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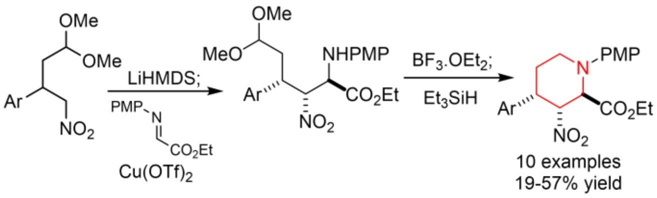

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Asymmetric Synthesis of Piperidines using the nitro-Mannich Reaction[†]

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ABSTRACT

A method for the synthesis of functionalised piperidines containing 3 contiguous stereocentres in the 2-,3- and 4- positions uses a diastereoselective nitro-Mannich to control stereochemistry. The nitro-Mannich reaction between a β-aryl/heteroaryl substituted nitroalkanes and glyoxylate imine provides β-nitro-amines with good selectivity (70:30 to >95:5) for the *syn*, *anti*-diastereoisomers. Reductive cyclisation with $BF_3.OEt_2$ and Et_3SiH gave, after purification, stereochemically pure piperidines in 19-57% yield for ten examples with different 4-aryl/heteroaryl substituents.

[†] Dedicated to the memory of Professor Jonathan M. J. Williams, a friend and kind colleague who had the knack of asking me the simplest questions that I did not know the answers to, but which always made me think.

1. Introduction

Piperidines are present in numerous biologically active natural products and are the most prevalent nitrogen ring system in FDA approved drugs.[1] Paroxetine is a common synthetic antidepressant drug and is the most potent, and one of the most specific, selective serotonin reuptake inhibitors.[2] Around 35% of all medicines have originated from natural products in some way.[3] Vincamine is a monoterpenoid indole alkaloid found in the leaves of Vinca minor and is sold in Europe as a prescription medicine for the treatment of primary degenerative and vascular dementia.[4] Schizozygine was one of a small class of alkaloids first isolated by Renner and co-workers in 1963 from *Schizozygia caffaeoides* (Boj.) Baill.[5] It demonstrated anti-fungal, anti-bacterial[6] and anti-plasmodial activities.[7] Some members of the family could not be assayed due to the scarcity of the compound from natural resources. There is a definite need to develop new methods to synthesis heterocycles that can deliver ever more complex structures.

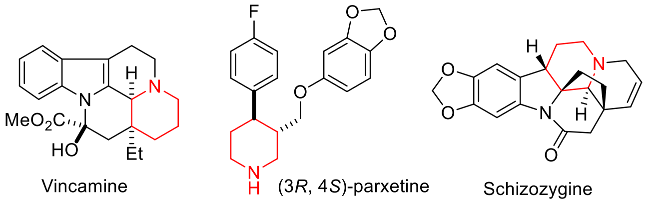

Figure 1. Piperidine ring containing natural products.

2. Results and Discussion

2.1. Development of a route to functionalized piperidines

We recently synthesized some of the Schizozygine alkaloids[8] and in one of our discontinued routes we investigated the synthesis of the core multi-functionalised piperidine **1** through a cyclisation by reductive amination of a highly functionalised β-nitro amino intermediate *syn*,*anti*-**2** (Scheme 1). Other substituted piperidines have been prepared by similar one pot multicomponent enantioselective strategies.[9] Stereodefined β-nitroamines are readily synthesized using the nitro-Mannich reaction[10] and are useful for heterocycle synthesis.[11] We have prepared similar *syn*,*anti*- intermediates **2** through a one pot conjugate addition nitro-Mannich reaction sequence.[12] The diastereoselectivity of the nitro-Mannich reaction is dictated by the chiral centre formed from the conjugate addition of a nucleophile (such as **3**) onto a nitro alkene (such as **4**). Initial attempts to use this one pot conjugate addition nitro-Mannich reaction sequence with the dialkyl zinc reagent **3**,[13] formed *in situ* from the known Grignard reagent, gave no reaction (Scheme 1, disconnection I). An alternative successful disconnection which still allowed the same mechanism for diastereocontrol involved a nitro-Mannich reaction between the known nitro compound **6** and imine **5** (Scheme 1, disconnection II). Enantiopure **6** can be prepared by an organo-catalysed conjugate addition of nitromethane to the corresponding α,β-unsaturated aldehyde **7** using the Hayashi catalyst.[14]

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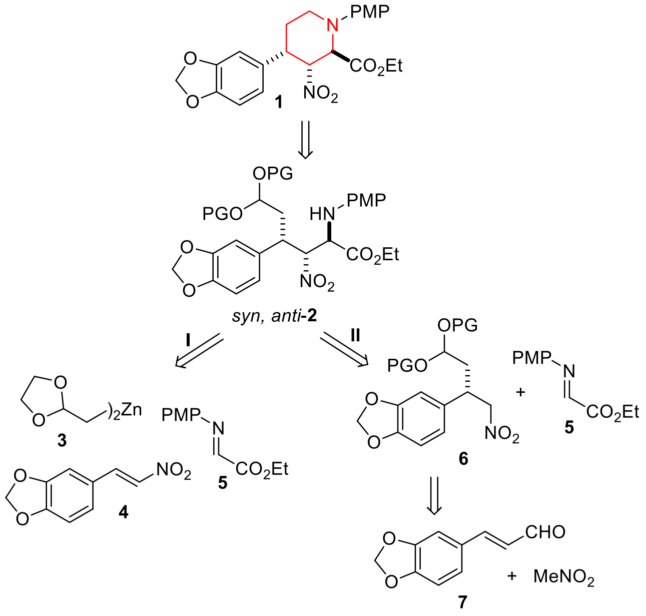
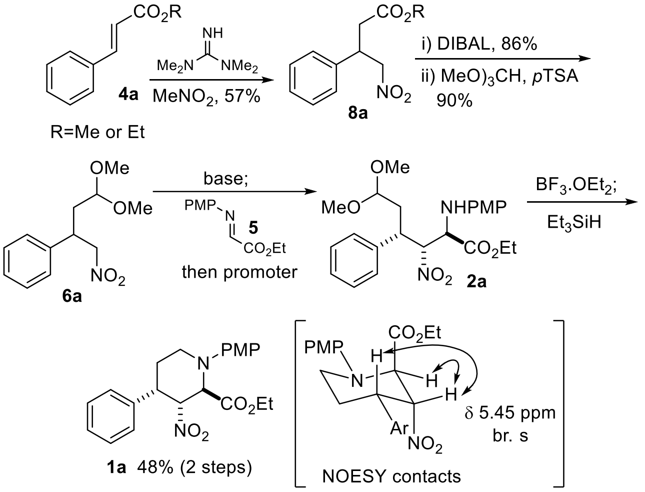


Scheme 1. Disconnection of functionalized piperidine.

2.2. Optimisation of nitro-Mannich/reductive cyclisation sequence

To optimize the key nitro-Mannich reaction and cyclisation, use was made of racemic β-substitued nitro compound **6a** derived from a tetramethylguanidine catalyzed Michael addition to give **8a** (Scheme 2).[15] Reduction of the ester to the aldehyde and then standard protection gave dimethyl acetal **6a** in high overall yield. Reaction with imine **5** under standard nitro-Mannich conditions [^{n}BuLi, then CF_3CO_2H (TFA)][16] gave a high yielding, but poorly diastereoselective reaction (60:40, *syn,anti*-:*syn,syn*-).[17] Our original conjugate addition/nitro-Mannich methodology used a catalytic amount (5 mol%) of $Cu(OTf)_2$ and an excess of $Zn(CF_3CO_2)_2$ was generated during the reaction, the presence of the latter had a profound effect on the diastereoselectivity of the reaction.[11] A screen of bases NaH, LDA and LiHMDS with excess TFA or Lewis acids $Cu(OTf)_2$ or $Zn(CF_3CO_2)_2$ promoters was performed (Table 1) to optimize this particular nitro-Mannich reaction (**6a** to **2a**, Scheme 2).



Scheme 2. Stereoselective synthesis of piperidines using the nitro-Mannich/reductive cyclisation sequence.

Table 1

Optimization of Base and Promoter for nitro-Mannich Reaction of 6a.[a]

Entry	Base	Promoter	Conversion (%)[b]	dr[c]
1	NaH	$Zn(CF_3CO_2)_2$	100	65:35
2	LDA	TFA	100%	70:30
3	LDA	$Zn(CF_3CO_2)_2$	75%	65:35
4	LDA	$Cu(OTf)_2$	65%	>95:5
5	LiHMDS	$Zn(CF_3CO_2)_2$	100%[d]	70:30
6	LiHMDS	$Cu(OTf)_2$	81%	>95:5

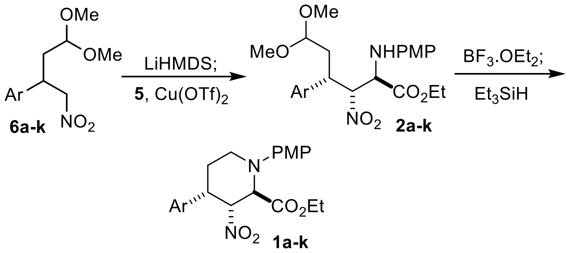
[a] **6a** (0.418 mmol) in THF (5 mL), NaH (1.1 equiv.) 0 °C then 40 °C 30 min. then -78 °C, or LDA or LiHMDS both (1.1 equiv.), -40 °C to 0 °C, 20 min then -78 °C, imine added (1.5 equiv.), 10 min at -78 °C, then TFA (2 equiv.) or $Zn(CF_3CO_2)_2$ (1.5 equiv.) with TFA (1.5 equiv.) or CuOTf (1.5 equiv.) added and then stirred for 1 h at -78 °C before work up.[b]From ^{1}H NMR. [c]From integration of C*H*NO_2 signals. [d]Major **2a** isolated in 67%yield.

All the reactions gave the desired product in good conversion and moderate to high diastereoselectivity in accord with our transition state model (Table 1).[12] Although a Bronsted acid promoter (Entry 2) gave a similar diastereoselectivity to the Lewis acid promoter $Zn(CF_3CO_2)$ (Entry 3), it was found that $Cu(OTf)_2$ was superior (Entry 4). The Lewis acid $Cu(OTf)_2$ was added as a solution in THF, $Zn(CF_3CO_2)_2$ was generated in situ from $ZnEt_2$ and excess TFA. Although the use of the promoter $Cu(OTf)_2$ gave a more diastereoselective reaction (Entries 4 and 6), the combination with $Zn(CF_3CO_2)_2$ gave a higher conversion (Entries 3 and 5). The combination of LiHMDS with the $Cu(OTf)_2$ promoter gave the highest conversion to the desired *syn,anti*-**2a** so these conditions were used to investigate the limitations of this particular reaction sequence.

The *anti*-nitro-Mannich products can be prone to retroadditon and degradation on silica gel chromatography.[12,16] Indeed *syn,anti*-**2a** was not amenable to purification, so the reductive cyclisation step was conducted on the crude material (**2a** to **1a**, Scheme 2). The reductive cyclisation was low yielding (<20%) using Nyori's Et_3SiH, TMSOTf catalyzed reaction conditions.[18] Use of stoichiometric $BF_3.OEt_2$ and Et_3SiH (2 equiv.) gave an improved yield of 25% for **1a**, but with substantial quantities of the reduced, non-cyclised methyl ether product. To avoid the undesired reduction of the oxonium ion intermediate before cyclisation with the amine, we investigated hydrolysis of the dimethyl acetal prior to subsequent reduction of the ring closed iminium ion. After extensive optimization we found that a one pot $BF_3.OEt_2$ mediated cyclisation (CH_2Cl_2, -40 C, 4h), followed by reduction using Et_3SiH (-10 C to rt, 1.5 h) gave an isolated yield of **1a** in 48% yield over 2 steps as the desired single diastereoisomer. Proof that the stereochemistry present in the β-nitroamine **2a** was reproduced in piperidine **1a** was provided by a NOESY experiment and corroborated by the multiplicity of the C*H*NO_2 signal in the ^{1}H NMR. The result was also consistent with our total synthesis studies of Schizozygine alkaloids.[8] The desired *syn, anti*- relative stereochemistry of **1a** would give rise to a favoured conformation dictated by an equatorial aryl group (Scheme 2). Although this conformer places the ester and nitro substituent in axial positions, the hyperconjugation between the lone pair on nitrogen and the anti-bonding orbital of the **C-**CO_2Et bond provides additional stabilization (n-σ* interaction).[19] NOE contacts between C*H*NO_2 its two vicinal protons were observed, but that between ArC*H* and C*H*CO_2Et was not. This conformation would result in two small coupling constants to C*H*NO_2 and in the ^{1}H NMR spectrum these were not resolved, giving rise to a broad singlet instead.

2.3. Scope of the nitro-Mannich/reductive cyclisation sequence

A survey of the nitro-Mannich/reductive cyclisation procedure for the synthesis of a series of 4-aryl piperidines was performed. The required nitroalkanes **6** were uneventfully prepared as in Scheme 1.



Scheme 3. Scope of the stereoselective synthesis of piperidines using the nitro-Mannich/reductive cyclisation sequence.

Table 2

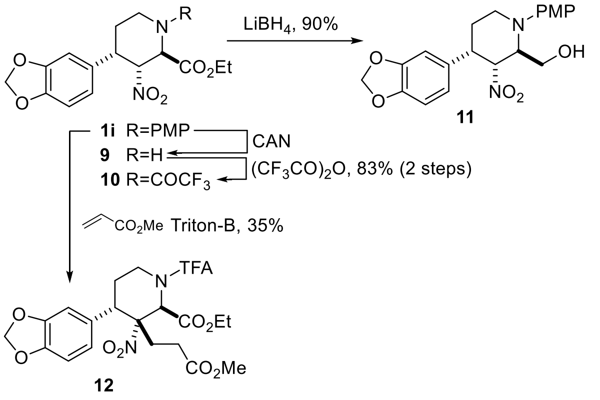
Scope of nitro-Mannich/reductive cyclisation for piperidines.

