental analysis. The fused-ring lactam products showed C=O absorptions at 1696–1651 cm^{-1} as expected, with the strained five-membered lactams appearing at slightly higher values than the six-membered systems. The ^{1}H NMR spectra showed aromatic signals and couplings predicted for substituted aromatic rings as well as complex coupling patterns typical of fused saturated rings. The ^{13}C NMR spectra showed the correct number of carbonyl, aromatic and saturated carbons for the target structures.



Scheme 1 Synthesis of angular tricyclic amides **1** and **2**. *Reagents and conditions*: (a) (i) py, DCM, 0–20 °C, (ii) *t*-BuOH, reflux, 82–84%; (b) (i) H_3B·THF, THF, reflux, 5 h, (ii) PBr_3, Et_2O, 0–20 °C, 12 h, 75–77%; (c) (i) NaH, **9a–e**, 0–20 °C, (ii) TFA, Et_3SiH, DCM, rt, 5 h, (iii) 130 °C, 5 min, 55–65%; (d) 1–2 atm H_2, 5% Pd/C, THF, rt, 12–18 h; (e) (i) LiOH, aq THF, rt, 12 h, (ii) EDC·HCl, DMAP, DCM, 60–70%.

Originally, it was planned that the ring closures from **10** to **1** and **11** to **2** would occur in domino fashion. However, treatment with hydrogen over 5% Pd/C at 1 atm and 23 °C afforded only the tetrahydroquinoline reductive amination products **12** and **13**. Attempts to run the reduction under more vigorous temperature and pressure conditions resulted in partial reduction of the aromatic ring. Closure of the 6-6-5 lactams proved easier than closure of the 6-6-6 systems and a number of reagents were screened (Table 1). The five-ring precursor **12a** was readily closed to **1a** in 48–73% yield using OSU-6,[23] an MCM-41-type hexagonal mesoporous silica with mild Brönsted acid properties (20 wt% in toluene, reflux, 6–12 h). This catalyst has previously been shown to facilitate amide formation directly from esters.[24] However, this catalyst was ineffective in closing the six-membered analog (**13a** → **2a**). Attempts to use other acid catalysts, such as Amberlyst-15® and *p*-toluenesulfonic acid

Table 1 Cyclization Conditions for Lactam Formation



12a (n = 1)
13a (n = 2)

1a (n = 1)
2a (n = 2)

n	Reagents/conditions	Yield (%)
1	cat. OSU-6, PhMe, reflux	72
1	(1) excess LiOH, aq THF, rt (2) 1 equiv EDC·HCl, DMAP, DCM, rt	73
2	cat. OSU-6, PhMe, reflux	0
2	cat. Amberlyst-15, PhMe, reflux	8
2	cat. *p*-TsOH, PhMe, reflux	11
2	1 equiv NaH, DMSO, rt	28
2	(1) excess LiOH, aq THF, rt (2) 1 equiv EDC·HCl, DMAP, DCM, rt	65

(*p*-TsOH) gave unacceptable (ca. 10%) conversions. Additionally, the use of sodium hydride in DMSO according to a literature procedure[25] provided only a modest 28% yield of the lactam. Finally, we subjected the six-membered precursor **13** to a two-step protocol involving hydrolysis of the ester with lithium hydroxide in aqueous THF[22] followed by lactam closure with EDC·HCl (1 equiv) and DMAP (1.6 equiv) in DCM.[21] This sequence proceeded in 65–75% yield and also proved effective for closing the five-membered lactams in similar yields.

Overall, the reactions used in our syntheses were very clean and only two chromatographic purifications were required, one for intermediates **10** and **11** and the other for the final products.

THF was distilled from $LiAlH_4$ prior to use. All other commercial reagents and solvents were used as received. Unless otherwise indicated, all reactions were carried out under dry N_2 in oven-dried glassware. Reactions were monitored by thin-layer chromatography (TLC) using silica gel GF plates (Analtech No.21521). Preparative separations were performed by column chromatography on silica gel (Davisil® grade 62, 60–200 mesh) containing UV-active phosphor (Sorbent Technologies No.UV-05) slurry packed into quartz columns, or by preparative thin-layer chromatography (PTLC) on 20cm×20cm silica gel GF plates (Analtech No.02015); band elution in all cases was monitored using a hand-held UV lamp.Melting points were obtained using a MEL-TEMP apparatus and are uncorrected. IR spectra were run as thin films or $CHCl_3$ solutions on NaCl discs using a Varian Scimitar FTS 800 spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded at 400/101MHz using a Bruker Avance 400 spectrometer. Samples were prepared in $CDCl_3$ and Me_4Si was used as the internal standard. High-resolution mass spectrometry (HRMS) was performed using a Thermo LTQ-Orbitrap XL mass spectrometer. Elemental analyses of the final products (±0.4%) were performed by Atlantic Microlabs, Norcross, GA.

1-(*tert*-Butyl) ω-Ethyl 3-Oxodiesters 6 and 7;[16,17] General Procedure

To a stirred solution of Meldrum's acid[15] (**5**) (5.00g, 34.7mmol) in DCM (50mL) at 0°C was added pyridine (6.64g, 6.80mL, 84.1mmol) dropwise and the reaction was stirred for 15min to give a colorless solution. To prepare **6**, a solution of ethyl succinyl chloride (**3**) (5.54g, 4.77mL, 33.7mmol) in DCM (20mL) was added dropwise at 0°C over a period of 45min. [Note: The same procedure was performed with ethyl glutaryl chloride (**4**) (6.01g, 5.28mL, 33.7mmol) to prepare **7**.] The mixture was stirred for 1h at 0°C and then for 1h at 23°C to give an orange solution. The reaction was diluted with DCM (20mL) and poured into a mixture of 2M HCl and crushed ice (ca. 150g). The organic phase was separated and the aqueous layer extracted with DCM (2×50mL). The combined organic extracts were washed with 2M HCl (2×25mL) and sat. NaCl (40mL), dried (Na_2SO_4), filtered, and concentrated under vacuum to afford the acyl Meldrum's acid derivative as an orange oil. This oil was carried forward to the next step without purification.

The crude acyl Meldrum's acid was dissolved in *tert*-BuOH (50mL) and heated under reflux for 3h. The solvent was removed by rotary evaporation and the resulting oil was distilled under vacuum to give the keto diester.

