A Two-Step Synthesis of 3,4-Disubstituted Piperidines from Acyclic Precursors through Tetrahydropyridine Intermediates

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Abstract: Cyclocondensation between acyclic 5-aminopent-2-enoate esters and aliphatic aldehydes containing an unsubstituted α-methylene unit affords 1,2,3,4-tetrahydropyridine derivatives in good yields. The reaction has been applied to a range of aldehydes, showing good functional group tolerance. Chemoselective hydride reduction of the enamine double bond provides 3,4-disubstituted tertiary piperidine derivatives with acceptable to good diastereoselectivities, whereas catalytic hydrogenation of N-benzyl derivatives leads directly to the corresponding secondary piperidines.

Key words: condensation, cyclizations, reductions, piperidines, stereoselective synthesis

The 1,2,3,4-tetrahydropyridine substructure **5** (Scheme 1) is interesting because of its presence in alkaloids such as cathenamine (**1**) and vallesiachotamine (**2**) and also as a key functionality in synthetic schemes leading to several natural products (Figure 1).[1]

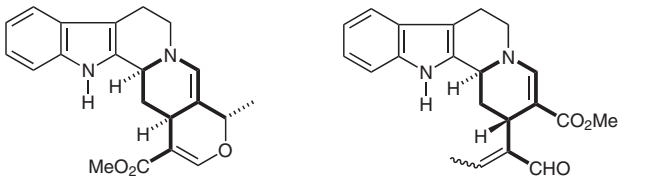
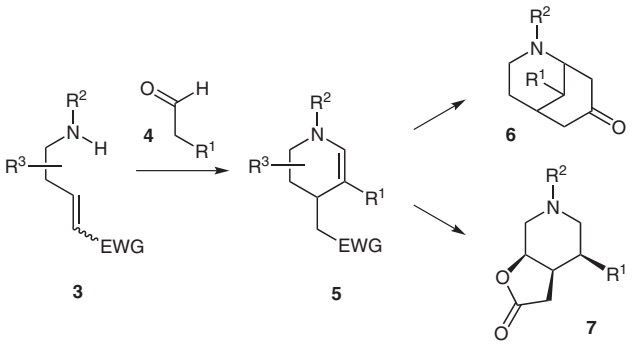


Figure 1

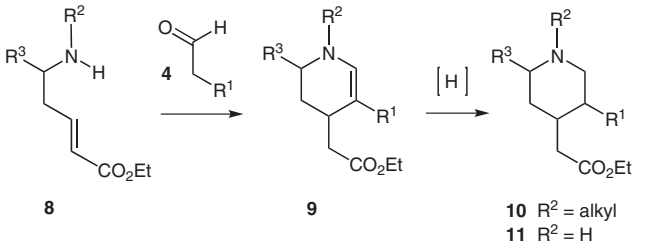
We have recently described the synthesis of 2-azabicyclo[3.3.1]nonanes **6**[2] and 3-hydroxypiperidine derivatives **7**[3] using tetrahydropyridine precursors **5** (where R^1, R^2 = alkyl). These applications took advantage of the ability of the enamine functionality to generate iminium ions or undergo double bond hydrogenation, respectively. Cyclic enamines **5** were readily accessed by condensation of the appropriate amine **3** and aldehyde **4** precursors through presumed acyclic enamine intermediates.[2–4] The preparation of bicyclic piperidines **7** was studied in some detail and found to be compatible with different substitution patterns at R^2, as well as with the presence at R^1 of functionality, which proved useful for further transformations.[3,4] Furthermore, in these rigid bicyclic systems good



Scheme 1

control of the relative stereochemistry over three contiguous stereogenic centers of **7** was easily attained.[3]

On the other hand, the application of this method to the preparation of monocyclic enamines of type **9** (Scheme 2) has been limited to N-benzyl-substituted examples (where additionally R^3 = H) derived from simple aliphatic unfunctionalized aldehydes **4**,[2] whereas studies devoted to evaluate the generality and stereoselectivity of piperidine synthesis using the strategy depicted in Scheme 2 are lacking.[5] In this paper we disclose the details of a study directed at determining the practicality of the preparation of substituted monocyclic piperidines **10** and **11** (Scheme 2) from selected acyclic amines **8** and aldehydes **4** through tetrahydropyridines **9**.



Scheme 2

Specific target areas of study have included: 1. the scope in the carbonyl component; 2. the determination of the stereoselectivity of the cyclization and reduction steps in these flexible systems (i.e., in the absence of the geometrical constraints imposed by the rigidity of the bicyclic systems **7**[3]); and 3. the possibility of extending this strategy to the preparation of secondary piperidines **11** (R^2 = H)

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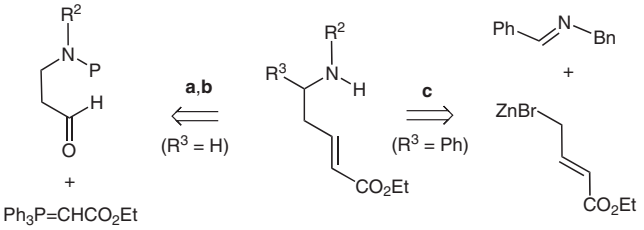
by using appropriate R^2 substituents in the secondary amine cyclization precursors **8**.