6	Ar	*dr* **2**[a]	Yield **1** (%)[b]
a	C_6H_5-	>95:5	48
b	*p*-$CH_3C_6H_5$-	90:10	51
c	*p*-$CH_3OC_6H_5$-	90:10	57
d	*p*-BrC_6H_5-	80:20	24
e	*p*-FC_6H_5-	75:25	34
f	*p*-$NO_2C_6H_5$-	70:30	-[c]
g	*o*-$CH_3OC_6H_5$-	95:5	30
h	*o*-BrC_6H_5-	-[d]	19
i	*m,p*-$(OCH_2O)C_6H_5$-	-[d]	41
j	2-furyl	85:15	21
k	2-thiophenyl	90:10	45

[a]From integration of C*H*NO_2 signals. [b]Isolated yield of major diastereosiomer. [c]No product could be isolated. [d]Not possible to determine by ^{1}H NMR.

Moderate yields over two steps for the nitro-Mannich/reductive cyclisation sequence to give functionalized piperidines were given in most cases (Table 2). The relative stereochemistry of the products were tentatively assigned based upon the assignment of the major diastereoisomer of the β-nitroamine coupled with the NMR characteristics of the corresponding piperidine being similar to **1a** (*vide supra*). Neutral or electron rich substituents in the *para*-position of the aryl substituent were well tolerated (**1b**,**c**), but *para*-electron withdrawing substituents gave decreased levels of diastereoselectivity for the β-nitroamines and a correspondingly lower yield of piperidine (**1d**,**e**), with the *p*-NO_2 analogue giving no cyclized product at all. Erosion of diastereoselectivity with increasingly electron withdrawing substituents had been noted before in our previous work on the one pot conjugate addition nitro-Mannich reaction sequence.[5] In a similar trend the *o*-methoxy analogue gave a higher yield of product (**1g**, 30%) compared to the *o*-bromo analogue (**1h**, 19%). The bromo-analogue **1h** could be useful for further annulation to a dihdropyridine by reduction of the nitro group and intramolecular transition metal catalyzed amination.[11c] The disubstituted dioxolane analogue gave a 41% yield of product (**1i**). Heterocyclic substituents were also tolerated (**1j**, **k**).

To demonstrate the potential use of these functionalised piperidines in target synthesis we investigated some transformations of **1i** as its 1,2-dioxolane motif is common in many natural products and drug substances. The PMP group could be easily removed with CAN to give the crude amine **9** which could be alternatively protected as its *N*-trifluoracetate **10** in 83% yield after purification. The small loss of yield is due to some small oxidation of **9** to a dihydroquinone derivative. The ester function of **1i** could be reduced to primary alcohol **11** in good yield with $LiBH_4$ (90%). Further C-C bond functionalization facilitated by the anion stabilizing character of the nitro function was investigated, but was found to be very difficult. Eventually it was found that stirring with Triton-B in the presence of methyl acrylate gave the conjugate addition product **12** in 35% yield. The formation of tertiary nitro compounds are difficult due to the deprotonation event suffering from steric inhibition of resonance and the product itself being very congested.



Scheme 4. Representative transformations of functionalized piperidines.

3. Conclusion

A method for the synthesis of stereochemically defined piperidines was inspired from total synthesis studies of the Schizozygine alkaloids. A homogeneous copper promoted nitro-Mannich reaction between a suitably functionalized nitroalkane **6** and glyoxylate imine **5** gave stereochemically defined β-nitroamines **2** containing 3 contiguous chiral centres. In line with our previous studies[12] the diastereoselectivity was controlled by the aryl stereocentre and the inherent kinetic *anti*- selectivity of the nitro-Mannich reaction to give the *syn, anti*-diastereoisomer **2** as the major compound. Reductive cyclisation of the crude amino acetal gave, after purification, moderate to good yields of the diastereochemically pure pipreridines **1**. Representative transformation of the functionalized piperidines were briefly investigated. The methodology provides a route to a rich source of functionalized piperidines and as the enantioselective synthesis of **6** has been reported,[14] enantiomerically pure building blocks could be prepared.

4. Experimental Section

4.1. General information

All non-aqueous reactions were carried out in oven-dried glassware under an inert atmosphere unless otherwise indicated. All reaction temperatures refer to the values of the external heating element and not that of the reaction mixture. Room temperature implies a temperature range of 20-25 °C. A temperature of 0 °C was achieved using an ice-water bath whereas cryogenic conditions (-78 °C or -40 °C) were achieved using a dry ice and acetone or acetonitrile bath respectively. All additions of reagent occurred as a single portion or fast unless otherwise stated. Column chromatography was carried out using Merk Geduran® silica gel 60 and analytical thin layer chromatography was carried out using Merck Keiselgel aluminium-backed plates coated with silica gel. Components were visualised using ultra-violet light (254 nm) and a basic potassium permanganate dip. Removal of solvent in vacuo was achieved using Büchi rotary evaporators and either the house vacuum or a Büchi Vac® V-500 pump.

All commercial chemicals and solvents were used as supplied unless otherwise stated. The dry solvents THF and CH_2Cl_2 were obtained from a solvent tower, where degassed solvents were passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure. Other anhydrous solvents were purchased bottled from the Aldrich chemical company and used as provided. Activation of 4 Å molecular sieves was achieved by heating under a high vacuum.

Melting points are uncorrected and were obtained using a Reichert Melting Point Apparatus. Infrared (IR) spectra were recorded on a Perkin Elmer spectrum 100 FT-IR (ATR mode). All ^{1}H and ^{13}C NMR data were recorded using Bruker AVANCE III 300 MHz, Bruker AVANCE III 400 MHz, Bruker AVANCE III 600 MHz at 300, 400 and 600 MHz for ^{1}H and 150 MHz for ^{13}C. Samples were made as dilute solutions of $CDCl_3$ and spectra recorded at 298 K. Data were analyzed using ACD/NMR processor academic edition. All chemical shifts (δ) are reported in parts per million (ppm), relative to residual solvent peaks of $CDCl_3$ δ=7.26 for ^{1}H NMR and δ=77.1 for ^{13}C NMR. Multiplicities for ^{1}H coupled signals are designated as s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, m=multiplet. Coupling constants (*J*) are reported in Hertz (Hz). Mass spectroscopy data were collected on Thermo Finnigan Mat900xp (EI/CI) and Waters LCT Premier XE (ES) instruments. Mass spectrometry data was collected on Thermo Finnigan Mat900xp (EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments.

4.2. Synthesis of *α,β*-unsaturated esters (*4*)

The known conjugate esters **4a**,[20] **b**,[20] **c**,[20] **d**,[20] **e**,[20] **f**,[20] **g**,[21] **h**,[21] **i**,[22] **j**,[20] **k**,[20] were obtained by reaction of the commercially available aldehydes with triethyl- or trimethylphosphonoacetate according to the representative procedure below and characterisation data (^{1}H and ^{13}C NMR) were in agreement with the literature.

4.2.1. Ethyl cinnamate (4a)

To a stirred solution of triethylphosphonoacetate (9.40 mL, 47.1 mmol) in THF (200 mL) was added potassium *tert*-butoxide (5.28 g, 47.1 mmol) portionwise at 0 °C. The cooling bath was removed, and the resulting mixture was stirred for 1 h. A solution of benzaldehyde (5.00 g, 47.1 mmol) in THF (50 mL) was added through an addition funnel dropwise and the stirring was continued for 2 h. The reaction mixture was concentrated then satd. Aq. NH_4Cl (100 mL) was added and the reaction mixture extracted with CH_2Cl_2 (2 x 80 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated. The resulting yellow oil was purified by flash column chromatography (20% EtOAc/Hexane) to give **4a** (7.64 g, 92%) as a colourless oil. Rf 0.65 (25% EtOAc/Hexane); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.69 (1H, d, *J* = 16.1), 7.53 (2H, dd, *J* = 7.0, 2.8), 7.43 - 7.36 (3H, m), 6.44 (1H, d, *J* = 16.1), 4.27 (2H, q, *J* = 7.3), 1.34 (3H, t, *J* = 7.2). This data was consistent with literature.[20]

4.3. Nitroalkane esters (*8*)

4.3.1. Ethyl 4-nitro-3-phenylbutanoate (8a)

To a stirred solution of **4a** (5.00 g, 28.3 mmol) in nitromethane (26 mL) was added tetramethylguanidine (0.88 mL, 7.1 mmol). The resulting mixture was heated to 70 °C and the stirring was continued for 21 h. The reaction mixture was cooled to room temperature, quenched with aqueous HCl solution (1.0 M, 75 mL) and then extracted with EtOAc (2 x 60 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (20% EtOAc/Hexane) to give the desired product **8a** (3.76 g, 56%) as a yellow oil. Rf (20% EtOAc in hexane) 0.24; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.37 - 7.31 (2 H, m), 7.31 - 7.27 (1 H, m), 7.25 - 7.21 (2 H, m), 4.73 (1 H, dd, *J* = 12.5, 7.0), 4.64 (1 H, dd, *J* = 12.5, 7.8), 4.11 - 4.05 (2 H, q, *J* = 7.0), 3.99 (1 H, quin, *J* = 7.5), 2.76 (2 H, dd, *J* = 7.4, 1.6), 1.17 (3 H, t, *J* = 7.2). Data consistent with literature.[23]

4.3.2. Ethyl 4-nitro-3-(p-tolyl)butanoate (8b)

The α,β-unsaturated ester **4b** (1.24 g, 4.86 mmol) was converted to the crude product **8b** as described for the synthesis of compound **8a**. The residue was purified by flash column chromatography (14% EtOAc/Hexane) to give the desired product **8b** (1.09 g, 54%) as a yellow oil. Rf (14% EtOAc/Hexane): 0.18; ^{1}H NMR (600MHz, $CDCl_3$) δ 7.18 – 7.05 (4 H, m), 4.79 (2 H, m), 4.08 (2 H, qd, *J* = 7.1, 1.5), 3.94 (1 H, quin, *J* = 7.4), 2.74 (2 H, dd, *J* = 7.4, 1.9), 2.32 (3H, s), 1.18 (3 H, t, *J* = 7.0); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.8 (C=O), 137.9 (*C*), 135.4 (*C*), 129.8 (*C*H), 127.3 (*C*H), 79.7 (CH_2), 61.0 (CH_2), 40.0 (*C*H), 38 (CH_2), 21.2 (CH_3), 14.2 (CH_3); FTIR (neat, film) 2984, 1730, 1551, 1376; HRMS (ESI) $[C_{13}H_{17}NO_4+Na]^+$ calcd 274.1050, found 274.1050.

4.3.3. Ethyl 3-(4-methoxyphenyl)-4-nitrobutanoate (8c)

To a stirred solution of **4c** (1.40 g, 6.79 mmol) in nitromethane (15 mL), was added tetramethylguanidine (0.21 mL, 1.7 mmol). The resulting mixture was heated to 70 °C and the stirring was continued overnight. The temperature was then raised to 90 °C and the mixture stirred for another 2 days. Workup and purification were as for **8b** to give the desired product **8c** (695 mg, 38%, 96% brsm) as a yellow oil. Rf (40% EtOAc/Hexane): 0.51; ^{1}H NMR (600MHz, $CDCl_3$) δ 7.16 – 7.12 (2 H, d, *J* = 8.7), 6.88 – 6.84 (2 H, d, *J* = 8.7), 4.70 (1 H, dd, *J* = 12.4, 8.1), 4.59 (1 H, dd, *J* = 12.4, 8.1), 4.08 (2 H, dq, *J* = 7.1, 3.1), 3.93 (2 H, quin, *J* = 7.5), 3.78 (3 H, s), 2.77-2.69 (2 H, m), 1.18 (3 H, t, *J* = 7.2). Data are consistent with literature.[24]

4.3.4. Ethyl 3-(4-bromophenyl)-4-nitrobutanoate (8d)

The α,β-unsaturated ester **4d** (1.24 g, 4.86 mmol) was converted to the crude product **8d** as described for the synthesis of compound **8a**. The residue was purified by flash column chromatography (14% EtOAc/Hexane) to give the desired product **8d** (1.08 g, 70%) as a yellow oil. Rf (11% EtOAc/Hexane): 0.1; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.52 – 7.39 (2 H, m), 7.13 - 7.04 (2 H, m), 4.72 (1 H, dd, *J* = 12.7, 7.5), 4.60 (1 H, dd, *J* = 12.7, 7.5), 4.09 (2 H, qd, *J* = 7.1, 1.3), 4.00 – 3.92 (1 H, m), 2.78-2.67 (2 H, m), 1.19 (3 H, t, *J* = 7.1). Data consistent with literature.[24]

4.3.5. Ethyl 3-(4-fluorophenyl)-4-nitrobutanoate (8e)

The α,β-unsaturated ester **4e** (1.50 g, 8.30 mmol) was converted to the crude product **8e** as described for the synthesis of compound **8a**. The residue was purified by flash column chromatography (30% EtOAc/Hexane) to give the desired product **8** (1.63 g, 81%) as a yellow oil. Rf (30% EtOAc in hexane): 0.53; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.23—7.17 (2H, m), 7.08—6.97 (2H, m), 4.72 (1H, dd, *J* = 12.6, 6.8), 4.61 (1H, dd, *J* = 12.7 8.1), 3.98 (1H, p, *J* = 7.4), 3.64 (3H, s), 2.77 (1H, dd, *J* = 16.3, 7.2), 2.73 (1H, dd, *J* = 16.3, 7.6); ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.04 (*C*), 162.48 (d, *J* = 247.1 Hz, *C*-F), 134.12 (d, *J* = 3.4 Hz, *C*), 129.13 (d, *J* = 8.2 Hz, *C*H), 116.22 (d, *J* = 21.6 Hz, *C*H), 79.49 (CH_2), 52.16 (CH_3), 39.61 (*C*H), 37.69 (CH_2). Data consistent with literature.[25]