1-(*tert*-Butyl) 6-Ethyl 3-Oxohexanedioate (6)

Yield: 6.74g, 27.6mmol (82%); colorless oil; bp 95–100°C (0.5mmHg).

IR (thin film): 1732 (C=O), 1720 (C=O) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ (contains some enol) = 4.15 (q, *J* = 7.5Hz, 2 H), 3.41 (s, 2 H), 2.86 (t, *J* = 7.1Hz, 2 H), 2.60 (t, *J* = 7.1Hz, 2 H), 1.47 (s, 9 H), 1.25 (t, *J* = 7.4Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 201.5, 172.4, 166.3, 82.0, 60.7, 30.5, 37.3, 27.89, 27.85, 14.1.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{12}H_{20}O_5$: 245.1389; found: 245.1388.

1-(*tert*-Butyl) 7-Ethyl 3-Oxoheptanedioate (7)

Yield: 7.30g, 28.3mmol (84%); colorless oil; bp 108–111°C (0.5mmHg).

IR (thin film): 1734 (C=O), 1718 (C=O) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ (contains some enol) = 4.13 (m, 2 H), 3.34 (s, 2 H), 2.62 (m, 2 H), 2.34 (m, 2 H), 2.91 (m, 2 H), 1.97 (s, 9 H), 1.25 (m, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 202.5, 173.0, 166.3, 81.9, 60.3, 50.6, 41.7, 33.1, 27.9, 18.6, 14.8.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{22}O_5$: 259.1545; found: 259.1542.

Benzylic Bromides 9; General Procedure

A solution of the carboxylic acid **8** (4.00g, 1 equiv) in anhydrous THF (50mL) at 0°C was treated dropwise with H_3B·THF complex (1M in THF, 2 equiv).[18] The reaction was stirred for 1h at 0°C, 1h at 23°C and then at reflux until TLC indicated the reaction was complete. The mixture was cooled and 10mL of sat. NaCl was cautiously added. The mixture was transferred to a separating funnel, sat. NaCl (50mL) was added and the mixture was extracted with Et_2O (3×50mL). The combined extracts were washed with one additional portion of sat. NaCl (50mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The resulting solid was crystallized from 2% Et_2O in hexanes and used directly in the next step.Yields ranged from 85–90%.

A magnetically stirred solution of the benzylic alcohol **8** in Et_2O (50mL) at 0°C was treated dropwise with phosphorus tribromide (2 equiv).[19] The mixture was stirred overnight with gradual warming to 23°C. The crude reaction was poured into cold H_2O (50mL) and extracted with Et_2O (3×50mL). The combined Et_2O extracts were washed with H_2O and sat. NaCl, dried ($MgSO_4$), filtered, and concentrated to give a light yellow oil that crystallized on standing. The solid was purified on a silica gel column (30cm×2cm) eluting with 1–3% Et_2O in hexanes to give the bromides **9** in 85–90% yield.

5-Methyl-2-nitrobenzyl Bromide (9b)

Yield: 3.89g, 16.9mmol (77% overall); light yellow solid; mp 49–50°C.

IR ($CHCl_3$): 1521 (NO_2), 1341 (NO_2) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4Hz, 1 H), 7.35 (s, 1 H), 7.27 (d, *J* = 8.4Hz, 1 H), 4.82 (s, 2 H), 2.45 (s, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 145.6, 145.1, 133.1, 132.9, 130.2, 125.8, 29.3, 21.4.

HRMS (ESI): *m*/*z* $[M+H]^+$ for $C_8H_8{}^{79}BrNO_2$: 229.9817; found: 229.9819.

3-Methyl-2-nitrobenzyl Bromide (9c)

Yield: 3.78g, 16.4mmol (75% overall); light yellow solid; mp 53–54°C.

IR ($CHCl_3$): 1528 (NO_2), 1366 (NO_2) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 7.37 (m, 2 H), 7.28 (m, 1 H), 4.47 (s, 2 H), 2.35 (s, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 150.6, 131.9, 130.9, 130.7, 129.7, 129.0, 26.9, 17.7.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_8H_8{}^{79}BrNO_2$: 229.9817; found: 229.9816.

5-Methoxy-2-nitrobenzyl Bromide (9d)

Yield: 3.86g, 15.7mmol (77% overall); light yellow solid; mp 55–56°C.

IR ($CHCl_3$): 2842 (OCH_3), 1515 (NO_2), 1337 (NO_2) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 8.15 (d, *J* = 9.2Hz, 1 H), 7.03 (d, *J* = 2.8Hz, 1 H), 6.93 (dd, *J* = 9.1, 2.8Hz, 1 H), 4.86 (s, 2 H), 3.92 (s, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 163.4, 140.7, 135.7, 128.4, 117.6, 114.0, 56.0, 29.9.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_8H_8{}^{79}BrNO_3$: 245.9766; found: 245.9763.

2-Nitro-4-(trifluoromethyl)benzyl Bromide (9e)

Yield: 3.74g, 13.1mmol (77% overall); light yellow solid; mp 39–40°C.

IR ($CHCl_3$): 1542 (NO_2), 1354 (NO_2), 1324 (CF_3) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 8.32 (s, 1 H), 7.88 (d, *J* = 8.4Hz, 1 H), 7.76 (d, *J* = 8.4Hz, 1 H), 4.86 (s, 2 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 148.0, 136.6, 133.5, 132.3 (q, *J* = 34.4Hz), 130.2 (q, *J* = 3.5Hz), 122.9 (q, *J* = 3.8Hz), 122.5 (q, *J* = 272.9Hz), 27.5.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_8H_5F_3{}^{79}BrNO_2$: 283.9534; found: 283.9536.

Ethyl 6-(2-Nitroaryl)-4-oxohexanoates (10) and Ethyl 7-(2-Nitroaryl)-5-oxoheptanoates (11);[20] General Procedure

A solution of **6** (244mg, 1.00mmol) in THF (5.0mL) at 0°C was treated with sodium hydride (40mg of a 60% dispersion in mineral oil, 1.00mmol) and stirred at 0°C for 10min. To the colorless anion was slowly added dropwise a solution of a 2-nitrobenzyl bromide **9** (1 equiv) in THF (5.0mL). The reaction was stirred with gradual warming to 23°C for 2h. Stirring was continued at 23°C for 4–8h, and then at 50°C for 1h. After cooling, the crude reaction was poured into sat. NH_4Cl (20mL) and extracted with Et_2O (2×25mL). The combined organic extracts were washed with sat. NaCl, dried ($MgSO_4$), filtered, and concentrated under vacuum to give a yellow oil that was used directly in the next reaction. A similar procedure was followed for the alkylation of **7** (258mg, 1.00mmol).