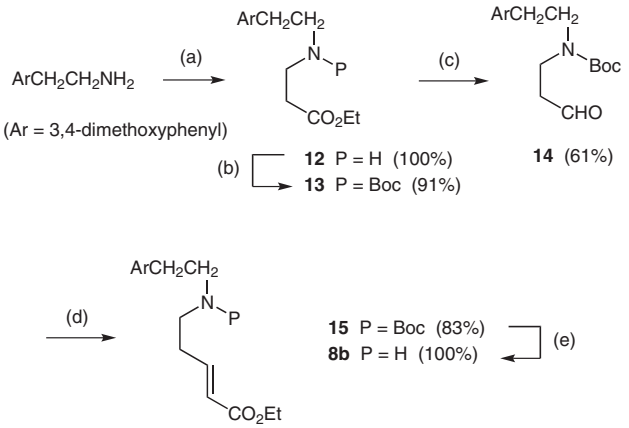
Amines **8** were prepared by one of the two routes indicated in Scheme 3 that involved either zinc dienolate addition to an imine[6] or Wittig-type homologation of appropriate aldehydes. Amines **8a**,**b** were selected to exemplify the preparation of both tertiary (using **8b**) and secondary piperidines (using **8a**[7] with a subsequent debenzylation step), whereas the use of the α-substituted amine **8c**[6a] would provide a test of diastereoselectivity in the formation of **9**.



8a R^2 = Bn, R^3 = H
8b R^2 = 2-(3,4-dimethoxyphenyl)ethyl, R^3 = H
8c R^2 = Bn, R^3 = Ph

Scheme 3

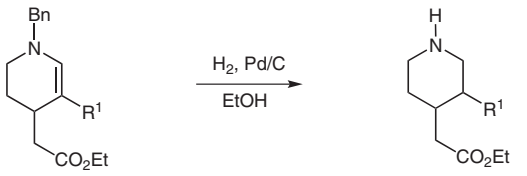
The previously unknown **8b** was prepared starting from 3,4-dimethoxyphenethylamine according to Scheme 4. Thus, initial conjugate addition to ethyl acrylate was followed by amine protection and carbonyl reduction to afford aldehyde **14**. Wittig reaction and acidic removal of the Boc-protecting group provided the desired **8b**.



Scheme 4 *Reagents and conditions:* (a) ethyl acrylate, EtOH, r.t.; (b) $(Boc)_2O$, EtOAc, 0 °C to r.t.; (c) DIBAL-H, toluene, –78 °C; (d) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, r.t.; (e) TFA, CH_2Cl_2, 0 °C.

Tetrahydropyridines **9** were then obtained by stirring under reflux equimolar amounts of amine **8** and aldehyde **4** in the appropriate solvent. Results are collected in Table 1, which also includes previously reported data (entries 3, 6, and 8) to enable appropriate comparisons. Acetonitrile and ethanol proved to be adequate solvents in this condensation, but benzene failed to give the desired products even with Dean–Stark removal of water. The use of molecular sieves was beneficial in terms of yield when acetonitrile was used as the solvent (cf. entries 1 and 2), but was not required in the case of ethanol (entries 13 and 14), a solvent that provided shorter reactions times. Both linear and branched aldehydes worked well. One exception was phenylacetaldehyde, which reacted rapidly with formation of a presumed acyclic enamine intermediate,[3,8] but this material failed to cyclize to the desired tetrahydropyridine. Likewise, ketones were found not to participate in this reaction, in this case the starting materials were recovered after prolonged heating when **8a** was treated with cyclohexanone, acetophenone, or diethyl ketone. As shown by entries 9–11 and 13–17, useful functionality, both at the amine and aldehyde components, was allowed in the preparation of **9**. However, branching at the amine α-position resulted in lower reactivity (entry 18) and, additionally, this cyclization was only moderately diastereoselective.