4.3.6. Ethyl 4-nitro-3-(4-nitrophenyl)butanoate (8f)

The α,β-unsaturated ester **4f** (1.55 g, 7.01 mmol) was converted to the crude product **8f** as described for the synthesis of compound **8a** using 0.5 eq of tetramethylguanidine. The residue was purified by flash column chromatography (20% EtOAc/Hexane) to give the desired product **8f** (777 mg, 39%) as a yellow oil. Rf 0.12 (20% EtOAc/Hexane); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.22 (2 H, d, *J* = 8.8), 7.44 (2 H, d, *J* = 8.5), 4.79 (1 H, dd, *J* = 12.9, 6.4), 4.69 (1 H, dd, *J* = 12.9, 8.4), 4.13 - 4.07 (3 H, m), 2.79 (2 H, dd, *J* = 7.4, 6.1), 1.19 (3 H, t, *J* = 7.2). Data are consistent with literature.[26]

*4.3.7. Ethyl 3-(2-methoxyphenyl)-4-nitrobutanoate (**8g**)*

The α,β-unsaturated ester **4g** (5.00 g, 24,2 mmol) was converted to the crude product **8g** as described for the synthesis of compound **8a**. The residue was purified by flash column chromatography (17% EtOAc/Hexane) to give the desired product **8g** (4.12 g, 64%) as a yellow oil. Rf 0.32 (20% EtOAc/Hexane); ^{1}H NMR (600MHz, $CDCl_3$) δ 7.28 - 7.24 (1 H, m), 7.16 (1 H, d, *J* = 7.2), 6.93 – 6.87 (2 H, m), 4.82 – 4.75 (2 H, m), 4.18 (1 H, quin, *J* = 7.5), 4.11 - 4.05 (2 H, m), 3.86 (3 H, s) 2.90-2.82 (2 H, m), 1.18 (3 H, t, *J* = 7.1); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4 (C=O), 157.3 (*C*), 129.5 (*C*H), 129.3 (*C*H), 126.1 (*C*H), 120.1 (*C*H), 111.1 (*C*), 78.0 (*C*H_2), 60.9 (*C*H_2), 55.5 (*C*H_3), 37.0 (*C*H), 36.0 (*C*H_2), 14.2 (*C*H_3); FTIR (neat, film) 2981, 1730, 1550, 1376, 1245 cm^{-1}; HRMS (ESI) $[C_{13}H_{17}NO_5+NH_4]^+$ calcd 285.14445, found 285.14445.

*4.3.8. Ethyl 3-(2-bromophenyl)-4-nitrobutanoate (**8h**)*

The α,β-unsaturated ester **4h** (1.96 g, 7.70 mmol) was converted to the crude product **8h** as described for the synthesis of compound **8a**. The residue was purified by flash column chromatography (17% EtOAc/Hexane) to give the desired product **8h** (1.66 g, 68%) as a yellow oil. Rf 0.30 (20% EtOAc/Hexane); ^{1}H NMR (600MHz, $CDCl_3$) δ 7.60 (1 H, dd, *J* = 8.1, 1.1), 7.32 - 7.28 (1 H, m), 7.22 (1 H, d, *J* = 7.8, 1.6), 7.15 (1 H, dt, *J* = 7.7, 1.6), 4.80 – 4.73 (2 H, m), 4.48 (1 H, quin, *J* = 7.1), 4.09 (2 H, dq, *J* = 7.2, 1.3), 2.90-2.82 (2 H, m), 1.18 (3 H, t, *J* = 7.1); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6 (*C*=O), 137.3 (*C*), 133.9 (*C*H), 129.5 (*C*), 128.1 (*C*H), 128.0 (*C*H), 124.7 (*C*H), 77.8 (*C*H_2), 61.1 (*C*H_2), 39.0 (*C*H), 36.4 (*C*H_2), 14.2 (*C*H_3); FTIR (neat, film) 2979, 1726, 1548, 1375; HRMS (ESI) $[C_{12}H_{14}NO_4Br+H]^+$ calcd 316.0179, found 316.0173.

*4.3.9. Methyl 3-(benzo[1,3]dioxol-5-yl)-4-nitrobutanoate (**8i**)*

The α,β-unsaturated ester **4i** (343 mg, 1.66 mmol) was converted to the crude product **8i** as described for the synthesis of compound **8a**. The residue was purified by flash column chromatography (30% EtOAc/Hexane) to give the desired product **8i** (408 mg, 92%) as a yellow oil. Rf (30% EtOAc in hexane): 0.63; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76—6.67 (3H, m), 5.95 (2H, s), 3.91 (1H, m), 3.65 (3H, s), 2.76—2.67 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1 (*C*), 148.2 (*C*), 147.4 (*C*), 131.9 (*C*), 120.8 (*C*H), 108.8 (*C*H), 107.6 (*C*H), 101.4 (*C*H_2), 79.7 (*C*H_2), 52.1 (*C*H_3), 40.1 (*C*H), 37.8 (*C*H_2); FTIR (neat, cm^{-1}) 2950, 1728, 1547, 1501, 1486, 1241, 1169, 1035; HRMS (EI) calcd. for $C_{12}H_{13}NO_6$ $[M]^{\cdot+}$ 267.0737, found 267.0738.

*4.3.10. Ethyl 3-(furan-2-yl)-4-nitrobutanoate (**8j**)*

The α,β-unsaturated ester **4j** (1.11 g, 6.71 mmol) was converted to the crude product **8j** as described for the synthesis of compound **8a**. The residue was purified by flash column chromatography (14% EtOAc/Hexane) to give the desired product **8j** (1.08 g, 71%) as a yellow oil. Rf 0.44 (17% EtOAc/Hexane); ^{1}H NMR (600MHz, $CDCl_3$) δ 7.35 (1 H, dd, *J* = 1.8, 0.8), 6.30 (1 H, dd, *J* = 3.3, 1.9), 6.17 (1 H, d, *J* = 3.3), 4.72 (2 H, d, *J* = 6.9), 4.14 (1 H, q, *J* = 7.1), 4.08 (2 H, q, *J* = 7.0), 2.78 (2 H, qd, *J* = 16.4, 7.1), 1.23 (3 H, t, *J* = 7.1); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.57 (C=O), 151.4 (*C*), 142.6 (*C*H), 110.6 (*C*H), 107.3 (*C*H), 77.2 (*C*H_2) 61.2 (*C*H_2), 35.5 (*C*H), 34.2 (*C*H_2), 14.2 (*C*H_3); FTIR (neat, film) 2984, 1729, 1553, 1375 cm^{-1}; HRMS (EI) $[C_{10}H_{13}NO_5+NH_4]$ calcd 245.1132, found 245.1131.

*4.3.11. Ethyl 4-nitro-3-(thiophen-2-yl)butanoate (**8k**)*

The α,β-unsaturated ester **4k** (1.09 g, 5.98 mmol) was converted to the crude product **8k** as described for the synthesis of compound **8a**. The residue was purified by flash column chromatography (11% EtOAc/Hexane) to give the desired product **8k** (972 mg, 67%) as a yellow oil. Rf 0.22 (11% EtOAc/Hexane); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.22 (1 H, dd, *J* = 4.9, 1.4), 6.96 – 6.91 (2 H, m), 4.77 (1 H, dd, *J* = 12.7, 7.1) 4.67 (1 H, dd, *J* = 12.7, 7.1), 4.31 (1 H, q, *J* = 7.2), 4.13 (2 H, q, *J* = 7.1), 2.81 (2 H, d, *J* = 7.2), 1.22 (3 H, t, *J* = 7.1). Data consistent with literature.[24]

*4.4. Nitroalkane acetals (**6**).*

*4.4.1. (4,4-dimethoxy-1-nitrobutan-2-yl)benzene (**6a**)*

To a cooled (-78 °C) and stirred solution of **4a** (2.00 g, 8.43 mmol) in CH_2Cl_2 (50 mL), was added DIBAL-H (1.0 M in hexane, 16.9 mL) dropwise. The resulting mixture was stirred at -78 °C for 1 h. The mixture was quenched with MeOH (20 mL) and slowly warmed up to 0 °C. Aqueous HCl (2.0 M, 30 mL) was added and the resulting mixture stirred for 10 min. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (25% EtOAc/Hexane) gave 4-nitro-3-phenylbutanal (1.38 g, 86%) as a yellow oil. Rf (25% EtOAc/Hexane): 0.13; ^{1}H NMR (400MHz, $CDCl_3$) δ 9.71 (1 H, s), 7.38 - 7.32 (2 H, m), 7.32 - 7.28 (1 H, m), 7.25 - 7.20 (2 H, m), 4.65 (2 H, dq, *J* = 12.7, 7.4), 4.11 - 4.04 (1 H, m), 3.02 - 2.89 (2 H, m, 2 H). Data consistent with literature.[27]

To a stirred solution of the aldehyde (1.00 g, 5.18 mmol) in MeOH (15 mL), $TsOH\cdot H_2O$ (493 mg, 2.59 mmol) and $HC(OMe)_3$ (1.13 mL, 10.4 mmol) were added and the resulting mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature and concentrated. The residue was then dissolved in CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ aqueous solution (20 mL). The organic layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried ($MgSO_4$) then concentrated. The residue was purified by flash column chromatography (20% EtOAc/Hexane) to afford the desired product **6a** (1.12 g, 90%) as a colourless oil. Rf (25% EtOAc/Hexane): 0.39; ^{1}H NMR (600MHz, $CDCl_3$) δ 7.36 - 7.32 (2 H, m), 7.30 - 7.27 (1 H, m), 7.23 - 7.20 (2 H, m), 4.66 (1 H, dd, *J* = 12.6, 7.2), 4.56 (1 H, dd, *J* = 12.5, 8.4), 4.14 (1 H, dd, *J* = 7.8, 3.7), 3.68 - 3.62 (1 H, m), 3.29 (3 H, s), 3.24 (3 H, s), 2.06 - 2.01 (1 H, m), 1.95 - 1.90 (1 H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 129.2 (*C*), 127.9 *C*H), 127.6 (*C*H), 102.2 (*C*H), 80.9 (*C*H_2), 53.2 (*C*H_3), 53.1 (*C*H_3), 40.4 (*C*H), 36.2 (*C*H_2); FTIR (neat, film) 2938, 1551, 1379, 1127 cm^{-1}; HRMS (EI) $[C_{12}H_{16}NO_4+Na]^+$ calcd 262.1055, found 262.1051.

*4.4.2. 1-(4,4-dimethoxy-1-nitrobutan-2-yl)-4-methylbenzene (**6b**)*

To a cooled (-78 °C) and stirred solution of **4b** (820 mg, 3.26 mmol) in CH_2Cl_2 (20 mL), was added dropwise DIBAL-H (1.0 M in hexane, 6.52 mL). The resulting mixture was stirred at -78 °C for 4 h. Additional DIBAL-H (1.0 M in hexane, 2.7 mL) was added and the mixture stirred at -78 °C for 2 h. No further conversion was observed and the mixture was quenched and worked up as for the aldehyde for **6a**. Purification of the residue by flash column chromatography (20% EtOAc/Hexane) gave 4-nitro-3-(p-tolyl)butanal (320 mg, 47%) as a pale yellow oil and some recovered starting material (274 mg, 33%) as a yellow oil; Rf (25% EtOAc/Hexane): 0.19; ^{1}H NMR (600MHz, $CDCl_3$) δ 9.70 (1 H, s), 7.15 (2 H, d, *J* = 8.1), 7.12 (2 H, d, *J* = 8.1), 4.67 – 4.57 (2 H, m), 4.04 (1 H, quin, *J* = 7.3), 2.96 – 2.88 (2 H, m), 2.32 (3 H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.0 (*C*HO), 138.1 (*C*), 135.1 (*C*), 130.0 (*C*H), 127.4 (*C*H), 79.7 (*C*H_2), 46.6 (*C*H_2), 37.8 (*C*H), 21.2 (*C*H_3); FTIR (neat, film) 2921, 1722, 1548, 1379; HRMS (ESI) $[C_{11}H_{13}NO_3+Na]^+$ calcd 230.0788, found 230.0788.

The aldehyde (308 mg, 1.49 mmol) was converted to the crude product **6b** in 2 h, as described for the synthesis of compound **6a**. The residue was purified by flash column chromatography (20% EtOAc/Hexane) to afford the desired product **6b** (262 mg, 70%) as a colourless oil. Rf 0.30 (25% EtOAc/Hexane); ^{1}H NMR (600MHz, $CDCl_3$) δ 7.15 (2 H, d, *J* = 8.1), 7.10 (2 H, d, *J* = 7.9), 4.63 (1 H, dd, *J* = 12.4, 7.2,), 4,53 (1 H, dd, *J* = 12.4, 8.3), 4.15 (1 H, dd, *J* = 7.7, 3.6), 3.63 - 3.58 (1 H, m), 3.29 (3 H, s), 3.24 (3 H, s), 2.33 (3 H, s), 2.05 – 1.99 (1 H, m), 1.93 - 1.88 (1 H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.6 (C), 136.0 (C), 129.8 (CH), 127.4 (CH), 102.3 (CH), 80.6 (CH_2), 53.2 (CH_3), 53.0 (CH_3), 40.1 (CH), 36.2 (CH_2), 21.2 (CH_3); FTIR (neat, film) 2950, 1550, 1377, 1126 cm^{-1}; HRMS (ESI) $[C_{13}H_{19}NO_4+Na]^+$ calcd 276.1206, found 276.1206.