The crude alkylation product, dissolved in DCM (3.0mL), was treated with triethylsilane (0.5mL) and trifluoroacetic acid (0.5mL) and stirred for 5h. The solvent, acid and silane were removed under vacuum and the crude product was heated at 130°C for 5min to promote decarboxylation. The resulting oil was purified by PTLC eluting with 35–40% Et_2O in hexanes. Band 2 afforded the keto diester products, which are characterized below. Small quantities of the unreacted bromide (5–8%) could be recovered from band 1.

Ethyl 6-(2-Nitrophenyl)-4-oxohexanoate (10a)

Yield: 187mg, 0.67mmol (67%); yellow oil.

IR (thin film): 1732 (C=O), 1716 (C=O), 1528 (NO_2), 1353 (NO_2) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.1Hz, 1 H), 7.53 (t, *J* = 7.6Hz, 1 H), 7.40 (d, *J* = 8.2Hz, 1 H), 7.37 (t, *J* = 8.0Hz, 1 H), 4.13 (q, *J* = 7.1Hz, 2 H), 3.17 (t, *J* = 7.7Hz, 2 H), 2.89 (t, *J* = 7.5Hz, 2 H), 2.73 (t, *J* = 6.5Hz, 2 H), 2.59 (t, *J* = 6.5Hz, 2 H), 1.25 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 207.3, 172.7, 149.2, 136.2, 133.2, 132.4, 127.4, 124.9, 60.7, 43.2, 37.0, 28.0, 27.2, 14.2.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{17}NO_5$: 280.1185; found: 280.1184.

Ethyl 6-(5-Methyl-2-nitrophenyl)-4-oxohexanoate (10b)

Yield: 191mg, 0.65mmol (65%); yellow oil.

IR (thin film): 1732 (C=O), 1716 (C=O), 1518 (NO_2), 1345 (NO_2) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.3Hz, 1 H), 7.17 (s, 1 H), 7.15 (d, *J* = 8.3Hz, 1 H), 4.14 (q, *J* = 7.1Hz, 2 H), 3.15 (t, *J* = 7.4Hz, 2 H), 2.87 (t, *J* = 7.2Hz, 2 H), 2.73 (t, *J* = 6.6Hz, 2 H), 2.61 (t, *J* = 6.6Hz, 2 H), 2.40 (s, 3 H), 1.25 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 207.4, 173.2, 146.8, 144.5, 136.5, 133.0, 128.1, 125.2, 60.7, 43.2, 37.0, 28.0, 27.5, 21.4, 14.2.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{19}NO_5$: 294.1341; found: 294.1343.

Ethyl 6-(3-Methyl-2-nitrophenyl)-4-oxohexanoate (10c)

Yield: 169mg, 0.58mmol (58%); yellow oil.

IR (thin film): 1735 (C=O), 1716 (C=O), 1527 (NO_2), 1369 (NO_2) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 7.30 (d, *J* = 7.6Hz, 1 H), 7.16 (m, 2 H), 4.13 (q, *J* = 7.1Hz, 2 H), 2.86 (m, 2 H), 2.81 (m, 2 H), 2.71 (t, *J* = 6.5Hz, 2 H), 2.59 (t, *J* = 6.5Hz, 2 H), 2.31 (s, 3 H), 1.25 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 207.0, 172.7, 151.7, 132.5, 130.2, 129.6, 129.4, 128.3, 60.7, 43.4, 37.1, 28.0, 25.3, 17.4, 14.2.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{19}NO_5$: 294.1341; found: 294.1338.

Ethyl 6-(5-Methoxy-2-nitrophenyl)-4-oxohexanoate (10d)

Yield: 189mg, 0.61mmol (61%); yellow oil.

IR (thin film): 2846 (OCH_3), 1730 (C=O), 1718 (C=O), 1513 (NO_2), 1341 (NO_2) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.8Hz, 1 H), 6.84 (s, 1 H), 6.83 (dd, *J* = 8.8, 2.8Hz, 1 H), 4.13 (q, *J* = 7.1Hz, 2 H), 3.88 (s, 3 H), 3.21 (t, *J* = 7.3Hz, 2 H), 2.88 (t, *J* = 7.3Hz, 2 H), 2.73 (t, *J* = 6.8Hz, 2 H), 2.60 (t, *J* = 6.8Hz, 2 H), 1.25 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 207.4, 172.7, 163.2, 141.9, 139.7, 127.9, 117.1, 112.6, 60.7, 55.8, 43.0, 37.0, 28.3, 28.0, 14.2.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{19}NO_6$: 310.1291; found: 310.1289.

Ethyl 6-[2-Nitro-4-(trifluoromethyl)phenyl]-4-oxohexanoate (10e)

Yield: 212mg, 0.61mmol (61%); white solid; mp 56–58°C.

IR ($CHCl_3$): 1731 (C=O), 1713 (C=O), 1538 (NO_2), 1333 (NO_2) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 7.79 (d, *J* = 8.6Hz, 1 H), 7.61 (d, *J* = 8.6Hz, 1 H), 4.13 (q, *J* = 7.3Hz, 2 H), 3.25 (t, *J* = 7.7Hz, 2 H), 2.93 (t, *J* = 7.5Hz, 2 H), 2.73 (t, *J* = 6.7Hz, 2 H), 2.61 (t, *J* = 6.7Hz, 2 H), 1.25 (t, *J* = 7.3Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 206.8, 172.6, 149.3, 140.3, 133.6, 130.2 (q, *J* = 34.1Hz), 129.5 (q, *J* = 3.6Hz), 122.8 (q, *J* = 272.6Hz), 122.1 (q, *J* = 4.1Hz), 60.7, 44.6, 37.0, 28.0, 27.0, 14.1.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{16}F_3NO_5$: 348.1059; found: 348.1055.

Ethyl 7-(2-Nitrophenyl)-5-oxoheptanoate (11a)

Yield: 184mg, 0.63mmol (63%); yellow oil.