Reduction of the enamine double bond afforded the corresponding saturated piperidines in good yields with moderate diastereoselectivity, the *trans*-isomer being formed predominantly (Table 2). Hydride-based and catalytic hydrogenation methods were both found to be effective. Conditions based on sodium cyanoborohydride/zinc chloride (Method A, entries 1, 2, 4, and 5) followed those previously described for **10a** (entry 1),[2] while initial protonation of the enamine, followed by sodium borohydride reduction, proved also effective in the single case tried (Method B, entry 3). Standard catalytic hydrogenation conditions provided yields and diastereoselectivities in line with those obtained in the hydride reductions (Method C, entries 6 and 7; see also Scheme 5). However, in comparison with the similar double bond reductions previously described leading to the more rigid bicyclic piperidines **7**,[3] the greater conformational flexibility of tetrahydropyridines **9** resulted in lower diastereoselectivities. Nevertheless, useful isolated overall yields for the major isomers were realized in all cases. The *cis*/*trans* relative configurations of piperidines **10** and **11** were assigned by analogy with the known product **10a**.[9] In support of these assignments, the expected γ-gauche effects were observed in the ^{13}C NMR resonances of the piperidine ring C3 and C4, which were deshielded in the *trans*-isomers relative to the more congested *cis* counterparts.[7,10–13]



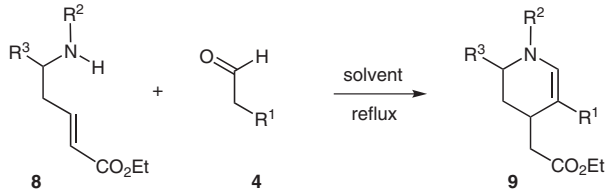
9c R^1 = *i*-Pr
9f R^1 = $(CH_2)_3CO_2Et$

11c (65%, *cis*/*trans* = 26:74)
11f (68%, *cis*/*trans* = 30:70)

Scheme 5

Synthetic advantage can be also taken from the choice between two alternative reducing methods for the enamine double bond. For example, the hydride method allowed

Table 1 Preparation of Tetrahydropyridines **9** from Amines **8** and Aldehydes **4**



Entry	Substrate	R^1	Solvent	Time (h)	Product	Yield[a] (%)
1	**8a**	Et	MeCN	9	**9a**	52
2	**8a**	Et	MeCN[b]	14	**9a**	71
3	**8a**	Et	EtOH	5.5	**9a**	77[c]
4	**8a**	Bu	EtOH[b]	7	**9b**	80
5	**8a**	*i*-Pr	MeCN[b]	19	**9c**	70
6	**8a**	*i*-Pr	EtOH[b]	3	**9c**	67[c]
7	**8a**	Bn	MeCN[b]	15	**9d**	79
8	**8a**	Bn	EtOH[b]	3	**9d**	75[c]
9	**8a**	CH_2Ar[d]	MeCN[b]	12	**9e**	81
10	**8a**	$(CH_2)_3CO_2Et$	MeCN[b]	20	**9f**	64
11	**8a**	$(CH_2)_2CH{=}CHCO_2Et$	MeCN[b]	14	**9g**	77
12	**8a**	Ph	MeCN[b]	3	–	0[e]
13	**8b**	Et	EtOH	2	**9h**	77
14	**8b**	Et	EtOH[b]	1.5	**9h**	75
15	**8b**	*n*-C_9H_{19}	EtOH	2.5	**9i**	77
16	**8b**	Bn	EtOH	2	**9j**	86
17	**8b**	$(CH_2)_3CO_2Et$	EtOH	3	**9k**	69
18	**8c**	Bn	EtOH	24	**9l**	59[f]

[a] Yield of chromatographically purified products.
[b] Addition of 4 Å MS.
[c] Ref. 2.
[d] Ar = 3,4-dimethoxyphenyl.
[e] See text.
[f] dr = 63:37.

chemoselective enamine reduction in the presence of a second C=C bond (entry 5), whereas hydrogenation conditions applied to benzyl-protected enamines **9** (R^2 = Bn) resulted in both double bond reduction and debenzylation leading to formation of secondary piperidines **11** (Scheme 5). Interestingly, under these conditions reduction of the enamine double bond was observed to take place rapidly, as evidenced by TLC monitoring of the reaction, and was then followed by slower removal of the benzyl group. In any case, two-step preparation of secondary piperidines **11** from amines **8** and aldehydes **4** is readily available.

In conclusion, secondary N-alkyl- and N-benzyl-substituted acyclic amines, containing a suitably positioned electron-deficient double bond, condense effectively with a range of aldehydes to afford substituted tetrahydropyridines, which undergo chemoselective enamine reduction to yield tertiary piperidine derivatives with acceptable to good diastereoselectivities. In the case of N-benzyl-substituted tetrahydropyridines, under catalytic hydrogenation conditions enamine double bond reduction is followed by debenzylation and this gives alternative access to the corresponding secondary piperidines.