*4.4.3. 1-(4,4-dimethoxy-1-nitrobutan-2-yl)-4-methoxybenzene (**6c**)*

The ester **4c** (685 mg, 2.56 mmol) was converted to the crude aldehyde in 3 h, as described for the synthesis of **6a**. Purification of the residue by flash column chromatography (20% EtOAc/Hexane) gave 3-(4-methoxyphenyl)-4-nitrobutanal (414 mg, 72%) as a pale-yellow oil. Rf 0.23 (25% EtOAc/Hexane); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.70 (1 H, s), 7.15 (2 H, d, *J* = 8.8), 6.86 (2 H, d, *J* = 8.8), 4.60 (2 H, m), 4.03 (1 H, quin, *J* = 7.2), 3.79 (3 H, s), 2.92 (2 H, d, *J* = 6.5). Data consistent with literature.[26]

The aldehyde (404 mg, 1.81 mmol) was converted to the crude product **6c** in 1.5 h, as described for the synthesis of compound **6a**. The residue was purified by flash column chromatography (20% EtOAc/Hexane) to afford the desired product **6c** (236 mg, 48%) as a yellow oil. Rf (20% EtOAc/Hexane): 0.15; ^{1}H NMR (600MHz, $CDCl_3$) δ 7.15 - 7.11 (2 H, m), 6.89 - 6.85 (2 H, m), 4.62 (1 H, dd, *J* = 12.3, 7.1), 4.52 (1 H, dd, *J* = 12.4, 8.5), 4.14 (1 H, dd, *J* = 7.9, 3.6), 3.79 (3 H, s), 3.63 - 3.57 (1 H, m), 3.29 (3 H, s), 3.24 (3 H, s), 2.01 (1 H, ddd, *J* = 13.8, 8.0, 5.6), 1.89 (1 H, ddd, *J* = 13.7, 9.6, 3.6); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.2 (C), 131.5 (C), 128.6 (CH), 114.5 (CH), 102.3 (CH), 80.7 (CH_2), 55.4 (CH_3), 53.2 (CH_3), 53.1 (CH_3), 39.7 (CH), 36.3 (CH_2); FTIR (neat, film) 2957, 1549, 1378, 1250, 1124 cm^{-1}; HRMS (ESI) $[C_{13}H_{19}NO_5+Na]^+$ calcd 292.1155, found 292.1156.

*4.4.4. 1-bromo-4-(4,4-dimethoxy-1-nitrobutan-2-yl)benzene (**6d**)*

The ester **4d** (1.04 g, 3.30 mmol) was converted to the product 3-(4-bromophenyl)-4-nitrobutanal (884 mg, 98%) in 5h as described for the synthesis of compound **6a**. The product was obtained without purification as a yellow oil. Rf 0.26 (20% EtOAc/Hexane); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.71 (1 H, s), 7.51 – 7.44 (2 H, m), 7.15 – 7.09 (2 H, m), 4.67 (1H, dd, *J* = 12.6, 7.4), 4.63 (1 H, dd, *J* = 12.6, 7.4), 4.05 (1 H, q, *J* = 7.1), 2.94 (2 H, d, *J* = 7.1). Data consistent with literature.[23]

The aldehyde (868 mg, 3.19 mmol) was converted to the crude product **6d** in 2 h, as described for the synthesis of compound **6a**. The residue was purified by flash column chromatography (12% EtOAc/Hexane) to afford the desired product **6d** (628 mg, 62%) as a colourless oil. Rf 0.62 (17% EtOAc/Hexane); ^{1}H NMR (600MHz, $CDCl_3$) δ 7.49 – 7.45 (2 H, m), 7.11 – 7.08 (2 H, m), 4.60 (1 H, dd, *J* = 12.7, 7.7), 4.52 (1 H, dd, *J* = 12.7, 7.7), 4,13 (1 H, dd, *J* = 7.6, 3.7), 3.63 (1 H, tt, *J* = 8.9, 6.3), 3.29 (3 H, s), 3.25 (3 H, s), 2.02 (1 H, ddd, *J* = 13.6, 7.6, 5.9), 1.88 (1 H, ddd, *J* = 14.0, 9.1, 3.7); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.3 (C), 132.4 (C), 129.3 (CH), 121.9 (CH), 102.2 (CH), 80.1 (CH_2), 53.3 (CH_3), 39.9 (CH), 36.15 (CH_2); FTIR (neat, film) 2937, 1552, 1378, 1127 cm^{-1}; HRMS (ESI) $[C_{14}H_{13}N_3O_2+Na]^+$ calcd 340.0155, found 340.0159.

*4.4.5. 1-(4,4-dimethoxy-1-nitrobutan-2-yl)-4-fluorobenzene (**6e**)*

The ester **4e** (1.11 g, 4.60 mmol) was converted to the desired product 3-(2-fluorophenyl)-4-nitrobutanal (1.36 g, 81%) as a dark pink oil, as described for the synthesis of compound **6a**. Rf 0.1 (25% EtOAc/Hexane); ^{1}H NMR (300MHz, $CDCl_3$) δ 9.71 (1 H, s), 7.21 (2 H, dd, *J* = 8.6, 5.2), 7.04 (2 H, t, *J* = 8.7), 4.71 – 4.54 (2 H, m), 4.08 (1 H, quin, *J* = 7.3), 2.94 (2 H, d, *J*= 7.2). Data consistent with literature.[28]

The aldehyde (788 mg, 3.73 mmol) was converted to the crude product **6e,** as described for the synthesis of compound **6a**. The residue was purified by flash column chromatography (33% EtOAc/Hexane) to afford the desired product **6e** (644 mg, 67%) as an orange oil. Rf 0.30 (33% EtOAc/Hexane); ^{1}H NMR (600MHz, $CDCl_3$) δ 7.20 - 7.17 (2 H, m), 7.05 - 7.02 (2 H, m), 4.63 (1 H, m), 4.52 (1 H, dd, *J* = 12.5, 8.8), 4.14 (1 H, d, *J* = 3.8), 3.67 - 3.62 (1 H, m), 3.29 (3 H, s), 3.25 (3 H, s), 2.03 (1 H, ddd, *J* = 13.9, 7.8, 5.8), 1.91 - 1.86 (1 H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.31 (d, *J* = 246.6 Hz), 134.90 (d, *J* = 3.3 Hz), 129.17 (d, *J* = 8.2 Hz), 116.13 (d, *J* = 21.5 Hz), 102.19 (CH), 80.43 (CH_2), 53.3 (CH_3), 53.2 (CH_3), 39.7 (CH), 36.3 (CH_2); FTIR (neat, film) 2930, 1551, 1510, 1377, 1225, 1126 cm^{-1}; HRMS (EI) $[C_{12}H_{15}FNO_4+Na]$ calcd 280.0961, found 280.0970.

*4.4.6. 1-(4,4-dimethoxy-1-nitrobutan-2-yl)-4-nitrobenzene (**6f**)*

The ester **4f** (770 mg, 2.70 mmol) was converted to the crude aldehyde**,** as described for the synthesis of compound **6a**. Purification of the residue by flash column chromatography (30% EtOAc/Hexane) gave 4-nitro-3-(4-nitrophenyl)butanal (256 mg, 40%) as an orange oil and some recovered starting material **4f** (183 mg, 24%) as a yellow oil. Rf 0.19 (25% EtOAc/Hexane); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.74 (1 H, s), 8.22 (2 H, d, *J* = 8.8), 7.45 (2 H, d, *J* = 8.8), 4.79 – 4.63 (2 H, m), 4.25 – 4.17 (1 H, m), 3.03 (2 H, d, *J* = 7.0). Data consistent with literature.[28]

The aldehyde (243 mg, 1.02 mmol) was converted to the crude product **6f** in 2 h, as described for the synthesis of compound **6a**. The residue was purified by flash column chromatography (40% EtOAc/Hexane) to afford the desired product **6f** (179 mg, 63%) as a colourless oil. Rf 0.29 (50% EtOAc/Hexane); ^{1}H NMR (600MHz, $CDCl_3$) δ 8.22 (2 H, d, *J* = 8.8), 7.42 (2 H, d, *J* = 8.7), 4.76 (1 H, dd, *J* = 13.0, 6.2), 4,61 (1 H, dd, *J* = 13.0, 9.2), 4.17 (1 H, dd, *J* = 7.2, 4.0), 3.89 - 3.75 (1 H, m), 3.31 (3 H, s), 3.27 (3 H, s), 2.08 (1 H, td, *J* = 14.0, 6.7), 1.95 (1 H, ddd, *J* = 14.1, 8.6, 3.9); ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.6 (C), 147.0 (C), 128.6 (CH), 124.4 (CH), 102.1 (CH), 79.6 (CH_2), 53.5 (CH_3 x 2), 40.1 (CH), 36.1 (CH_2); FTIR (neat, film) 2937, 1551, 1519, 1346, 1377, 1126 cm^{-1}; HRMS (ESI) $[C_{12}H_{16}N_2O_6+Na]^+$ calcd 307.0901, found 307.0901.

*4.4.7. 1-(4,4-dimethoxy-1-nitrobutan-2-yl)-2-methoxybenzene (**6g**)*

The ester **4g** (2.00 g, 7.48 mmol) was converted to the crude aldehyde as described for the synthesis of compound **6a**. Purification of the residue by flash column chromatography (25% EtOAc/Hexane) gave 3-(2-methoxyphenyl)-4-nitrobutanal (1.36 g, 81%) as a colourless oil. Rf 0.30 (25% EtOAc/Hexane); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.70 (1 H, s), 7.30 - 7.26 (1 H, m), 7.15 (1 H, dd, *J* = 7.7, 1.6), 6.95 – 6.88 (2 H, m), 4.78 – 4.68 (2 H, m), 4.29 (1 H, quin, *J* = 7.1), 3.87 (3 H, s), 3.07 - 2.94 (2 H, m). Data are consistent with literature.[28]

The aldehyde (1.00 g, 4.48 mmol) was converted to the crude product **6g** in 1.5 h, as described for the synthesis of compound **6a**. The residue was purified by flash column chromatography (20% EtOAc/Hexane) to afford the desired product **6g** (424 mg, 35%) as a yellow oil and some recovered starting aldehyde (197 mg, 20%) as a colourless oil. Rf 0.40 (25% EtOAc/Hexane); ^{1}H NMR (600MHz,CDCl$_3$) δ 7.24 (1 H, d, *J* = 1.5), 7.13 (1 H, dd, *J* = 7.5, 1.3), 6.93 – 6.87 (2 H, m), 4.79 – 4.71 (2 H, m), 4.18 (1 H, dd, *J* = 7.7, 3.8), 3.85 (4 H, m), 3.28 (3 H, s), 3.24 (3 H, s), 2.13 - 2.01 (2 H, m); ^{13}C NMR (151 MHz, CDCl$_3$) δ 157.5 (*C*), 129.8 (*C*H), 129.0 (*C*H), 126.8 (*C*), 121.0 (*C*H), 111.2 (*C*H), 102.7 (*C*H), 78.9 (*C*H$_2$), 55.4 (*C*H$_3$), 52.7 (*C*H$_3$), 37.2 (*C*H), 34.2 (*C*H$_2$); FTIR (neat, film) 2925, 1549, 1378, 1244, 1124 cm^{-1}; HRMS (ESI) $[C_{13}H_{18}NO_5+Na]^+$ calcd 292.1161, found 292.1164.

*4.4.8. 1-bromo-2-(4,4-dimethoxy-1-nitrobutan-2-yl)benzene (**6h**)*

The ester **4h** (1.63 g, 5.15 mmol) was converted to the crude aldehyde in 2.5 h, as described for the synthesis of compound **6a**. Purification of the residue by flash column chromatography (25% EtOAc/Hexane) 3-(2-bromophenyl)-4-nitrobutanal (912 mg, 65%) as a colourless oil. Rf 0.25 (40% EtOAc/Hexane); ^{1}H NMR (600MHz,CDCl$_3$) δ 9.73 (1 H, s), 7.62 (1 H, dd, *J* =1.1, 8.1), 7.35 – 7.27 (1 H, m), 7.22 – 7.13 (2 H, m), 4.81 – 4.65 (2 H, m), 4.56 (1 H, quin, *J* = 6.9), 3.11 - 2.93 (2 H, m); ^{13}C NMR (151 MHz, CDCl$_3$) δ 198.6 (*C*HO), 137.1 (*C*), 134.0 (*C*H), 129.7 (*C*H), 128.3 (*C*H), 124.5 (*C*), 77.6 (*C*H$_2$), 45.4 (*C*H$_2$), 37.0 (*C*H); FTIR (neat, film) 2920, 1722, 1549, 1378; HRMS (ESI) $[C_{10}H_{10}NO_3Br+NH_4]^+$ calcd 289.0182, found 289.0182.

The aldehyde (887 mg, 3.26 mmol) was converted in 2.5 h to the desired product **6h** (943 g, 91%) as a pale yellow oil, as described for the synthesis of compound **6a**. Rf 0.23 (25% EtOAc/Hexane); ^{1}H NMR (600MHz, CDCl$_3$) δ 7.60 (1 H, dd, *J* = 8.0, 1.2), 7.31 (1 H, t, *J* = 7.5), 7.22 (1 H, dd, *J* = 7.8, 1.6), 7.14 (1 H, dt, *J* = 7.6, 1.7), 4.71 – 4.63 (2 H, m), 4.24 (2 H, dd, *J* = 6.6, 4.7), 3.31 (3 H, s), 3.26 (3 H, s), 2.11 - 2.00 (2 H m); ^{13}C NMR (151 MHz, CDCl$_3$) δ 138.4 (*C*), 133.9 (*C*H), 129.2 (*C*) 128.1 (*C*H), 102.5 (*C*H), 78.9 (*C*H$_2$), 53.7 (*C*H$_3$), 52.9 (*C*H$_3$), 38.9 (*C*H), 35.5 (*C*H$_2$); FTIR (neat, film) 2931, 1547, 1376, 1122 cm^{-1}; HRMS (ESI) $[C_{12}H_{16}BrNO_4+Na]^+$ calcd 340.0155, found 340.0154.