IR (thin film): 1732 (C=O), 1716 (C=O), 1528 (NO_2), 1347 (NO_2) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.1Hz, 1 H), 7.52 (td, *J* = 7.5, 1.4Hz, 1 H), 7.40 (d, *J* = 7.4Hz, 1 H), 7.37 (t, *J* = 7.6Hz, 1 H), 4.12 (q, *J* = 7.2Hz, 2 H), 3.15 (t, *J* = 7.4Hz, 2 H), 2.82 (t, *J* = 7.4Hz, 2 H), 2.49 (t, *J* = 7.2Hz, 2 H), 2.32 (t, *J* = 7.2Hz, 2 H), 1.90 (quin, *J* = 7.2Hz, 2 H), 1.24 (t, *J* = 7.2Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 208.4, 173.1, 149.2, 136.3, 133.2, 132.4, 127.4, 124.9, 60.4, 43.2, 41.6, 33.3, 27.3, 18.9, 14.2.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{19}NO_5$: 294.1341; found: 294.1340.

Ethyl 7-(5-Methyl-2-nitrophenyl)-5-oxoheptanoate (11b)

Yield: 200mg, 0.65mmol (65%); yellow oil.

IR (thin film): 1730 (C=O), 1717 (C=O), 1519 (NO_2), 1344 (NO_2) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.89 (m, 1 H), 7.18 (s, 1 H), 7.15 (d, *J* = 8.3Hz, 1 H), 4.12 (q, *J* = 7.1Hz, 2 H), 3.13 (t, *J* = 7.2Hz, 2 H), 2.81 (t, *J* = 7.2Hz, 2 H), 2.49 (t, *J* = 7.2Hz, 2 H), 2.40 (s, 3 H), 2.32 (t, *J* = 7.2Hz, 2 H), 1.90 (quin, *J* = 7.2Hz, 2 H), 1.25 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 208.5, 173.1, 146.8, 144.5, 136.5, 133.0, 128.0, 125.2, 60.4, 43.2, 41.6, 33.3, 27.6, 21.4, 18.9, 14.2.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{21}NO_5$: 308.1498; found: 308.1495.

Ethyl 7-(3-Methyl-2-nitrophenyl)-5-oxoheptanoate (11c)

Yield: 169mg, 0.55mmol (55%); yellow oil.

IR (thin film): 1729 (C=O), 1716 (C=O), 1528 (NO_2), 1373 (NO_2) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.29 (t, *J* = 7.6Hz, 1 H), 7.15 (d, *J* = 7.6Hz, 2 H), 4.12 (q, *J* = 7.1Hz, 2 H), 2.84 (t, *J* = 7.6Hz, 2 H), 2.73 (t, *J* = 7.5Hz, 2 H), 2.46 (t, *J* = 7.1Hz, 2 H), 2.30 (t, *J* = 7.1Hz, 2 H), 2.30 (s, 3 H), 1.88 (quin, *J* = 7.1Hz, 2 H), 1.25 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 208.1, 173.0, 151.7, 132.5, 130.2, 129.6, 129.4, 128.3, 60.4, 43.4, 41.6, 33.2, 25.4, 18.8, 17.4, 14.2.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{21}NO_5$: 308.1498; found: 308.1499.

Ethyl 7-(5-Methoxy-2-nitrophenyl)-5-oxoheptanoate (11d)

Yield: 194mg, 0.60mmol (60%); yellow oil.

IR (thin film): 2848 (OCH_3), 1729 (C=O), 1716 (C=O), 1515 (NO_2), 1340 (NO_2) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.8Hz, 1 H), 6.83 (s, 1 H), 6.82 (d, *J* = 8.8Hz, 1 H), 4.12 (q, *J* = 7.1Hz, 2 H), 3.88 (s, 3 H), 3.19 (t, *J* = 7.4Hz, 2 H), 2.82 (t, *J* = 7.4Hz, 2 H), 2.50 (t, *J* = 7.1Hz, 2 H), 2.32 (t, *J* = 7.1Hz, 2 H), 1.90 (quin, *J* = 7.1Hz, 2 H), 1.25 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 208.6, 173.2, 163.2, 141.9, 139.8, 127.9, 117.1, 112.5, 60.4, 55.8, 43.0, 41.6, 33.3, 28.4, 18.9, 14.2.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{21}NO_6$: 324.1447; found: 324.1443.

Ethyl 7-[2-Nitro-4-(trifluoromethyl)phenyl]-5-oxoheptanoate (11e)

Yield: 220mg, 0.61mmol (61%); light yellow solid; mp 58–60°C.

IR ($CHCl_3$): 1732 (C=O), 1714 (C=O), 1533 (NO_2), 1351 (NO_2) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.20 (d, *J* = 1.4Hz, 1 H), 7.78 (dd, *J* = 8.1, 1.4Hz, 1 H), 7.60 (d, *J* = 8.1Hz, 1 H), 4.12 (q, *J* = 7.2Hz, 2 H), 3.22 (t, *J* = 7.3Hz, 2 H), 2.85 (t, *J* = 7.3Hz, 2 H), 2.49 (t, *J* = 7.3Hz, 2 H), 2.32 (t, *J* = 7.2Hz, 2 H), 1.90 (quin, *J* = 7.2Hz, 2 H), 1.25 (t, *J* = 7.2Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 207.8, 173.0, 149.1, 140.4, 133.6, 130.2 (q, *J* = 34.3Hz), 129.5 (q, *J* = 3.4Hz), 122.8 (q, *J* = 272.6Hz), 122.2 (q, *J* = 3.9Hz), 60.4, 42.7, 41.5, 33.2, 27.1, 18.8, 14.2.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{18}F_3NO_5$: 362.1215; found: 362.1212.

Reductive Ring Closure of 10 to 12 and 11 to 13; General Procedure

To a solution of the (2-nitroaryl)-substituted keto ester **10** or **11** (150mg) in THF (20mL) under nitrogen was added 5% Pd/C (ca. 5mg) and the solution was stirred at 23°C under 1–2 atm of hydrogen in a glass-lined 125mL stainless steel reactor (Parr No.4750) equipped with a magnetic stirrer. After 12–18 h, TLC indicated the reaction was complete. The solvent was removed, the residue was diluted with Et_2O and the solution was filtered through a plug of Celite® to remove the catalyst. Concentration of the filtrate under vacuum gave the 2-substituted tetrahydroquinoline **12** or **13**, which was used without further purification.

Ethyl (±)-3-(1,2,3,4-Tetrahydroquinolin-2-yl)propanoate (12a)

Yield: 114mg, 0.49mmol (91%); yellow oil.