All reactions involving air- and moisture-sensitive materials were performed under an atmosphere of dry argon. CH_2Cl_2, toluene, and MeCN were freshly distilled from CaH_2. Et_2O was freshly distilled from Na/benzophenone. EtOH and MeOH were dried with Mg/I_2. Flash column chromatography was performed on silica gel (230–

Table 2 Reduction of Enamines **9**[a]

9 **10**

Entry	Substrate	R^1	R^2	Method	Product	Yield[b] (%) (ratio *cis*/*trans*)
1	**9a**	Et	Bn	A	**10a**	79 (30:70)[c]
2	**9c**	*i*-Pr	Bn	A	**10c**	89 (18:82)
3	**9d**	Bn	Bn	B	**10d**	76 (25:75)
4	**9e**	CH_2Ar[d]	Bn	A	**10e**	91 (13:87)
5	**9g**	$(CH_2)_2CH{=}CHCO_2Et$	Bn	A	**10g**	73 (26:74)
6	**9h**	Et	$(CH_2)_2Ar$[d]	C	**10h**	82 (37:63)
7	**9j**	Bn	$(CH_2)_2Ar$[d]	C	**10j**	95 (22:78)

[a] Method A: $NaBH_3CN$, $ZnCl_2$, MeOH, r.t.; B: 1. TFA, Et_2O, 0 °C; 2. evaporate; 3. $NaBH_4$, EtOH, 0 °C to r.t.; C: Pd/C, H_2.
[b] Yield of isolated pure product.
[c] Ref. 2.
[d] Ar = 3,4-dimethoxyphenyl.

400 mesh). NMR spectra were obtained at 250 MHz for ^1H and 62.9 MHz for ^{13}C with $CDCl_3$ as solvent and internal reference [δ = 7.26 (^1H), δ = 77.0 (^{13}C)]. The DEPT sequence was routinely used for ^{13}C multiplicity assignment. IR data include only characteristic absorptions. Mass spectra were obtained at 70 eV. The following compounds have been previously reported: **8a**,[7] **8c**,[6a] **9a**,[2] **9c**,[2] **9d**,[2,7] **9e**,[7] and **10a**.[9]

Ethyl 3-{[2-(3,4-Dimethoxyphenyl)ethyl]amino}propanoate (12)

Ethyl acrylate (19.3 mL, 0.178 mol) was added to a soln of 2-(3,4-dimethoxyphenyl)ethylamine (30.7 mL, 0.178 mol) in anhyd EtOH (135 mL) at r.t. The resulting mixture was stirred for 25 h and evaporated under reduced pressure to afford **12** (50.1 g, quantitative) as an orange oil.

IR (neat): 3320 (N–H), 1735 cm^{-1} (C=O).

^1H NMR: δ = 1.07 (t, *J* = 7.1 Hz, 3 H), 1.19 (br s, 1 H), 2.33 (t, *J* = 6.5 Hz, 2 H), 2.55–2.61 (m, 2 H), 2.68–2.77 (m, 4 H), 3.68 (s, 3 H), 3.71 (s, 3 H), 3.95 (q, *J* = 7.1 Hz, 2 H), 6.57–6.66 (m, 3 H).

^{13}C NMR: δ = 13.7, 34.3, 35.4, 44.5, 50.7, 55.2, 55.3, 59.8, 110.7, 111.4, 120.0, 132.0, 146.8, 148.3, 172.1.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_{23}NO_4$: 281.1627; found: 281.1637.

Ethyl 3-{(*tert*-Butoxycarbonyl)[2-(3,4-dimethoxyphenyl)ethyl]amino}propanoate (13)

$(Boc)_2O$ (0.34 mL, 1.47 mmol) was added to a soln of **12** (412 mg, 1.47 mmol) in EtOAc (1 mL) at 0 °C. The resulting mixture was allowed to warm to r.t. and stirred for 20 h. After dilution with EtOAc (9 mL) the soln was washed successively with 1 M HCl (5 mL), sat. $NaHCO_3$ (5 mL), and brine (5 mL) and dried (Na_2SO_4). After evaporation, the crude product was purified by flash chromatography (hexanes–EtOAc, 80:20) to yield **13** (510 mg, 91%) as a pale yellow oil as a rotamer mixture.

IR (neat): 1740 (C=O), 1700 cm^{-1} (NCO).

^1H NMR: δ = 1.24 (t, *J* = 7.1 Hz, 3 H), 1.44 (s, 9 H), 2.52–2.54 (br, 2 H), 2.74–2.76 (br, 2 H), 3.38–3.40 (br, 4 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 6.67–6.81 (m, 3 H).

^{13}C NMR: δ = 14.0, 28.2, 33.3, 33.9, 34.7, 43.5, 43.7, 49.7, 49.9, 55.5, 55.6, 60.3, 79.3, 79.4, 111.0, 111.8, 120.5, 131.5, 147.3, 148.6, 154.9, 171.7, 171.9.

Anal. Calcd for $C_{20}H_{31}NO_6$: C, 62.96; H, 8.20; N, 3.67. Found: C, 62.80; H, 8.26; N, 3.51.