*4.4.9. 5-(4,4-dimethoxy-1-nitrobutan-2-yl)benzo[1,3]dioxole (**6i**)*

The ester **4i** (2.50 g, 9.36 mmol) was converted to the crude aldehyde in 2.5 h, as described for the synthesis of compound **6a**. Purification of the residue by flash column chromatography (30% EtOAc/Hexane) 3-(benzo[1,3]dioxol-5-yl)-4-nitrobutanal (1.75 g, 80%) as a colourless oil. R_f (30% EtOAc in Hexane) 0.16; ^{1}H NMR (600 MHz, CDCl$_3$) δ 9.70 (1H, s), 7.27—6.68 (3H, m), 5.96 (2H, s), 4.65—4.62 (1H, dd, *J* = 12.0, 6.6), 4.57—4.54 (1H, dd, *J* = 12.0, 7.8), 4.01—3.99 (1H, m), 2.91—2.89 (2H, m); ^{13}C NMR (151 MHz, CDCl$_3$) δ 198.9 (*C*HO), 148.4 (*C*), 147.5 (*C*), 131.8 (*C*), 120.9 (*C*H), 108.9 (*C*H), 107.7 (*C*H), 101.4 (*C*H$_2$), 79.7 (*C*H$_2$), 46.6 (*C*H$_2$), 37.9 (*C*H); Data consistent with literature.[14]

The aldehyde (146 mg, 0.62 mmol) was converted in 2.5 h to the desired product **6i** (178 mg, 100%) as a pale-yellow oil, as described for the synthesis of compound **6a**. R_f (20% EtOAc in hexnae) 0.34; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.77—6.66 (3H, m), 5.95 (2H, s), 4.60 (1H, dd, *J* = 12.5, 7.0), 4.49 (1H, dd, *J* = 8.5, 12.5), 4.16 (1H, dd, *J* = 7.5, 3.5), 3.58—3.54 (1H, m), 3.29 (3H, s), 3.25 (3H, s,), 2.01—1.96 (1H, m), 1.88—1.83 (1H, m); ^{13}C NMR (126 MHz, CDCl$_3$) δ 148.2 (*C*), 147.2 (*C*), 132.7 (*C*), 120.9 (*C*H), 108.8 (*C*H), 107.6 (*C*H), 102.1 (*C*H), 101.3 (*C*H$_2$), 80.6 (*C*H$_2$), 53.2 (*C*H$_3$), 53.0 (*C*H$_3$), 40.2 (*C*H$_2$), 36.2 (*C*H); FTIR (neat, cm^{-1}) 2937, 2834, 1743, 1550, 1443, 1247 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{18}NO_6$ $[M+H]^+$ 483.1050, found 283.1051.

*4.4.10. 2-(4,4-dimethoxy-1-nitrobutan-2-yl)furan (**6j**)*

The ester **4j** (991 mg, 4.36 mmol) was converted to the crude aldehyde in 2h as described for the synthesis of compound **6a**. Purification of the residue by flash column chromatography (20% EtOAc/Hexane) gave 3-(furan-2-yl)-4-nitrobutanal (550 mg, 69%) as a yellow oil. Rf 0.33 (20% EtOAc/Hexane); ^{1}H NMR (400MHz, CDCl$_3$) δ 9.76 (1 H, s), 7.39 – 7.22 (1 H, m), 6.31 (1 H, dd, *J* = 3.3, 1.9), 6.18 (1 H, dt, *J* = 3.3, 0.7), 4.73 – 4.60 (2 H, m), 4.18 (1 H, q, *J* = 7.0), 3.08 – 2.84 (2 H, m). Data are consistent with literature.[24]

The aldehyde (515 mg, 2.81 mmol) was converted to the crude product **6j** (613 mg, 95%) in 2 h, as described for the synthesis of compound **6a**. The product was obtained with no purification as a pale brown oil. Rf 0.58 (20% EtOAc/Hexane); ^{1}H NMR (600 MHz, CDCl3) δ 7.36 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.16 (d, J = 3.2 Hz, 1H), 4.65 – 4.59 (m, 2H), 4.26 (dd, *J* = 7.1, 4.2 Hz, 1H), 3.79 (dt, *J* = 14.7, 7.3 Hz, 1H), 3.30 (d, *J* = 16.0 Hz, 6H), 2.06 – 1.95 (m, 2H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 152.2, 142.5, 110.5, 107.4, 102.4, 78.2, 53.5, 53.3, 34.2 (d, *J* = 12.4 Hz); FTIR (neat, film) 2936, 1551, 1436, 1125, 1051, 739 cm^{-1}; HRMS (ESI) $[C_{10}H_{15}NO_5+H]^+$ calcd 229.0950, found 229.0952.

*4.4.11. 2-(4,4-dimethoxy-1-nitrobutan-2-yl)thiophene (**6k**)*

The ester **4k** (941 mg, 3.87 mmol) was converted to the crude aldehyde (771 mg, 95%) in 3 h, as described for the synthesis of compound **6a**. The product 4-nitro-3-(thiophen-2-yl)butanal_was obtained with no purification as a brown oil. Rf 0.12 (11% EtOAc/Hexane); ^{1}H NMR (600MHz, CDCl$_3$) δ 9.73 (1 H, t, *J* = 0.9), 7.23 (1 H, dd, *J* =5.0, 1.2), 6.97 – 6.91 (2 H, m), 4.68(1 H, dd, *J* = 12.7, 7.1), 4.63 (1H, dd, *J* = 12.7, 7.1), 4.39 (1 H, quin, *J* = 7.0), 3.05 - 2.95 (2 H, m); ^{13}C NMR (151 MHz, CDCl$_3$) δ 198.5 (*C*HO), 141.0 (*C*), 127.4 (*C*H), 125.9 (*C*H), 125.2 (*C*H), 79.8 (*C*H$_2$), 47.2 (*C*H$_2$), 33.6 (*C*H); FTIR (neat, film) 2840, 1720, 1548, 1378; HRMS (ESI) $[C_{10}H_{15}NO_4S+H]^+$ calcd 246.0800, found 246.0805.

The aldehyde (703 mg, 3.53 mmol) was converted to the crude product **6k** in 2 h, as described for the synthesis of compound **6a**. The residue was purified by flash column chromatography (14% EtOAc/Hexane) to afford the desired product **6k** (710 mg, 82%) as a yellow oil. Rf 0.58 (20% EtOAc/Hexane); ^{1}H NMR (600MHz, CDCl$_3$) δ 7.23 (1 H,dd, *J* = 5.1, 0.9), 6.95 (1 H, dd, *J* = 5.1, 3.5), 6.91 (1 H, ddd, *J* = 3.5, 1.1, 0.5), 4.66 (1 H, dd, *J* = 12.7, 7.5), 4.55 (1H, dd, *J* = 12.7, 7.5), 4.26 (1 H, dd, *J* = 7.6, 3.7), 4.02 – 3.97 (1 H, m), 3.31 (3 H, s), 3.28 (3 H, s), 2.09 – 1.94 (2 H, m); ^{13}C NMR (151 MHz, CDCl$_3$) δ 142.1 (*C*), 127.3 (*C*H), 125.7 (*C*H), 124.9 (*C*H), 102.3 (*C*H), 80.9 (*C*H$_2$), 53.5 (*C*H$_3$), 53.3 (*C*H$_3$), 37.4 (*C*H), 35.9 (*C*H$_2$); FTIR (neat, film) 2936, 1549, 1377, 1123 cm^{-1}; HRMS (ESI) $[C_{10}H_{15}NO_4S+H]^+$ calcd 268.0614, found 268.0616.

*4.5. Ethyl (E)-2-((4-methoxyphenyl)imino)acetate (**5**)*

To a solution of *p*-anisidine in dry CH$_2$Cl$_2$ (40 mL), was added Na$_2$SO$_4$ (5.00 g, 40.6 mmol), then ethylglyoxylate and left to stir for 60 h. The reaction mixture was filtered and concentrated to afford the imine **5** (9.30 g, 100%) contains residual toluene. The crude product was used without further purification. Rf 0.44 (50% EtOAc/Hexane); ^{1}H NMR (400MHz, CDCl$_3$) δ 7.94 (1 H, s), 7.39 - 7.33 (2 H, m), 6.96 - 6.91 (2 H, m), 4.41 (2 H, q, *J* = 7.3), 3.84 (3 H, s), 1.40 (3 H, t, *J* = 7.2). Data consistent with literature.[29]

*4.6. Optimization of Base and Promoter for nitro-Mannich Reaction of Ethyl 6,6-dimethoxy-2-((4-methoxyphenyl)amino)-3-nitro-4-phenylhexanoate (**6a, Table 1**)*

4.6.1. Entry 1

To a cooled (0 ºC) and stirred solution of nitroalkane **6a** (100 mg, 0.418 mmol) in dry THF (5 mL) under N_2 atmosphere, was added NaH (15.1 mg, 0.450 mmol). The reaction mixture was slowly warmed up to room temperature then heated at 40 ºC for 30 min. The mixture was cooled to room temperature then -78 ºC and a solution of imine **5** (127 mg, 0.615 mmol) in THF (1 mL) was added dropwise. The mixture was stirred for 10 min. In another flask TFA (0.10 mL) was added dropwise to a solution of $ZnEt_2$ (1.0 M in hexane, 0.62 mL) in THF (0.30 mL) at -40 ºC, under N_2. The resulting solution was stirred for 10 min and transferred to the nitronate solution dropwise. The reaction mixture was stirred at -78 ºC for 1 h. The reaction mixture was quenched with TFA (0.1 mL), diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ (2 x 15 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated to give the crude nitroamine (*dr* 65:35, *syn-anti* major) as a brown oil. Rf 0.26 (20% EtOAc/Hexane).

4.6.2. Entry 2

To a cooled (-40 ºC, MeCN/dry ice bath) and stirred solution of nitroalkane **6a** (100 mg, 0.418 mmol) in dry THF (5 mL) under N_2 atmosphere, was added dropwise LDA (0.23 mL, 0.45 mmol). After 10 min the reaction was warmed up to (0 ºC) and stirred for 20 min. The mixture was cooled to -78 ºC and a solution of imine **5** (127 mg, 0.615 mmol) in THF (1 mL) was added dropwise. The mixture was stirred for 10 min. The reaction mixture was quenched with TFA (0.1 mL) and worked up identical to Method 1 to give the crude nitroamine (*dr* 70:30, *syn-anti* major) as a brown oil. Rf 0.26 (20% EtOAc/Hexane.

4.6.3. Entry 3

To a cooled (-40 ºC, MeCN/dry ice bath) and stirred solution of nitroalkane **6a** (100 mg, 0.418 mmol) in dry THF (5 mL) under N_2 atmosphere, was added dropwise LDA (0.23 mL, 0.45 mmol). After 10 min the reaction was warmed up to (0 ºC) and stirred for 20 min. The mixture was cooled to -78 ºC and a solution of imine **5** (127 mg, 0.615 mmol) in THF (1 mL) was added dropwise. The remainder of the reaction was performed identical to Method 1 to give the crude nitroamine (*dr* 65:35, *syn-anti* major) as a brown oil. Rf 0.26 (20% EtOAc/Hexane).

4.6.4. Entry 4

To a cooled (-40 ºC, MeCN/dry ice bath) and stirred solution of nitroalkane **6a** (100 mg, 0.418 mmol) in dry THF (5 mL) under N_2 atmosphere, was added dropwise LDA (0.23 mL, 0.45 mmol). After 10 min the reaction was warmed up to (0 ºC) and stirred for 20 min. The mixture was cooled to -78 ºC and a solution of imine **5** (127 mg, 0.615 mmol) in THF (1 mL) was added dropwise. The mixture was stirred for 10 min. A solution of $Cu(OTf)_2$ (222 mg, 0.615 mmol) in THF (2 mL) was added dropwise and the reaction mixture was stirred at -78 ºC for 1 h. The reaction mixture was quenched with EtOH (5 mL), diluted with EtOAc (15 mL) and washed with EDTA (15 mL). The aqueous layer was extracted with EtOAc (2 x 15 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated to give the crude nitroamine (*dr* >95:5, *syn-anti* major) as a brown oil. Rf 0.26 (20% EtOAc/Hexane).

4.6.5. Entry 5

Identical to method 3 with LiHMDS (1.0 M in THF) as a base to give the crude nitroamine (*dr* 70:30, *syn-anti* major) as a brown oil. The residue was purified by flash column chromatography (20% EtOAc/Hexane) to afford the desired nitroamine **2a** (122 mg, 67%). Rf 0.26 (20% EtOAc/Hexane); ^{1}H NMR (600MHz, $CDCl_3$) δ 7.47 – 7.33 (5 H, m), 6.69 – 6.64 (2 H, m), 6.26 – 6.20 (2 H, m), 5.04 (1 H, dd, *J* = 11.7, 2.6, C*H*NO_2), 4.40 – 4.33 (1 H, m), 4.30 – 4.21 (2 H, m), 4.04 (1 H, dd, *J* = 8.7, 2.6), 3.94 (1 H, dd, *J* = 8.8, 3.2), 3.89 (1 H, dt, *J* = 11.6, 3.8), 3.72 (3 H, s), 3.22 – 3.17 (6 H, m), 1.97 – 1.84 (2 H, m) 1.42 (3 H, t, *J* = 7.2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.7 (C=O), 153.4 (*C*), 137.6 (*C*), 129.3 (*C*H), 129.0 (*C*H), 128.5 (*C*H), 115.8 (*C*H), 114.9 (*C*H), 101.2 (*C*H), 93.8 (*C*H), 62.6 (*C*H_2), 58.2 (*C*H), 55.8 (*C*H_3), 53.1 (*C*H_3), 51.4 (*C*H_3), 41.6 (*C*H), 35.3 (*C*H_2), 14.3 (*C*H_3); FTIR (neat, film) 3376, 2938, 1741, 1553, 1514, 1370, 1239, 1127 cm^{-1}; HRMS (EI) $[C_{23}H_{30}N_2O_7]^{+\cdot}$ calcd 447.2131, found 447.2110.