IR (thin film): 3393 (N–H), 1729 (C=O) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 6.95 (superimposed t, *J* = 8.0Hz, 1 H and d, *J* = 7.5Hz, 1 H), 6.60 (t, *J* = 7.8Hz, 1 H), 6.47 (d, *J* = 7.8Hz, 1 H), 4.14 (q, *J* = 7.1Hz, 2 H), 3.86 (br s, 1 H), 3.31 (m, 1 H), 2.80 (ddd, *J* = 16.2, 10.3, 5.5Hz, 1 H), 2.73 (dt, *J* = 16.3, 5.0Hz, 1 H), 2.43 (m, 2 H), 1.92 (m, 1 H), 1.85 (q, *J* = 7.5Hz, 2 H), 1.64 (m, 1 H), 1.26 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.6, 144.4, 129.2, 126.8, 121.1, 117.1, 114.2, 60.6, 50.8, 31.3, 30.5, 27.4, 26.1, 14.3.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{19}NO_2$: 234.1494; found: 234.1492.

Ethyl (±)-3-(6-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)propanoate (12b)

Yield: 112mg, 0.45mmol (89%); yellow oil.

IR (thin film): 3399 (N–H), 1730 (C=O) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 6.79 (m, 2 H), 6.43 (d, *J* = 8.6Hz, 1 H), 4.14 (q, *J* = 7.1Hz, 2 H), 3.75 (br s, 1 H), 3.29 (m, 1 H), 2.78 (ddd, *J* = 16.2, 10.4, 4.6Hz, 1 H), 2.70 (dt, *J* = 16.2, 5.0Hz, 1 H), 2.44 (m, 2 H), 2.20 (s, 3 H), 1.95 (m, 1 H), 1.84 (q, *J* = 7.3Hz, 2 H), 1.65 (m, 1 H), 1.25 (t, *J* = 7.2Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.6, 141.6, 129.8, 127.3, 126.8, 121.4, 114.7, 60.6, 51.0, 31.2, 30.5, 27.6, 26.0, 20.4, 14.2.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{21}NO_2$: 248.1651; found: 248.1654.

Ethyl (±)-3-(8-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)propanoate (12c)

Two treatments under 2 atm of H_2, 36h total.

Yield: 98mg, 0.40mmol (78%); yellow oil.

IR (thin film): 3412 (N–H), 1731 (C=O) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 6.86 (m, 2 H), 6.55 (t, *J* = 7.4Hz, 1 H), 4.15 (q, *J* = 7.2Hz, 2 H), 3.45 (br s, 1 H), 3.36 (m, 1 H), 2.84 (ddd, *J* = 16.2, 10.5, 5.5Hz, 1 H), 2.75 (dt, *J* = 16.2, 5.0Hz, 1 H), 2.46 (m, 2 H), 2.08 (s, 3 H), 1.97–1.87 (m, 3 H), 1.65 (m, 1 H), 1.26 (t, *J* = 7.2Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.7, 142.3, 127.9, 127.1, 121.2, 120.5, 116.5, 60.6, 51.1, 31.3, 30.5, 27.3, 26.4, 17.2, 14.3.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{21}NO_2$: 248.1651; found: 248.1652.

Ethyl (±)-3-(6-Methoxy-1,2,3,4-tetrahydroquinolin-2-yl)propanoate (12d)

Yield: 112mg, 0.43mmol (87%); yellow oil.

IR (thin film): 3379 (N–H), 2837 (OCH_3), 1732 (C=O) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 6.60 (dd, *J* = 8.5, 2.8Hz, 1 H), 6.57 (d, *J* = 2.8Hz, 1 H), 6.45 (d, *J* = 8.5Hz, 1 H), 4.14 (q, *J* = 7.1Hz, 2 H), 3.72 (s, 3 H), 3.59 (br s, 1 H), 3.24 (m, 1 H), 2.81 (ddd, *J* = 16.5, 10.7, 5.8Hz, 1 H), 2.71 (dt, *J* = 16.3, 4.9Hz, 1 H), 2.42 (m, 2 H), 1.91 (m, 1 H), 1.84 (q, *J* = 7.4Hz, 2 H), 1.63 (m, 1 H), 1.26 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.6, 151.9, 138.5, 122.5, 115.5, 114.6, 113.0, 60.5, 55.8, 51.1, 31.3, 30.5, 27.7, 26.5, 14.3.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{21}NO_3$: 264.1600; found: 264.1597.

Ethyl (±)-3-[7-(Trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-yl]propanoate (12e)

Yield: 116mg, 0.39mmol (90%); yellow oil.

IR (thin film): 3390 (N–H), 1722 (C=O), 1331 (CF_3) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 7.01 (d, *J* = 7.8Hz, 1 H), 6.81 (d, *J* = 7.7Hz, 1 H), 6.68 (s, 1 H), 4.15 (superimposed q, *J* = 7.1Hz, 2 H and br s, 1 H), 3.35 (m, 1 H), 2.79 (m, 2 H), 2.44 (m, 2 H), 1.93 (m, 1 H), 1.86 (q, *J* = 7.3Hz, 2 H), 1.63 (m, 1 H), 1.26 (q, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.5, 144.4, 129.4, 129.2 (q, *J* = 31.8Hz), 124.6, 124.4 (q, *J* = 271.9Hz), 113.1 (q, *J* = 3.8Hz), 110.3 (q, *J* = 3.9Hz), 60.7, 50.7, 31.1, 30.4, 36.8, 25.9, 14.2.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{18}F_3NO_2$: 302.1368; found: 302.1365.

Ethyl (±)-4-(1,2,3,4-Tetrahydroquinolin-2-yl)butanoate (13a)

Yield: 110mg, 0.45mmol (87%); yellow oil.

IR (thin film): 3397 (N–H), 1747 (C=O) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 6.94 (t, *J* = 7.6Hz, 1 H), 6.93 (d, *J* = 7.6Hz, 1 H), 6.59 (t, *J* = 7.5Hz, 1 H), 6.46 (d, *J* = 7.6Hz, 1 H), 4.13 (q, *J* = 7.1Hz, 2 H), 3.80 (br s, 1 H), 3.25 (m, 1 H), 2.79 (ddd, *J* = 16.3, 10.6, 5.5Hz, 1 H), 2.71 (dt, *J* = 16.3, 5.0Hz, 1 H), 2.34 (t, *J* = 7.4Hz, 2 H), 1.95 (m, 1 H), 1.73 (m, 2 H), 1.61 (m, 1 H), 1.52 (dt, *J* = 9.2, 6.4Hz, 2 H), 1.25 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.5, 144.5, 129.3, 126.8, 121.2, 117.0, 114.1, 60.4, 51.2, 36.1, 34.3, 27.9, 26.3, 22.1, 14.3.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{21}NO_2$: 248.1651; found: 248.1648.