***tert*-Butyl [2-(3,4-Dimethoxyphenyl)ethyl](3-oxopropyl)carbamate (14)**

A 1 M soln of DIBAL-H in hexanes (3.3 mL, 3.3 mmol) was added dropwise to a soln of **13** (1.0 g, 2.6 mmol) in toluene (8 mL) at –78 °C under argon. The resulting mixture was stirred for 10 min and anhyd EtOH (0.13 mL) was added dropwise, followed by $Na_2SO_4{\cdot}10\ H_2O$ (200 mg). The mixture was then allowed to warm to r.t. and it was filtered over Celite. The solid was washed with EtOAc (150 mL) and the combined filtrate and washings were evaporated to dryness. The crude product was purified by flash chromatography (hexanes–EtOAc, 72:28) to yield **14** (0.55 g, 61%) as a colorless oil as a rotamer mixture.

IR (neat): 1725 (CHO), 1695 cm^{-1} (NCO).

^1H NMR: δ = 1.40 (br s, 9 H), 2.61–2.71 (br, 4 H), 3.38 (br, 4 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 6.65–6.78 (m, 3 H), 9.73 (s, 1 H).

^{13}C NMR: δ = 28.2, 34.0, 34.7, 41.4, 43.2, 43.6, 49.7, 50.0, 55.7, 55.7, 79.6, 79.9, 111.1, 111.8, 120.6, 131.5, 147.4, 148.7, 154.9, 155.2, 200.7, 201.1.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{18}H_{27}NO_5$: 337.1889; found: 337.1890.

Ethyl 5-{(*tert*-Butoxycarbonyl)[2-(3,4-dimethoxyphenyl)ethyl]amino}pent-2-enoate (15)

A soln of $Ph_3P{=}CHCO_2Et$ (661 mg, 1.8 mmol) and **14** (552 mg, 1.6 mmol) in CH_2Cl_2 (6 mL) was stirred at r.t. for 11 h and then it was evaporated under reduced pressure. The residue was purified by flash chromatography (hexanes–EtOAc, 80:20) to yield (*Z*)-**15** (21

mg, 3%) and (*E*)-**15** (548 mg, 83%) as rotamer mixtures; ratio *Z*/*E* 4:96.

***E*-Isomer (*E*)-15**
Colorless oil.

IR (neat): 1720 (C=O), 1695 (NCO), 1655 cm^{-1} (C=C).

^1H NMR: δ = 1.27 (t, *J* = 7.1 Hz, 3 H), 1.45 (br s, 9 H), 2.36 (br, 2 H), 2.75 (br, 2 H), 3.22–3.33 (br, 4 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 5.81 (d, *J* = 15.5 Hz, 1 H), 6.66–6.94 (m, 4 H).

^{13}C NMR: δ = 14.1, 28.2, 31.2, 31.8, 34.0, 34.7, 46.1, 46.4, 49.3, 49.7, 55.7, 55.7, 60.1, 79.5, 111.1, 111.8, 120.6, 122.8, 131.5, 145.5, 147.3, 148.7, 155.1, 166.1.

Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.83; H, 8.17; N, 3.44. Found: C, 64.54; H, 8.33; N, 3.75.

***Z*-Isomer (*Z*)-15**
Colorless oil.

IR (neat): 1720 (C=O), 1695 (NCO), 1645 cm^{-1} (C=C).

^1H NMR: δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 1.43 (br s, 9 H), 2.74–2.88 (br, 4 H), 3.25–3.35 (br, 4 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 5.81 (d, *J* = 11.5 Hz, 1 H), 6.20 (br, 1 H), 6.70–6.80 (br, 3 H).

^{13}C NMR: δ = 14.1, 27.9, 28.2, 33.9, 34.6, 45.8, 46.5, 48.9, 55.6, 55.7, 59.7, 79.2, 111.0, 111.8, 120.6, 121.1, 131.7, 146.2, 146.5, 147.2, 148.6, 155.3, 166.0.

Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.83; H, 8.17; N, 3.44. Found: C, 64.75; H, 8.31; N, 3.30.

Ethyl (*E*)-5-[2-(3,4-Dimethoxyphenyl)ethylamino]pent-2-enoate (8b)
TFA (1.5 mL) was added dropwise to a soln of (*E*)-**15** (458 mg, 1.10 mmol) in anhyd CH_2Cl_2 (8.4 mL) at 0 °C under argon. The mixture was allowed to warm to r.t. and then stirred for 3 h. After evaporation, the residue was dissolved in EtOAc (20 mL) and the soln was washed with sat. $NaHCO_3$ (20 mL) and dried (Na_2SO_4). Solvent evaporation afforded **8b** (346 mg, quantitative yield) as a pale yellow oil, which was used without further purification.

IR (neat): 3310 (N–H), 1720 (C=O), 1660 cm^{-1} (C=C).

^1H NMR: δ = 1.28 (t, *J* = 7.1 Hz, 3 H), 1.72 (br s, 1 H), 2.35–2.42 (m, 2 H), 2.72–2.89 (m, 6 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 5.84 (d, *J* = 15.7 Hz, 1 H), 6.72–6.96 (m, 4 H).