4.6.6. Entry 6

Identical to method 4 with LiHDMS (1.0 M in THF) as a base to give the crude nitroamine **2a** (*dr* >95:5, *syn-anti* major) as a brown oil. Purification by flash column chromatography was attempted but degradation of the product was observed. Rf 0.26 (20% EtOAc/Hexane).

*4.7. General procedure for the synthesis of piperidines using the nitro-Mannich/reductive cyclisation sequence (**1, Table 2**)*

Identical to entry 6, Table 1, except for the work up procedure. The reaction was quenched with MeOH (5 mL), concentrated, then dissolved in CH_2Cl_2 (10 mL), filtered through celite and concentrated to give the crude β-nitroamine which was then subjected to the cyclisation conditions described for **1a** above.

*4.7.1. Ethyl 1-(4-methoxyphenyl)-3-nitro-4-phenylpiperidine-2-carboxylate (**1a**)*

To a cooled (-40 ºC) solution of crude nitroamine from above (1.16 g, 2.60 mmol) in CH_2Cl_2 (40 mL) under N_2 atmosphere, was added $BF_3.OEt_2$ (2.37 mL, 7.80 mmol) dropwise and the reaction mixture stirred for 4 h. The cooling bath was left but not recharged and the temperature was kept below 0 ºC. TLC (20% EtOAc/Hexane) showed complete consumption of starting material. Then Et_3SiH (0.62 mL, 3.9 mmol) was added, the mixture was warmed up to room temperature and stirred for 1.5 h. The reaction was quenched with saturated $NaHCO_3$ (50 mL) and the mixture extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified flash column chromatography (14% EtOAc/Hexane) to give the desired product **1a** (290 mg, 48%) as a yellow solid; mp 105 – 112 ºC; Rf 0.25 (20% EtOAc/Hexane); ^{1}H NMR (600MHz, $CDCl_3$) δ 7.39 - 7.35 (2 H, m), 7.35 - 7.31 (2 H, m), 7.29 (1 H, d, *J* = 7.0), 6.92 (1 H, d, *J* = 9.0), 6.83 (1 H, d, *J* = 8.8), 5.45 (1 H, s, br), 5.17 (1 H, s), 4.31 - 4.18 (2 H, m), 3.77 (3 H, s), 3.64 - 3.59 (1 H, m), 3.49 (1 H, td, *J* = 12.2, 3.0), 3.23 (1 H, dt, *J* = 13.1, 3.3), 2.82 (1 H, qd, *J* = 12.8, 5.3), 1.99 (1 H, d, *J* = 12.2), 1.29 (3 H, t, *J* = 7.2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.3 (C=O), 154.4 (*C*), 144.2 (*C*). 139.6 (*C*), 128.7 (*C*H), 127.5 (*C*H), 119.9 (*C*H), 114.5 (*C*H), 86.2 (*C*H), 65.6 (*C*H), 61.9 (*C*H_2), 55.7 (*C*H_3), 45.2 (*C*H_2), 40.1 (*C*H), 24.1 (*C*H_2), 14.4 (*C*H_3); FTIR (neat, film) 2955, 1713, 1545, 1507,1366, 1228 cm^{-1}; HRMS (ESI) $[C_{21}H_{24}N_2O_5+H]^+$ calcd 385.1758, found 385.1756.

*4.7.2. Ethyl 1-(4-methoxyphenyl)-3-nitro-4-(p-tolyl)piperidine-2-carboxylate (**1b**)*

The nitroalkane **6b** (73.0 mg, 0.288 mmol) was converted to the crude nitroamine (*dr* 90:10, *syn-anti* major) as a yellow oil according to the general method. Rf 0.22 (25% EtOAc/Hexane); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.27 – 7.22 (4 H, m), 6.70 – 6.67 (2 H, m), 6.25 – 6.22 (2 H, m), 5.03 (1 H, dd, *J* = 11.7, 2.6, C*H*NO_2), 4.39 – 4.32 (1 H), 4.28 – 4.20 (2 H, m), 4.06 (1 H, dd, *J* = 8.7, 2.6), 3.97 – 3.93 (1 H, m), 3.88 – 3.80 (1 H, m), 3.73 (3 H, s), 3.21 (3 H, s), 3.14 (3 H, s), 2.40 (3 H, s) 1.95 – 1.79 (2 H, m) 1.41 (3 H, t, *J* = 7.2).

The crude nitroamine (134 mg, 0.288 mmol) was converted to the crude piperidine **1b** according to the general method. The residue was purified flash column chromatography (11%

EtOAc/Hexane) to give the desired product **1b** (59.0 mg, 51%) as a yellow gum. Rf 0.42 (25% EtOAc/Hexane); ^{1}H NMR (600MHz, CDCl$_3$) δ 7.22 (2 H, d, J = 8.1), 7.18 (2 H, d, J = 7.9), 6.94 – 6.90 (2 H, m), 6.86 – 6.80 (2 H, m), 5.43 (1 H, t, J = 2.5), 5.15 (1 H, s), 4.20 – 4.18 (2 H, m), 3.78 (3 H, s), 3.61 (1 H, dd, J = 12.2, 4.7), 3.49 (1 H, td, J = 12.2, 3.2), 3.20 (1 H, dt, J = 13.2, 3.7), 2.80 (1 H, qd, J = 12.8, 5.3), 2.35 (3 H, s), 1.98 - 1.93 (1 H, m), 1.29 (3 H, t, J = 7.2); ^{13}C NMR (151 MHz, CDCl$_3$) δ 169.3 (C=O), 154.3 (*C*), 144.3 (*C*), 137.0 (*C*H), 136.5 (*C*H), 129.4 (*C*H), 127.3 (*C*H), 119.9 (*C*H), 114.5 (*C*H) 86.2 (*C*H), 65.5 (*C*H), 61.9 (*C*H$_2$), 55.7 (*C*H$_3$), 45.2 (*C*H$_2$), 39.8 (*C*H), 24.3 (*C*H$_2$), 21.16 (*C*H$_3$), 14.4 (*C*H$_3$); FTIR (neat, film) 2931, 1721, 1549, 1509, 1387, 1241 cm^{-1}; HRMS (ESI) [C$_{22}$H$_{26}$N$_2$O$_5$+H]$^+$ calcd 399.19150, found 399.19145.

*4.7.3. Ethyl 1,4-bis(4-methoxyphenyl)-3-nitropiperidine-2-carboxylate (**1c**)*

The nitroalkane **6c** (30.0 mg, 0.110 mmol) was converted to the crude nitroamine (*dr* 90:10, *syn-anti* major) as a yellow oil according to the general method. Rf 0.15 (20% EtOAc/Hexane); ^{1}H NMR (400MHz, CDCl$_3$) δ 7.29 – 7.26 (2 H, m), 7.00 – 6.94 (2 H, m), 6.72 – 6.66 (2 H, m), 6.26 – 6.22 (2 H, m), 5.00 (1 H, dd, J = 11.7, 2.6, C*H*NO$_2$), 4.40 – 4.32 (1 H, m), 4.28 – 4.20 (2 H, m), 4.08 (1 H, dd, J = 8.8, 2.8), 3.95 (1 H, dd, J = 8.8, 3.3), 3.83 – 3.80 (1 H, m), 3.73 (3 H, s), 3.20 (3 H, s), 3.15 (3 H, s), 1.96 – 1.77 (2 H, m) 1.41 (3 H, t, J = 7.2).

The crude nitroamine (52.4 mg, 0.110 mmol) was converted to the crude piperidine **1c** according to the general method. The residue was purified flash column chromatography (14% EtOAc/Hexane) to give the desired product **1c** (26 mg, 57%) as a brown gum. Rf 0.36 (20% EtOAc/Hexane); ^{1}H NMR (600MHz,CDCl$_3$) δ 7.23 (2 H, d, J = 8.7), 6.91 – 6.87 (4 H, m), 6.82 (2 H, d, J = 9.0), 5.38 (1 H, s, br), 5.12 (1 H, s), 4.23 (2 H, qd, J = 7.2, 1.7), 3.80 (3 H, s), 3.76 (3 H, s), 3.62 – 3.58 (1 H, m), 3.47 (1 H, dt, J = 12.2, 3.2), 3.17 (1 H, td, J = 13.3, 3.7), 2.79 (1 H, qd, J = 12.8, 5.1), 1.93 (1 H, d, J = 13.0), 1.27 (3 H, t, J = 7.2); ^{13}C NMR (151 MHz, CDCl$_3$) δ 169.3 (C=O), 158.8 (*C*), 154.3 (*C*), 144.2 (*C*H), 131.5 (*C*H), 128.6 (*C*H), 119.9 (*C*H), 114.4 (*C*H), 114.1 (*C*H) 83.4 (*C*H), 64.8 (*C*H), 61.9 (*C*H$_2$), 55.7 (*C*H$_3$), 45.1 (*C*H$_2$), 40.3 (*C*H), 24.8 (*C*H$_2$), 14.4 (*C*H$_3$); FTIR (neat, film) 2934, 1742, 1550, 1365, 1244 cm^{-1}; HRMS (ESI) [C$_{22}$H$_{26}$N$_2$O$_6$+H]$^+$ calcd 415.1864, found 415.1864.

*4.7.4. Ethyl 4-(4-bromophenyl)-1-(4-methoxyphenyl)-3-nitropiperidine-2-carboxylate (**1d**)*

The nitroalkane **6d** (100 mg, 0.31 mmol) was converted to the crude nitroamine (*dr* 80:20, *syn-anti* major) as a yellow oil according to the general method. Rf 0.49 (20% EtOAc/Hexane); ^{1}H NMR (300MHz, CDCl$_3$) δ 7.57 (2 H, d, J = 8.4), 7.29 – 7.18 (2 H, m), 6.71 (2 H, d, J = 8.9), 6.26 (2 H, d, J = 8.9), 5.01 (1 H, dd, J = 11.4, 2.9, C*H*NO$_2$), 4.36 (1 H, m), 4.20 (2 H, m), 4.06 – 3.97 (1 H, m), 3.96 – 3.88 (1 H, m), 3.73 (3 H, s), 3.19 (3 H, s), 3.14 (3 H, s), 2.40 (3 H, s) 1.98 – 1.76 (2 H, m) 1.39 (3 H, t, J = 7.2).

The crude nitroamine (163 mg, 0.310 mmol) was converted to the crude piperidine **1d** according to the general method. The residue was purified flash column chromatography (11% EtOAc/Hexane) to give the desired product **1d** (35.0 mg, 24%) as a yellow gum. Rf 0.68 (20% EtOAc/Hexane); ^{1}H NMR (600MHz, CDCl$_3$) δ 7.48 (2 H, d, J = 8.5), 7.20 (2 H, d, J = 8.2), 6.89 (2 H, d, , J = 9.1), 6.82 (2 H, d, J = 9.1,), 5.38 (1 H, t, J = 2.5), 5.16 (1 H, s), 4.26 - 4.19 (2 H, m), 3.76 (3 H, s), 3.61 – 3.57 (1 H, m), 3.45 (1 H, td, J = 12.2, 3.2), 3.18 (1 H, dt, J = 13.2, 3.7), 2.75 (1 H, qd, J = 12.9, 5.2), 1.94 (1 H, d, J = 11.8), 1.26 (3 H, t, J = 7.1); ^{13}C NMR (151 MHz, CDCl$_3$) δ 169.3 (C=O), 154.5 (*C*), 144.1 (*C*), 138.7 (*C*H), 131.8 (*C*H), 129.3 (*C*H), 121.4 (*C*H), 120.0 (*C*H), 114.5 (*C*H), 85.9 (*C*H), 65.6 (*C*H), 62.0 (*C*H$_2$), 55.7 (O*C*H$_3$), 45.1 (*C*H$_2$), 39.6 (*C*H), 24.1 (*C*H$_2$), 14.4 (*C*H$_3$); FTIR (neat, film) 2925, 1722, 1549, 1510, 1242 cm^{-1}; HRMS (ESI) [C$_{21}$H$_{23}$N$_2$O$_5$Br+H]$^+$ calcd 463.0863, found 463.0862.

*4.7.5. Ethyl 4-(4-fluorophenyl)-1-(4-methoxyphenyl)-3-nitropiperidine-2-carboxylate (**1e**)*

The nitroalkane **6e** (300 mg, 1.17 mmol) to the crude nitroamine (*dr* 75:25, *syn-anti* major) as a brown oil according to the general method. Rf 0.30 (20% EtOAc/Hexane); ^{1}H NMR (400MHz, CDCl$_3$) δ 7.33 (2 H, dd, J = 8.8, 5.3), 7.17 – 7.10 (2 H, m), 6.69 (2 H, d, J = 8.8), 6.24 (2 H, d, J = 8.8), 5.00 (1 H, dd, J = 11.5, 2.8, C*H*NO$_2$), 4.38 – 4.31 (1 H, m), 4.26 – 4.15 (2 H, m), 4.07 – 4.00 (1 H, m), 3.94 – 3.86 (2 H, m), 3.72 (3 H, s), 3.19 (3 H, s), 3.14 (3 H, s), 1.98 – 1.78 (2 H, m) 1.40 (3 H, t, J = 7.2).