Ethyl (±)-4-(6-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)butanoate (13b)

Yield: 116mg, 0.44mmol (90%); yellow oil.

IR (thin film): 3397 (N–H), 1733 (C=O) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 6.77 (m, 2 H), 6.41 (d, *J* = 8.5Hz, 1 H), 4.14 (q, *J* = 7.1Hz, 2 H), 3.48 (br s, 1 H), 3.22 (m, 1 H), 2.76 (ddd, *J* = 16.2, 10.7, 5.6Hz, 1 H), 2.67 (dt, *J* = 16.2, 4.9Hz, 1 H), 2.34 (t, *J* = 7.4Hz, 2 H), 2.19 (s, 3 H), 1.93 (m, 1 H), 1.74 (m, 2 H), 1.62 (m, 1 H), 1.51 (dt, *J* = 9.2, 6.4Hz, 2 H), 1.26 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.5, 142.2, 129.8, 127.3, 126.3, 121.3, 114.3, 60.4, 51.3, 36.0, 34.3, 28.1, 26.2, 21.1, 20.4, 14.3.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{23}NO_2$: 262.1807; found: 262.1802.

Ethyl (±)-4-(8-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)butanoate (13c)

Two treatments under 2 atm of H_2, 36h total.

Yield: 92mg, 0.35mmol (72%); yellow oil.

IR (thin film): 3429 (N–H), 1733 (C=O) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 6.86 (apparent t, *J* = 8.1Hz, 2 H), 6.55 (t, *J* = 7.4Hz, 1 H), 4.14 (q, *J* = 7.1Hz, 2 H), 3.49 (br s, 1 H), 3.31 (m, 1 H), 2.83 (ddd, *J* = 16.2, 10.7, 5.5Hz, 1 H), 2.74 (dt, *J* = 16.3, 4.9Hz, 1 H), 2.36 (t, *J* = 7.4Hz, 2 H), 2.09 (s, 3 H), 1.97 (m, 1 H), 1.77 (quin, *J* = 7.6Hz, 2 H), 1.68–1.53 (m, 3 H), 1.26 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.5, 142.4, 127.9, 127.1, 121.0, 120.6, 116.4, 60.4, 51.4, 36.2, 34.3, 27.7, 26.5, 21.1, 17.2, 14.3.

HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{23}NO_2$: 262.1807; found: 262.1806.

Ethyl (±)-4-(6-Methoxy-1,2,3,4-tetrahydroquinolin-2-yl)butanoate (13d)

Yield: 117mg, 0.42mmol (91%); yellow oil.

IR (thin film): 3387 (N–H), 2842 (OCH_3), 1729 (C=O) cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ = 6.59 (dd, *J* = 8.5, 2.8Hz, 1 H), 6.57 (d, *J* = 2.8Hz, 1 H), 6.45 (d, *J* = 8.5Hz, 1 H), 4.13 (q, *J* = 7.1Hz, 2 H), 3.71 (s, 3 H), 3.53 (br s, 1 H), 3.19 (m, 1 H), 2.81 (ddd, *J* = 16.5, 10.9, 5.8Hz, 1 H), 2.70 (dt, *J* = 16.3, 4.8Hz, 1 H), 2.34 (t, *J* = 7.4Hz, 2 H), 1.95 (m, 1 H), 1.74 (quin, *J* = 7.4Hz, 2 H), 1.61 (m, 1 H), 1.51 (m, 2 H), 1.26 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.5, 151.9, 138.5, 122.7, 115.5, 114.6, 112.9, 60.4, 55.8, 51.5, 36.0, 34.3, 28.1, 26.6, 21.1, 14.3.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{16}H_{23}NO_3$: 278.1756; found: 278.1756.

Ethyl (±)-4-[7-(Trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-yl]butanoate (13e)

Yield: 116mg, 0.37mmol (88%); yellow oil.

IR (thin film): 3396 (N–H), 1727 (C=O), 1332 (CF_3) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.01 (d, *J* = 7.8Hz, 1 H), 6.80 (d, *J* = 7.8Hz, 1 H), 6.70 (s, 1 H), 4.14 (q, *J* = 7.1Hz, 2 H), 4.03 (br s, 1 H), 3.30 (m, 1 H), 2.78 (m, 2 H), 2.36 (t, *J* = 7.3Hz, 2 H), 1.97 (m, 1 H), 1.74 (quin, *J* = 7.4Hz, 2 H), 1.62 (m, 1 H), 1.54 (m, 2 H), 1.26 (t, *J* = 7.1Hz, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.4, 144.6, 129.4, 128.8 (q, *J* = 31.8Hz), 124.6, 124.4 (q, *J* = 271.4Hz), 113.1 (q, *J* = 3.9Hz), 110.2 (q, *J* = 3.7Hz), 60.5, 51.1, 35.8, 34.1, 27.2, 26.1, 20.9, 14.3.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{16}H_{20}F_3NO_2$: 316.1524; found: 316.1521.

Ester Hydrolysis and Ring Closure; General Procedure

A solution of the 1,2,3,4-tetrahydroquinolin-2-yl ester (100mg) in THF (5.0mL) was treated with 5% aqueous LiOH (2.0mL) and the mixture was stirred overnight. The crude hydrolysate was extracted with 6M HCl (3×5mL). An aqueous solution of 5% NaOAc was then added to the aqueous extract until a pH of 6 (pH paper) was achieved.[22] The cloudy aqueous mixture was extracted with Et_2O (3×15mL) and the combined Et_2O layers were washed with sat. NaCl, dried ($MgSO_4$), filtered, and concentrated under vacuum. The resulting oil was dissolved in DCM (4.0mL) and 4-(dimethylamino)pyridine (1.6 equiv) and EDC·HCl (1 equiv), based on the equivalents of the starting ester above, were added.[21] The reaction was stirred for 2–3h at which time TLC indicated complete conversion of the starting material. The reaction was added to H_2O and extracted with DCM (3×10mL). The combined organic extracts were washed with 1M HCl, sat. $NaHCO_3$ and sat. NaCl, dried (Na_2SO_4), filtered, and concentrated under vacuum. Final purification was accomplished by PTLC eluting with 50% Et_2O in hexanes.