^{13}C NMR: δ = 13.9, 32.4, 35.5, 47.6, 50.8, 55.4, 55.5, 59.9, 110.9, 111.5, 120.2, 122.4, 132.0, 146.2, 147.1, 148.5, 166.0.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{17}H_{25}NO_4$: 307.1784; found: 307.1790.

Tetrahydropyridines 9; General Procedure
A mixture of amine **8** (1.9 mmol) and aldehyde **4** (1.9 mmol) in anhyd solvent (26 mL) was refluxed for the time indicated in Table 1. Where appropriate (Table 1), 4 Å MS (4.8 g) was also used. After cooling, the mixture was filtered over Celite and the solvents were evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel saturated with Et_3N). Purification details and characterization data are provided below for the individual cases.

Ethyl (1-Benzyl-5-butyl-1,2,3,4-tetrahydropyridin-4-yl)acetate (9b)
Chromatography: hexanes–Et_3N, 98:2; yellowish oil.

IR (neat): 1740 (C=O), 1680 cm^{-1} (C=C).

^1H NMR: δ = 0.89 (t, *J* = 6.9 Hz, 3 H), 1.22–1.45 (m, 7 H), 1.59–1.69 (m, 1 H), 1.78–2.00 (m, 3 H), 2.06 (dd, *J* = 15.7, 11.3 Hz, 1 H), 2.52–2.81 (m, 4 H), 3.91 (s, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 5.81 (s, 1 H), 7.22–7.35 (m, 5 H).

^{13}C NMR: δ = 14.0, 14.2, 22.4, 27.4, 30.3, 30.8, 32.4, 39.7, 43.3, 59.6, 60.2, 111.1, 127.0, 128.2, 128.3, 132.4, 138.5, 173.2.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{29}NO_2$: 315.2198; found: 315.2198.

Ethyl {1-Benzyl-5-[3-(ethoxycarbonyl)propyl]-1,2,3,4-tetrahydropyridin-4-yl}acetate (9f)
Chromatography: hexanes–Et_3N, 98:2; yellowish oil.

IR (neat): 1730 (C=O), 1660 cm^{-1} (C=C).

^1H NMR: δ = 1.23 (t, *J* = 7.1 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.60–1.94 (m, 5 H), 2.00–2.10 (m, 2 H), 2.17–2.34 (m, 2 H), 2.49–2.57 (m, 2 H), 2.64–2.80 (m, 2 H), 3.91 (s, 2 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 5.81 (s, 1 H), 7.20–7.34 (m, 5 H).

^{13}C NMR: δ = 14.2, 23.8, 27.3, 29.9, 32.0, 33.6, 39.6, 43.1, 59.5, 60.1, 60.1, 109.1, 127.0, 128.0, 128.2, 133.2, 138.3, 172.9, 173.8.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{22}H_{31}NO_4$: 373.2253; found: 373.2245.

Ethyl {(*E*)-1-Benzyl-5-[4-(ethoxycarbonyl)but-3-enyl]-1,2,3,4-tetrahydropyridin-4-yl}acetate (9g)
Chromatography: hexanes–Et_3N, 98:2; yellowish oil.

IR (neat): 1730 (C=O), 1660 cm^{-1} (C=C).

^1H NMR: δ = 1.24 (t, *J* = 7.1 Hz, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.60–1.70 (m, 1 H), 1.81–2.44 (m, 6 H), 2.47–2.58 (m, 2 H), 2.58–2.82 (m, 2 H), 3.92 (s, 2 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 5.81 (dt, *J* = 15.7, 1.4 Hz, 1 H), 5.82 (s, 1 H), 6.96 (dt, *J* = 15.6, 6.6 Hz, 1 H), 7.01–7.35 (m, 5 H).

^{13}C NMR: δ = 14.3, 27.4, 30.2, 31.3, 31.6, 39.7, 43.1, 59.5, 60.1, 60.3, 108.6, 121.3, 127.1, 128.1, 128.3, 133.3, 138.4, 149.0, 166.7, 172.9.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{23}H_{31}NO_4$: 385.2253; found: 373.2258.

Ethyl {1-[2-(3,4-Dimethoxyphenyl)ethyl]-5-ethyl-1,2,3,4-tetrahydropyridin-4-yl}acetate (9h)
Chromatography: hexanes–EtOAc–Et_3N, 90:8:2; pale yellow oil.

IR (neat): 1735 (C=O), 1660 cm^{-1} (C=C).

^1H NMR: δ = 0.97 (t, *J* = 7.4 Hz, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.64–1.74 (m, 1 H), 1.84–1.97 (m, 3 H), 2.09 (dd, *J* = 15.6, 11.2 Hz, 1 H), 2.53–2.60 (m, 2 H), 2.65–2.78 (m, 2 H), 2.81–2.93 (m, 2 H), 2.97–3.03 (m, 2 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 5.67 (s, 1 H), 6.70–6.81 (m, 3 H).