The crude nitroamine (295 mg, 0.64 mmol) was converted to the crude piperidine **1e** according to the general method. The residue was purified flash column chromatography (20% EtOAc/Hexane) to give the desired product **1e** (110 mg, 34%) as a yellow gum. Rf 0.27 (20% EtOAc/Hexane); ^{1}H NMR (600MHz, CDCl$_3$) δ 7.29 (2 H, dd, J = 8.5, 5.3), 7.05 (2 H, t, J = 8.7), 6.92 – 6.88 (2 H, m), 6.84 – 6.80 (2 H, m), 5.38 (1 H, s, br), 5.15 (1 H, s), 4.23 (2 H, q, J = 7.2), 3.77 (3 H, s), 3.60 (1 H, dd, J = 12.1, 5.0), 3.46 (1 H, dt, J = 12.2, 3.1), 3.20 (1 H, td, J = 13.1, 3.6), 2.77 (1 H, dq, J = 12.8, 5.3), 1.94 (1 H, d, J = 13.7), 1.27 (3 H, t, J = 7.2); ^{13}C NMR (151 MHz, CDCl$_3$) δ 169.3 (C=O), 154.4 (*C*), 144.1 (*C*), 129.1 (*C*H), 120.0 (*C*H), 115.7 (*C*H), 115.5 (*C*H), 114.4 (*C*H), 86.1 (*C*H), 65.6 (*C*H), 62.0 (*C*H$_2$), 55.7 (*C*H$_3$), 45.1 (*C*H$_2$), 39.5 (*C*H), 24.3 (*C*H$_2$), 14.4 (*C*H$_3$); FTIR (neat, film) 2924, 1708, 1549, 1365, 1225 cm^{-1}; HRMS (ESI) [C$_{21}$H$_{23}$FN$_2$O$_5$+H]$^+$ calcd 403.1669, found 403.1657.

*4.7.6. Ethyl 1-(4-methoxyphenyl)-3-nitro-4-(4-nitrophenyl)piperidine-2-carboxylate (**1f**)*

The nitroalkane **6f** (62 mg, 0.22 mmol) was converted to the crude nitroamine (*dr* 70:30, *syn-anti* major) as a yellow oil according to the general method. Rf 0.12 (25% EtOAc/Hexane); ^{1}H NMR (400MHz, CDCl$_3$) δ 8.29 – 8.24 (2 H, m), 7.68 – 7.63 (2 H, m), 7.38 – 7.32 (2 H, m), 6.92 (2 H, dd, J = 8.9, 1.9), 5.08 (1 H, dd, J = 10.8, 3.3, C*H*NO$_2$), 4.40 (2 H, q, J = 7.0), 4.19 – 4.14 (1 H, m), 4.02 (1 H, dd, J = 10.8, 3.5), 3.97 (1 H, dd, J = 9.0, 3.5), 3.90 (1 H, dd, J = 8.2, 3.4), 3.83 (3 H, s), 3.31 (6 H, m), 1.96 – 1.85 (2 H, m) 1.42 – 1.36 (3 H, m).

The crude nitroamine (108 mg, 0.218 mmol) was converted to the crude piperidine **1f** as described for the synthesis of compound **2a**. The residue was purified flash column chromatography (25% EtOAc/Hexane), desired product **1f** was not isolated. Rf 0.27 (25% EtOAc/Hexane).

*4.7.7. Ethyl 4-(2-methoxyphenyl)-1-(4-methoxyphenyl)-3-nitropiperidine-2-carboxylate (**1g**)*

Nitroalkane **6g** (110 mg, 0.408 mmol) was converted to the crude nitroamine (*dr* 95:5, *syn-anti* major) as a brown oil according to the general method. Rf 0.22 (20% EtOAc/Hexane). Rf 0.22 (20% EtOAc/Hexane); ^{1}H NMR (400MHz, CDCl$_3$) δ 7.37 – 7.27 (2 H, m), 7.01 – 6.92 (2 H, m), 6.71 – 6.66 (2 H, m), 6.36 – 6.34 (2 H, m), 5.56 (1 H, d, J = 10.0), 4.30 – 4.15 (2 H, m), 4.13 – 4.09 (1 H, m), 4.07 – 4.01 (1 H, m), 3.96 (1 H, dd, J = 8.5, 3.3), 3.71 (3 H, s), 3.19 (3 H, s), 3.12 (3 H, s), 2.27 – 2.14 (1 H, m), 1.86 – 1.79 (1 H, m) 1.37 – 1.32 (3 H, m).

The crude nitroamine (212 mg, 0.445 mmol) was converted to the crude piperidine **1g** according to the general method. The residue was purified flash column chromatography (11% EtOAc/Hexane) to give the desired product **1g** (56 mg, 30%) as a yellow gum. Rf 0.56 (20% EtOAc/Hexane); ^{1}H NMR (700MHz,CDCl$_3$) δ 7.35 (1 H, d, *J* = 7.0), 7.28 – 7.26 (1 H, m), 6.99 (1 H, t, *J* = 7.5), 6.95 – 6.90 (2 H, m), 6.88 (1 H, d, *J* = 8.2), 6.86 – 6.78 (2 H, m), 5.64 (1 H, t, *J* = 2.2), 5.16 (1 H, s), 4.29 – 4.19 (2 H, m), 3.86 (3 H, s), 3.77 (3 H, s), 3.67 (1 H, td, *J* = 12.1, 3.1), 3.59 (1 H, dd, *J* = 11.9, 4.6), 3.51 (1 H, dt, *J* = 13.5, 3.5), 2.80 (1 H, qd, *J* = 12.8, 5.1), 1.84 (1 H, dd, *J* = 12.8, 2.5), 1.31 (3 H, t, *J* = 7.1); ^{13}C NMR (176 MHz, CDCl$_3$) δ 169.3 (C=O), 156.7 (*C*), 154.2 (*C*), 144.4 (*C*), 128.8 (*C*H), 128.5 (*C*H), 127.3 (*C*H), 120.9 (*C*H), 119.8 (*C*H), 114.5 (*C*H), 110.0 (*C*H), 83.7 (*C*H), 65.1 (*C*H), 61.7 (*C*H$_2$), 55.7 (*C*H$_3$), 55.4 (*C*H$_3$), 45.2 (*C*H$_2$), 34.7 (*C*H), 24.0 (*C*H$_2$), 14.4 (*C*H$_3$); FTIR (neat, film) 2935, 1727, 1552, 1377, 1265 cm^{-1}; HRMS (ESI) [$C_{22}H_{26}N_2O_6$+H]$^+$ calcd 415.1864, found 415.1870.

*4.7.8. Ethyl 4-(2-bromophenyl)-1-(4-methoxyphenyl)-3-nitropiperidine-2-carboxylate (**1h**)*

The nitroalkane **6h** (60.0 mg, 0.189 mmol) was converted to the crude nitroamine as a yellow oil according to the general method. Rf 0.15 (20% EtOAc/Hexane); ^{1}H NMR (400MHz, CDCl$_3$) δ 7.37 (2 H, dd, *J* = 9.0, 2.8), 6.94 (2 H, m), 6.83 – 6.78 (2 H, m), 6.76 – 6.69 (2 H, m), 5.30 (1 H, dd, *J* = 10.2, 4.4, C*H*NO$_2$), 4.42 (2 H, m), 4.35 – 4.27 (1 H, m), 4.17 – 4.10 (1 H, m), 4.09 – 4.00 (2 H, m), 3.20 (3 H, s), 3.15 (3 H, s), 2.15 – 2.03 (2 H, m) 1.41 (3 H, t, *J* = 7.7).

The crude nitroamine (89.0 mg, 0.170 mmol) was converted to the crude piperidine **1h** according to the general method. The residue was purified flash column chromatography (14% EtOAc/Hexane) to give the desired product **1h** (15 mg, 19%) as a yellow solid; mp 117 – 122 ºC; Rf 0.32 (20% EtOAc/Hexane); ^{1}H NMR (600MHz, CDCl$_3$) δ 7.58 (1 H, dd, *J* = 8.0, 1.0), 7.49 - 7.45 (1 H, m), 7.37 – 7.33 (1 H, m), 7.19 – 7.15 (1 H, m), 6.96 – 6.91 (1 H, m), 6.86 – 6.81 (1 H, m), 5.62 (1 H, br.s), 5.17 (1 H, s), 4.26 (1 H, qd, *J* = 10.7, 7.2), 4.18 (1 H, qd, *J* = 10.7, 7.2) 3.77 (3 H, s), 3.76 - 3.73 (1 H, m), 3.63 – 3.54 (2 H, m), 2.85 (1 H, dq, *J* = 12.8, 5.3), 1.91 – 1.86 (1 H, m), 1.29 (3 H, t, *J* = 7.2); ^{13}C NMR (151 MHz, CDCl$_3$) δ 168.9 (C=O), 154.4 (*C*), 144.0 (*C*). 137.9 (*C*), 130.5 (*C*H), 129.3 (*C*H), 127.8 (*C*H), 124.5 (*C*H), 119.9 (*C*H), 114.5 (*C*H), 86.2 (*C*H), 65.6 (*C*H), 61.9 (*C*H$_2$), 55.7 (*C*H$_3$), 45.2 (*C*H$_2$), 40.1 (*C*H), 24.1 (*C*H$_2$), 14.4 (*C*H$_3$); FTIR (neat, film) 2955, 1713, 1545, 1507,1366, 1228 cm^{-1}; HRMS (ESI) [$C_{21}H_{23}N_2O_5Br$+H]$^+$ calcd 463.0863, found 463.0864.

*4.7.9. Ethyl 4-(benzo[1,3]dioxol-5-yl)-1-(4-methoxyphenyl)-3-nitropiperidine-2-carboxylate (**1i**)*

The nitroalkane 6i (263 mg, 0.93 mmol) was converted to the crude nitroamine as a yellow oil according to the general method. Rf (20% EtOAc in hexane) 0.26; 1H NMR (600 MHz, CDCl3) δ 6.88—6.82 (3H, m), 6.72—6.70 (2H, m), 6.30—6.29 (2H, m), 6.03 (2H, dd, *J* = 6.8, 1.5), 4.98 (1H, dd, *J* =11.5, 2.7), 4.39—4.33 (1H, m), 4.28—4.21 (2H, m), 4.15—4.10 (1H, m), 4.01 (1H, dd, *J* = 8.8, 3.0), 3.83—3.77 (1H, m), 3.74 (3H, s), 3.22 (3H, s), 3.18 (3H, s), 1.93—1.88 (1H, m), 1.82—1.76 (1H, m), 1.41 (3H, t, *J* = 7.1).

The crude nitroamine was converted to the crude piperidine **1i** according to the general method. The residue was purified flash column chromatography (14% EtOAc/Hexane) to give the desired product **1i** (134 mg, 41%). R$_f$ (30% EtOAc in hexane): 0.38; ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.90—6.76 (7H, m), 5.96 (2H, s), 5.37—5.35 (1H, m), 5.11 (1H, brs), 4.22 (2H, q, *J* = 7.2), 3.76 (3H, s), 3.61—3.57 (1H, m), 3.45 (1H, dt, *J* = 12.0, 3.2), 3.14 (1H, td, *J* = 13.2, 4.0), 2.74 (1H, dq, *J* = 12.8, 5.2), 1.91 (1H, d, *J* = 13.1), 1.27 (3H, t, *J* = 7.2); ^{13}C NMR (151 MHz, CDCl$_3$) δ 169.2 (*C*O$_2$Et), 154.3 (*C*), 148.0 (*C*), 146.8 (*C*), 144.2 (*C*), 133.4 (*C*), 120.7 (C*H*), 119.9 (C*H*), 114.4 (C*H*), 108.4 (C*H*), 108.1 (C*H*), 101.2 (*C*H$_2$), 86.3 (C*H*), 65.4 (*C*H), 61.9 (*C*H$_2$), 55.7 (*C*H$_3$), 45.2 (*C*H$_2$), 39.9 (*C*H), 24.4 (*C*H$_2$), 14.4 (*C*H$_3$); FTIR (neat, film) 2904, 1731, 1551, 1511, 1487, 1238, 1037 cm^{-1}; HRMS (ESI) $C_{22}H_{25}N_2O_7$ [M+H]$^+$ calcd for 429.1662, found 429.1660.

*4.7.10. Ethyl 4-(furan-2-yl)-1-(4-methoxyphenyl)-3-nitropiperidine-2-carboxylate (**1j**)*

The nitroalkane 6j (100 mg, 0.44 mmol) was converted to the crude nitroamine (dr 85:15, syn-anti major) as a yellow oil according to the general method. Rf 0.40 (20% EtOAc/Hexane); 1H NMR (300MHz, CDCl3) δ 7.48 (1 H, d, *J* = 1.3), 7.39 – 7.33 (1 H, m), 6.95 – 6.90 (1 H, m), 6.75 – 6.70 (2 H, m), 6.39 – 6.34 (2 H, m), 5.14 (1 H, dd, *J* = 11.0, 2.9, CHNO2), 4.35 – 4.13 (4 H, m), 4.09 – 4.01 (1 H, m), 3.72 (3 H, s), 3.22 (3 H, s), 3.19 (3 H, s), 2.03 – 1.82 (2 H, m) 1.36 (3 H, t, *J* = 7.2).