(±)-3,3a,4,5-Tetrahydropyrrolo[1,2-*a*]quinolin-1(2*H*)-one (1a)

Yield: 58mg, 0.31mmol (72%); white solid; mp 105–107°C (Lit.[8] 109–111°C).

IR ($CHCl_3$): 1688 (C=O) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.70 (d, *J* = 8.4Hz, 1 H), 7.20 (t, *J* = 8.0Hz, 1 H), 7.12 (d, *J* = 7.5Hz, 1 H), 7.01 (t, *J* = 7.5Hz, 1 H), 3.91 (m, 1 H), 2.97 (ddd, *J* = 17.2, 12.6, 5.7Hz, 1 H), 2.86 (ddd, *J* = 16.9, 5.4, 2.0Hz, 1 H), 2.63 (ddd, *J* = 17.0, 11.3, 9.3Hz, 1 H), 2.50 (ddd, *J* = 17.0, 9.6, 2.2Hz, 1 H), 2.29 (m, 1 H), 2.18 (ddt, *J* = 10.5, 5.2, 2.4Hz, 1 H), 1.81–1.65 (m, 2 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.6, 136.7, 129.1, 126.8, 125.7, 123.5, 119.1, 58.2, 32.3, 29.4, 27.8, 25.5.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{12}H_{13}NO$: 188.1075; found: 188.1074.

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48.Found: C, 77.01; H, 7.04; N, 7.37.

(±)-7-Methyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinolin-1(2*H*)-one (1b)

Yield: 60mg, 0.30mmol (74%); off-white powder; mp 155–156°C.

IR ($CHCl_3$): 1683 (C=O) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.57 (d, *J* = 8.4Hz, 1 H), 7.01 (d, *J* = 8.4Hz, 1 H), 6.94 (s, 1 H), 3.88 (m, 1 H), 2.94 (ddd, *J* = 17.2, 12.8, 5.7Hz, 1 H), 2.81 (dd, *J* = 16.8, 5.3Hz, 1 H), 2.61 (ddd, *J* = 16.8, 10.9, 9.5Hz, 1 H), 2.48 (ddd, *J* = 16.8, 9.5, 1.9Hz, 1 H), 2.28 (obscured m, 1 H), 2.28 (s, 3 H), 2.15 (m, 1 H), 1.80–1.60 (m, 2 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.3, 134.3, 133.0, 129.5, 127.4, 125.6, 119.0, 58.1, 32.2, 29.6, 27.7, 25.5, 20.8.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{13}H_{15}NO$: 202.1232; found: 202.1233.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96.Found: C, 77.46; H, 7.50; N, 6.92.

(±)-9-Methyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinolin-1(2*H*)-one (1c)

Yield: 61mg, 0.30mmol (75%); white solid; mp 117–118°C.

IR ($CHCl_3$): 1696 (C=O) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.10 (d, *J* = 7.2Hz, 1 H), 7.06 (t, *J* = 7.3Hz, 1 H), 6.97 (d, *J* = 7.2Hz, 1 H), 3.93 (tt, *J* = 10.8, 7.0Hz, 1 H), 2.78 (m, 2 H), 2.60 (ddd, *J* = 16.8, 9.7, 6.9Hz, 1 H), 2.47 (ddd, *J* = 16.9, 9.2, 6.3Hz, 1 H), 2.34 (m, 1 H), 2.29 (s, 3 H), 2.00–1.85 (m, 3 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 172.7, 134.9, 133.6, 132.2, 128.9, 125.7, 125.4, 56.4, 30.5, 30.4, 26.0, 25.5, 19.3.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{13}H_{15}NO$: 202.1232; found: 202.1230.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96.Found: C, 77.51; H, 7.55; N, 6.87.

(±)-7-Methoxy-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinolin-1(2*H*)-one (1d)

Yield: 63mg, 0.29mmol (75%); light tan powder; mp 59–61°C.

IR ($CHCl_3$): 2840 (OCH_3), 1671 (C=O) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.62 (d, *J* = 9.1Hz, 1 H), 6.76 (dd, *J* = 9.1, 2.9Hz, 1 H), 6.66 (d, *J* = 2.9Hz, 1 H), 3.86 (m, 1 H), 3.77 (s, 3 H), 2.95 (ddd, *J* = 17.2, 12.8, 5.8Hz, 1 H), 2.82 (ddd, *J* = 16.8, 5.1, 1.4Hz, 1 H), 2.60 (ddd, *J* = 16.9, 11.1, 9.3Hz, 1 H), 2.47 (ddd, *J* = 16.9, 9.6, 2.2Hz, 1 H), 2.28 (m, 1 H), 2.15 (ddt, *J* = 13.1, 4.8, 2.3Hz, 1 H), 1.82–1.63 (m, 2 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 172.9, 155.5, 130.4, 127.3, 120.3, 114.0, 112.0, 58.0, 55.4, 32.1, 29.6, 28.0, 25.4.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{13}H_{15}NO_2$: 218.1181; found: 218.1178.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45.Found: C, 71.94; H, 6.99; N, 6.41.

(±)-8-(Trifluoromethyl)-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinolin-1(2*H*)-one (1e)

Yield: 63mg, 0.25mmol (74%); white solid; mp 162–163°C.

IR ($CHCl_3$): 1694 (C=O), 1323 (CF_3) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 9.07 (s, 1 H), 7.24 (d, *J* = 8.1Hz, 1 H), 7.22 (d, *J* = 8.1Hz, 1 H), 3.92 (m, 1 H), 2.95 (m, 2 H), 2.64 (ddd, *J* = 17.1, 11.6, 9.1Hz, 1 H), 2.53 (ddd, *J* = 17.1, 9.5, 1.9Hz, 1 H), 2.33 (m, 1 H), 2.23 (m, 1 H), 1.84–1.64 (m, 2 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 173.9, 137.0, 129.5, 129.3, 129.2 (obscured q, *J* = 31.8Hz), 124.1 (q, *J* = 272.2Hz), 119.8 (q, *J* = 3.9Hz), 116.0 (q, *J* = 4.1Hz), 58.0, 32.1, 28.8, 27.8, 25.5.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{13}H_{12}F_3NO$: 256.0949; found: 256.0946.