^{13}C NMR: δ = 13.3, 14.1, 25.4, 27.5, 30.2, 33.6, 39.6, 43.2, 55.6, 55.7, 57.3, 60.0, 111.0, 111.8, 111.9, 120.4, 130.9, 132.4, 147.1, 148.6, 173.0.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{21}H_{31}NO_4$: 361.2253; found: 361.2272.

Ethyl {1-[2-(3,4-Dimethoxyphenyl)ethyl]-5-nonyl-1,2,3,4-tetrahydropyridin-4-yl}acetate (9i)
Chromatography: hexanes–EtOAc–Et_3N, 90:8:2; yellowish oil.

IR (neat): 1735 (C=O), 1660 cm^{-1} (C=C).

^1H NMR: δ = 0.87 (t, *J* = 6.3 Hz, 3 H), 1.26–1.30 (m, 17 H), 1.65–1.95 (m, 4 H), 2.08 (dd, *J* = 15.8, 11.5 Hz, 1 H), 2.54–2.60 (m, 2 H), 2.67–2.75 (m, 2 H), 2.86–2.90 (m, 2 H), 2.99 (t, *J* = 7.7 Hz, 2 H), 3.86 (2 s, 6 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 5.68 (s, 1 H), 6.70–6.81 (m, 3 H).

^{13}C NMR: δ = 14.1, 14.2, 22.6, 27.6, 28.7, 29.3, 29.6, 30.2, 31.9, 32.7, 33.6, 39.7, 43.3, 55.7, 55.8, 57.4, 60.2, 110.7, 111.0, 111.9, 120.5, 131.8, 132.5, 147.2, 148.6, 173.1.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{28}H_{45}NO_4$: 459.3349; found: 459.3338.

Ethyl {1-[2-(3,4-Dimethoxyphenyl)ethyl]-5-benzyl-1,2,3,4-tetrahydropyridin-4-yl}acetate (9j)
Chromatography: hexanes–EtOAc–Et_3N, 86:12:2; orange oil.

IR (neat): 1730 (C=O), 1660 cm^{-1} (C=C).

^1H NMR: δ = 1.23 (t, *J* = 7.1 Hz, 3 H), 1.63–1.73 (m, 1 H), 1.77–1.90 (m, 1 H), 2.10 (dd, *J* = 14.5, 10.1 Hz, 1 H), 2.38–2.47 (m, 1 H), 2.53 (dd, *J* = 14.5, 3.5 Hz, 1 H), 2.63–2.81 (m, 2 H), 2.93 (dd, *J* = 7.5, 3.9 Hz, 2 H), 3.05 (t, *J* = 7.6 Hz, 2 H), 3.20 and 3.24 (AB q, *J* = 15.3 Hz, 2 H), 3.87 (s, 3 H), 3.87 (s, 3 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 5.74 (s, 1 H), 6.70–6.82 (m, 3 H), 7.14–7.30 (m, 5 H).

^{13}C NMR: δ = 14.2, 27.3, 30.1, 33.8, 39.4, 39.6, 42.8, 55.7, 55.8, 57.2, 60.1, 108.8, 111.1, 111.9, 120.5, 125.7, 128.1, 128.5, 132.4, 133.7, 141.2, 147.2, 148.7, 172.8.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{26}H_{33}NO_4$: 423.2410; found: 423.2405.

Ethyl {1-[2-(3,4-Dimethoxyphenyl)ethyl]-5-[3-(ethoxycarbonyl)propyl]-1,2,3,4-tetrahydropyridin-4-yl}acetate (9k)
Chromatography: hexanes–EtOAc–Et_3N, 84:14:2; yellow oil.

IR (neat): 1735 (C=O), 1655 cm^{-1} (C=C).

^1H NMR: δ = 1.21–1.28 (m, 6 H), 1.55–1.90 (m, 5 H), 1.92–2.13 (m, 2 H), 2.22–2.32 (m, 2 H), 2.50–2.58 (m, 2 H), 2.63–2.75 (m, 2 H), 2.86–2.90 (m, 2 H), 2.99 (t, *J* = 7.7 Hz, 2 H), 3.84, 3.85, 3.86 (3 s, 6 H), 4.06–4.17 (m, 4 H), 5.68 (s, 1 H), 6.69–6.80 (m, 3 H).

^{13}C NMR: δ = 14.2, 23.8, 27.5, 29.9, 32.0, 33.6, 33.7, 39.6, 43.1, 55.7, 55.8, 57.3, 60.1, 60.2, 108.6, 111.1, 111.9, 120.5, 132.4, 132.6, 147.2, 148.7, 173.0, 173.8.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{25}H_{37}NO_6$: 447.2621; found: 447.2681.

Ethyl (1,5-Dibenzyl-2-phenyl-1,2,3,4-tetrahydropyridin-4-yl)acetate (9l)
Chromatography: hexanes–Et_3N, 98:2; orange oil; dr 63:37.