The crude nitroamine (192 mg, 0.44 mmol) was converted to the crude piperidine **1j** according to the general method. The residue was purified flash column chromatography (11% EtOAc/Hexane) to give the desired product **1j** (34.0 mg, 21%) as a yellow gum. Rf 0.67 (20% EtOAc/Hexane); ^{1}H NMR (600MHz, CDCl$_3$) δ 7.35 – 7.33 (1 H, m), 6.92 (2 H, d, *J* = 9.0), 6.81 (2 H, d, *J* = 9.0), 6.35 (1 H, dd, *J* = 3.3, 1.9), 6.19 – 6.17 (1 H, m), 5.53 (1 H, t, *J* = 3.2), 5.13 (1 H, d, *J* = 3.0), 4.20 – 4.14 (2 H, m), 3.76 (3 H, s), 3.49 (1 H, d, *J* = 3.2), 3.48 (1 H, t, *J* = 3.5), 3.34 (1 H, dt, *J* = 12.2, 3.8), 2.52 (1 H, tdd, *J* = 12.8, 10.1, 6.9), 2.07 (1 H, dd, *J* = 13.2, 3.5), 1.22 (3 H, t, *J* = 7.1); ^{13}C NMR (151 MHz, CDCl$_3$) δ 169.0 (C=O), 154.7 (*C*), 153.3 (*C*), 144.1 (*C*), 141.6 (*C*H), 120.5 (*C*H), 114.4 (*C*H), 110.7 (*C*H), 106.1 (*C*H), 82.9 (*C*H), 64.9 (*C*H), 61.9 (*C*H$_2$), 55.7 (*C*H$_3$), 44.9 (*C*H$_2$), 35.0 (*C*H), 24.0 (*C*H$_2$), 14.3 (*C*H$_3$); FTIR (neat, film) 2932, 1725, 1553, 1511, 1267 cm^{-1}; HRMS (ESI) [$C_{19}H_{22}N_2O_6$+H]$^+$ calcd 375.1551, found 375.1550.

*4.7.11. Ethyl 1-(4-methoxyphenyl)-3-nitro-4-(thiophen-2-yl)piperidine-2-carboxylate (**1k**)*

The nitroalkane **6k** (100 mg, 0.44 mmol) was converted to the crude nitroamine (*dr* 90:10, *syn-anti* major) as a brown oil according to the general method. Rf 0.15 (20% EtOAc/Hexane); ^{1}H NMR (300MHz, CDCl$_3$) δ 7.36 (1 H, dd, *J* = 4.9, 1.3), 7.09 (2 H, dd, *J* = 5.1, 2.0), 6.71 (2 H, d, *J* = 8.9), 6.33 (2 H, *J* = 8.9), 5.03 (1 H, dd, *J* = 11.3, 2.7, C*H*NO$_2$), 4.29 – 4.18 (4 H, m), 4.09 (1 H, dd, *J* = 8.6, 3.2), 3.72 (3 H, s), 3.23 (3 H, s), 3.19 (3 H, s), 2.40 (3 H, s) 2.02 – 1.81 (2 H, m) 1.41 (3 H, t, *J* = 7.2). The *dr* was calculated using the crude proton NMR of the subsequent piperidine **1k**.

The crude nitroamine (368 mg, 0.815 mmol) was converted to the crude piperidine **1k** according to the general method. The residue was purified flash column chromatography (11% EtOAc/Hexane) to give the desired product **1k** (143 mg, 45%) as a yellow oil. Rf 0.35 (14% EtOAc/Hexane); ^{1}H NMR (600MHz, CDCl$_3$) δ 7.22 (1 H, dd, *J* = 4.9, 1.4), 6.99 – 6.96 (2 H, m), 6.91 – 6.87 (2 H, m), 6.83 – 6.80 (2 H, m), 5.43 (1 H, t, *J* = 2.9), 5.07 (1 H, d, *J* = 2.1), 4.20 (2 H, q, *J* = 7.1), 3.76 (3 H, s), 3.57 – 3.44 (3 H, m), 2.78 (1 H, ddd, *J* = 24.7, 12.6, 5.3), 2.09 (1 H, dd, *J* = 13.1, 2.7), 1.24 (3 H, t, *J* = 7.1); ^{13}C NMR (151 MHz, CDCl$_3$) δ 169.0 (C=O), 154.7 (*C*), 144.0 (*C*), 143.0 (*C*), 127.1 (*C*H), 124.9 (*C*H), 124.4 (*C*H), 120.3 (*C*H), 114.5 (*C*H), 85.9 (*C*H), 65.4 (*C*H), 62.0 (*C*H$_2$), 55.7 (*C*H$_3$), 45.3 (*C*H$_2$), 36.6 (*C*H), 26.4 (*C*H$_2$), 14.3 (*C*H$_3$); FTIR (neat, film) 2929, 1723, 1550, 1509, 1240, 700 cm^{-1}; HRMS (EI) [$C_{19}H_{22}N_2O_5S$+H] calcd 391.1322, found 391.1318.

*4.8. Ethyl 4-(benzo[d][1,3]dioxol-5-yl)-3-nitropiperidine-2-carboxylate (**9**)*

To a cooled (0 ºC) and stirred solution of **1i** (25.0 mg, 0.058 mmol) in MeCN (1.00 mL) under N$_2$ was added a solution of CAN

(80.0 mg, 0.146 mmol) in H_2O (1.00 mL) dropwise. The resulting mixture was stirred at 0 °C for 30 min during which time the colour of mixture changed from wine red to orange. The reaction mixture was diluted with EtOAc (10 mL) and quenched with 10% $Na_2S_2O_3$ aq. solution (10 mL). Aqueous layer was extracted with another portion of EtOAc (10 mL) and combined organic layers were dried (Na_2SO_4) and concentrated to the free piperidine **9** (16.8 mg, quant, contain small amount of hydroquinone) as a brown oil which was used directly into next step. R$_f$ (70% EtOAc in hexane) 0.47; FTIR (neat, cm^{-1}) 3358, 2957, 2923, 1730, 1549, 1504, 1490, 1442, 1256, 1237, 1037; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.77 (1H, d, *J* = 8.0), 6.75 (1H, d, *J* = 1.8), 6.72—6.67 (1H, m), 5.95 (2H, q, *J* = 1.5), 5.29 (1H, dd, *J* = 4.2, 2.1), 4.36 (1H, dq, *J* = 10.8, 7.2, *A*BX$_3$ system), 4.33 (1H, dq, *J* = 10.8, 7.1, A*B*X$_3$ system), 4.27 (1H, d, *J* = 2.2), 3.26—3.15 (2H, m), 2.86 (1H, ddd, *J* = 13.4, 12.1, 3.2), 2.48 (1H, qd, *J* = 12.7, 4.5), 1.71 (1H, dq, *J* = 13.2, 3.3), 1.38 (3H, t, *J* = 7.1); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1 (*C*), 148.0 (*C*), 147.0 (*C*), 133.3 (*C*), 120.7 (*C*H), 108.5 (*C*H), 108.0 (*C*H), 101.3 (*C*H$_2$), 85.7 (*C*H), 62.4 (*C*H$_2$), 59.5 (*C*H), 42.4 (*C*H$_2$), 40.8 (*C*H), 24.8 (*C*H$_2$), 14.4 (*C*H$_3$). HRMS not recorded.

*4.9. Ethyl 4-(benzo[d][1,3]dioxol-5-yl)-3-nitro-1-(2,2,2-trifluoroacetyl)piperidine-2-carboxylate (**10**)*

To a cooled (-10 °C) and stirred solution of above free piperidine **9** in CH_2Cl_2 (1.00 mL) under N_2 was added TFAA (10 µL, 0.070 mmol) and pyridine (5.5 µL, 0.070 mmol) and the resulting mixture was stirred at this temperature for 10 min. The reaction was quenched with 1 M HCl aq (5.0 mL) and extracted with CH_2Cl_2 (10 mL). Combined organic layers were dried (Na_2SO_4) and concentrated. Chromatography of reside on silica gel, using 30% EtOAc in hexane, gave **10** (20.0 mg, 83% overall) as a colourless oil. R$_f$ (30% EtOAc in hexane) 0.32; FTIR (neat, cm^{-1}) 2984, 2908, 1742, 1697, 1554, 1506, 1491, 1446, 1235, 1205, 1170, 1147; HRMS (ESI-TOF) ; ^{1}H NMR (400 MHz, $CDCl_3$) a mixture of diastereomers, *dr* 85:15; major isomer: δ 6.77 (1H, d, *J* = 7.8), 6.70—6.59 (2H, m), 5.96 (2H, s), 5.89 (1H, t, *J* = 1.7), 5.49—5.42 (1H, m), 4.47—4.17 (3H, m), 3.39 (1H, ddd, *J* = 14.3, 13.0, 2.9), 3.19 (1H, dt, *J* = 13.3, 3.4), 2.67 (1H, qd, *J* = 13.3, 4.4), 1.92—1.78 (1H, m), 1.36 (3H, t, *J* = 7.1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (*C*), 157.2 (q, *J* = 37.2, *C*(O)CF$_3$), 148.3 (*C*), 147.6 (*C*), 130.9 (*C*), 120.5 (*C*H), 116.3 (q, *J* = 287.4, *C*F$_3$), 108.8 (*C*H), 107.5 (*C*H), 101.4 (*C*H$_2$), 84.5 (*C*H), 63.5 (*C*H$_2$), 55.5 (*C*H), 43.4 (*C*H$_2$), 41.2 (*C*H), 23.8 (*C*H$_2$), 14.2 (*C*H$_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.90 (minor isomer), -68.97 (major isomer). HRMS (ESI-TOF, m/z) calcd. For $C_{17}H_{18}N_2O_7F_3$ [M+H]$^+$ 419.1066, found 419.1047.

*4.10. 4-(benzo[d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)-3-nitropiperidin-2-yl)-methanol (**11**)*

To a cooled (0 °C) and stirred solution of ester **1i** (130 mg, 0.30 mmol) in THF (5.00 mL) was added $LiBH_4$ (20.0 mg, 0.91 mmol) in one portion and the resulting mixture was stirred at 0 °C for 10 min and then at room temperature until full consumption of starting material. The reaction mixture was cooled to 0 °C and quenched with sat. NH_4Cl aqueous solution (10.0 mL), followed by extraction with EtOAc (10.0 mL x 3). The combined organic layers were dried (Na_2SO_4) and concentrated to give alcohol **11** (104 mg, 90%) as a white foam. R$_f$ (33% EtOAc in hexane) 0.25; FTIR (neat, cm^{-1}) 3385, 2894, 1545, 1501, 1238, 1037; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91—6.77 (7H, m), 5.96—5.94 (2H, m), 5.12—5.10 (1H, m), 4.45—4.40 (1H, m), 3.92—3.89 (2H, m), 3.77 (3H, s), 3.63—3.60 (1H, m), 3.33 (1H, q, *J* = 4.2 Hz), 3.31—3.29 (1H, m), 2.86 (1H, dq, *J* = 12.6, 4.8 Hz), 1.91—1.89 (1H, m), 1.67 (1H, t, *J* = 5.4 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) □ 154.0 (Ar*C*), 148.0 (Ar*C*), 146.9 (Ar*C*), 144.0 (Ar*C*), 133.2 (Ar*C*), 120.8 (Ar*C*H), 119.1 (Ar*C*H), 114.7 (Ar*C*H), 108.5 (Ar*C*H), 108.1 (Ar*C*H), 101.2 (*C*H$_2$), 85.7 (*C*H), 63.3 (*C*H), 58.4 (*C*H$_2$), 55.7 (*C*H$_3$), 43.7 (*C*H$_2$), 38.8 (*C*H), 24.2 (*C*H$_2$). HRMS (ESI, m/z) calcd. for $C_{20}H_{23}N_2O_6$ [M+H]$^+$ 387.1566, found 387.1567.

*4.11. Ethyl -4-(benzo[d][1,3]dioxol-5-yl)-3-(3-methoxy-3-oxopropyl)-1-(4-methoxy-phenyl)-3-nitropiperidine-2-carboxylate (**12**)*

To a stirred solution of **1i** (50.0 mg, 0.117 mmol) in MeCN (1.00 mL) was added methyl acrylate (0.03 mL, 0.035 mmol) and Triton-B (40% w/w in MeOH, 2 drops) and the resulting solution was stirred at room temperature overnight. The reaction mixture was quenched with sat. NH_4Cl aqueous solution (10.0 mL) and extracted with EtOAc (10.0 mL x 2). The combined organic layers were dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel, using 20% EtOAc in hexane, gave **12** (21.0 mg, 35%) as a yellow solid. R$_f$ (20% EtOAc in hexane) 0.14; FTIR (neat, cm^{-1}) 2958, 1731, 1542, 1508, 1487, 1440, 1239, 1191, 1037; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.94 (2H, d, *J* = 9.0 Hz), 6.84 (2H, d, *J* = 9.0 Hz), 6.75 (1H, d, *J* = 8.0 Hz), 6.71 (1H, d, *J* = 1.8 Hz), 6.64 (1H, dd, *J* = 8.0, 1.9 Hz), 6.02 – 5.91 (2H, m), 4.45 (1H, s), 4.31 (1H, dd, *J* = 13.3, 4.1 Hz), 4.07 (2H, qd, *J* = 7.2, 0.9 Hz), 3.89 (1H, td, *J* = 12.2, 3.9 Hz), 3.78 (3H, s), 3.67 (3H, s), 3.28 (1H, ddd, *J* = 11.9, 5.7, 1.8 Hz), 2.86–2.75 (1H, m), 2.53–2.28 (4H, m), 2.04–1.98 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.7 (*C*O$_2$), 168.8 (*C*O$_2$), 155.2 (Ar*C*), 147.7 (Ar*C*), 147.3 (Ar*C*), 143.1 (Ar*C*), 131.4 (Ar*C*), 122.9 (Ar*C*H), 120.5 (Ar*C*H), 114.6 (Ar*C*H), 109.6 (Ar*C*H), 108.3 (Ar*C*H), 101.3 (*C*H$_2$), 94.8 (*C*), 64.2 (*C*H), 60.9 (*C*H$_2$), 55.7 (*C*H$_3$), 52.1 (*C*H$_3$), 44.3 (*C*H$_2$), 43.7 (*C*H), 28.8 (*C*H$_2$), 28.5 (*C*H$_2$), 24.81 (*C*H$_2$), 14.1 (*C*H$_3$). HRMS (ESI-TOF, m/z) calcd. For $C_{26}H_{31}N_2O_9$ [M+H]$^+$ 515.2029, found 515.2023.

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Supplementary Material

NMR spectra for all compounds (PDF).