Anal. Calcd for $C_{13}H_{12}F_3NO$: C, 61.17; H, 4.74: N, 5.49.Found: C, 61.14; H, 4.71; N, 5.45.

(±)-2,3,4,4a,5,6-Hexahydro-1*H*-pyrido[1,2-*a*]quinolin-1-one (2a)

Yield: 53mg, 0.26mmol (65%); off-white powder; mp 47–48°C.

IR ($CHCl_3$): 1659 (C=O) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 8.1, 1.2Hz, 1 H), 7.17 (td, *J* = 8.1, 1.2Hz, 1 H), 7.10 (d, *J* = 8.0Hz, 1 H), 7.03 (td, *J* = 7.4, 1.3Hz, 1 H), 3.67 (m, 1 H), 2.86 (m, 2 H), 2.65 (dt, *J* = 17.4, 7.2Hz, 1 H), 2.48 (ddt, *J* = 17.3, 7.1, 5.9Hz, 1 H), 2.15 (m, 1 H), 2.03 (m, 1 H), 1.98–1.78 (m, 3 H), 1.70 (m, 1 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 170.0, 138.5, 129.7, 128.8, 125.6, 125.1, 124.5, 55.5, 34.1, 31.2, 29.8, 26.5, 18.4.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{13}H_{15}NO$: 202.1232; found: 202.1229.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96.Found: C, 77.55; H, 7.43; N, 6.82.

(±)-8-Methyl-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolin-1-one (2b)

Yield: 56mg, 0.26mmol (68%); white solid; mp 62–63°C.

IR ($CHCl_3$): 1658 (C=O) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.4Hz, 1 H), 6.96 (dd, *J* = 8.4, 1.2Hz, 1 H), 6.91 (d, *J* = 1.2Hz, 1 H), 3.63 (m, 1 H), 2.82 (dd, *J* = 8.6, 5.4Hz, 2 H), 2.63 (dt, *J* = 17.4, 7.2Hz, 1 H), 2.45 (ddd, *J* = 17.4, 7.2, 5.9Hz, 1 H), 2.27 (s, 3 H), 2.14 (m, 1 H), 2.00 (m, 1 H), 1.94–1.76 (m, 3 H), 1.67 (m, 1 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 168.7, 139.2, 134.3, 133.9, 128.3, 126.1, 125.4, 55.5, 33.3, 31.7, 29.0, 26.0, 18.61, 18.59.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{14}H_{17}NO$: 216.1388; found: 216.1390.

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51.Found: C, 77.97; H, 7.93; N, 6.39.

(±)-10-Methyl-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolin-1-one (2c)

Yield: 57mg, 0.27mmol (70%); white solid; mp 103–104°C.

IR ($CHCl_3$): 1656 (C=O) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.07 (m, 2 H), 6.98 (m, 1 H), 3.65 (m, 1 H), 2.80 (dt, *J* = 15.7, 7.8Hz, 1 H), 2.73 (ddd, *J* = 15.7, 7.6, 5.3Hz, 1 H), 2.58 (ddd, *J* = 17.2, 8.9, 6.0Hz, 1 H), 2.49 (ddt, *J* = 17.2, 5.7, 1.1Hz, 1 H), 2.15 (s, 3 H), 2.14 (m, 1 H), 2.09–1.75 (m, 5 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 169.1, 139.6, 134.7, 134.2, 128.6, 126.5, 125.8, 55.9, 33.7, 32.1, 29.4, 26.3, 18.98, 18.97.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{14}H_{17}NO$: 216.1388; found: 216.1387.

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51.Found: C, 78.03; H, 7.95; N, 6.49.

(±)-8-Methoxy-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolin-1-one (2d)

Yield: 58mg, 0.24mmol (69%); off-white solid; mp 99–100°C.

IR ($CHCl_3$): 2840 (OCH_3), 1651 (C=O) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.77 (d, *J* = 9.0Hz, 1 H), 6.73 (dd, *J* = 9.0, 2.7Hz, 1 H), 6.62 (d, *J* = 2.7Hz, 1 H), 3.77 (s, 3 H), 3.63 (m, 1 H), 2.84 (dd, *J* = 8.5, 5.5Hz, 2 H), 2.63 (dt, *J* = 17.4, 6.9Hz, 1 H), 2.45 (dt, *J* = 17.4, 6.4Hz, 1 H), 2.14 (m, 1 H), 1.99 (m, 1 H), 1.91–1.75 (m, 3 H), 1.68 (m, 1 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 169.6, 156.2, 131.8, 131.1, 126.2, 113.3, 111.5, 55.5, 55.4, 34.0, 31.2, 29.8, 26.8, 18.5.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{14}H_{17}NO_2$: 232.1338; found: 232.1335.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06.Found: C, 72.76; H, 7.43; N 5.95.

(±)-9-(Trifluoromethyl)-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolin-1-one (2e)

Yield: 57mg, 0.21mmol (67%); white solid; mp 89–90°C.

IR ($CHCl_3$): 1661 (N–H), 1327 (CF_3) cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 7.25 (dd, *J* = 8.1, 1.1Hz, 1 H), 7.20 (d, *J* = 8.1Hz, 1 H), 3.67 (m, 1 H), 2.90 (dd, *J* = 8.1, 5.6Hz, 2 H), 2.67 (dt, *J* = 17.5, 7.1Hz, 1 H), 2.49 (dt, *J* = 17.5, 6.7Hz, 1 H), 2.17 (m, 1 H), 2.06 (m, 1 H), 1.97–1.79 (m, 3 H), 1.71 (m, 1 H).

^{13}C NMR (101MHz, $CDCl_3$): δ = 170.3, 138.7, 133.4, 129.4, 128.0 (q, *J* = 32.4Hz), 124.1 (q, *J* = 272.2Hz), 122.2 (q, *J* = 4.0Hz), 120.8 (q, *J* = 3.2Hz), 55.5, 34.1, 30.6, 29.7, 26.6, 18.3.

HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{14}H_{14}F_3NO$: 270.1106; found: 270.1099.

Anal. Calcd for $C_{14}H_{14}F_3NO$: C, 62.45; H, 5.24; N, 5.20. Found: C, 62.39; H, 5.21; N, 5.25.

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Supporting Information

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