IR (neat): 1730 (C=O), 1660 cm^{-1} (C=C).

^1H NMR: δ = 1.14 and 1.18 (2 t, *J* = 7.1 Hz, 3 H), 1.77–2.15 (m, 3 H), 2.40–2.57 and 2.69–2.72 (2 m, 2 H), 3.21–3.35 (m, 2 H), 3.63 and 3.66 (2 d, *J* = 14.6 Hz, 1 H), 3.84 (td, *J* = 10.7, 3.1 Hz, 1 H), 3.91–4.08 (m, 3 H), 5.99 (s, 1 H), 7.04–7.39 (m, 15 H).

^{13}C NMR: δ = 14.1, 14.2, 30.6, 31.5, 37.4, 37.9, 38.5, 39.5, 39.7, 39.9, 55.6, 55.7, 60.1, 60.2, 110.3, 110.5, 125.8, 125.9, 127.1, 127.2, 127.2, 127.3, 128.2, 128.2, 128.2, 128.4, 128.5, 128.5, 128.6, 128.6, 128.7, 134.2, 135.1, 137.7, 137.8, 140.6, 141.1, 142.9, 143.0, 172.6, 172.8.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{29}H_{31}NO_2$: 425.2355; found: 425.2353.

Piperidines 10; General Procedures
Method A: 0.5 M $ZnCl_2$ in THF (4.1 mL, 2.05 mmol) was added to a suspension of $NaBH_3CN$ (0.268 g, 4.20 mmol) in MeOH (2.9 mL) under argon, and the mixture was stirred at r.t. for 1 h and then added to a soln of **9** (2.02 mmol) in MeOH (4.4 mL). The soln was stirred further 2 h and poured over 1 M NaOH (50 mL). The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried (Na_2SO_4). After evaporation, the residue was purified by flash chromatography (silica gel saturated with Et_3N).

Method B: TFA (2.57 mmol) was added dropwise to a soln of **9** (1.85 mmol) in Et_2O (28 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, allowed to warm to r.t. and evaporated under reduced pressure. The residue was dissolved in anhyd EtOH (7 mL) and to the cool soln (0 °C) $NaBH_4$ (3.80 mmol) was added. The resulting mixture was allowed to warm to r.t. and evaporated under reduced pressure. After addition of 1 M KOH (25 mL), the soln was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extracts were dried (Na_2SO_4). After evaporation, the crude product was purified by flash chromatography (silica gel saturated with Et_3N).

Method C: A deoxygenated mixture of **9** (1.0 mmol), 10% Pd/C (14 mg), and abs EtOH (12 mL) was treated with H_2 (1 atm) for 2 h. The resulting mixture was filtered over Celite, and the solid was washed with EtOAc (50 mL). The combined filtrate and washings were evaporated under reduced pressure and the residue after evaporation was purified by flash chromatography (silica gel saturated with Et_3N). Purification details and characterization data are provided below for the individual cases.

Ethyl (1-Benzyl-3-isopropylpiperidin-4-yl)acetate (10c)
Chromatography: hexanes–Et_3N, 99:1; colorless oil; ratio *cis*/*trans* 19:81.

IR (neat): 1740 cm^{-1} (C=O).

^1H NMR: δ = 0.79 (d, *J* = 7.0 Hz, 3 H, *trans*), 0.87 (d, *J* = 6.3 Hz, 6 H, *cis*), 0.90 (d, *J* = 7.0 Hz, 3 H, *trans*), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.22–1.60 (m, 2 H), 1.67–2.39 (m, 6 H), 2.54 (dd, *J* = 14.7, 4.1 Hz, 1 H), 2.61–2.84 (m, 2 H), 3.40 and 3.56 (AB q, *J* = 13.1 Hz, 2 H, *trans*), 3.43 and 3.57 (AB q, *J* = 13.1 Hz, 2 H, *cis*), 4.12 (q, *J* = 7.1 Hz, 2 H), 7.20–7.34 (m, 5 H).

^{13}C NMR: δ = 14.0, 16.1, 20.3 (*cis*), 21.0, 26.1, 27.2 (*cis*), 29.2 (*cis*), 30.1 (*cis*), 30.6 (*cis*), 31.4, 34.6, 38.0, 45.4 (*trans*), 45.7 (*cis*), 47.6 (*cis*), 52.8, 52.9, 59.8, 59.9 (*cis*), 63.3, 126.6, 127.8, 128.7, 138.2, 172.9 (*trans*), 173.2 (*cis*).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{19}H_{29}NO_2$: 303.2198; found: 303.2195.

Ethyl (1,3-Dibenzylpiperidin-4-yl)acetate (10d)
Chromatography: hexanes–Et_3N, 98:2; pale yellow oils.

***trans*-Isomer**
IR (neat): 1730 cm^{-1} (C=O).

^1H NMR: δ = 1.27 (t, *J* = 7.1 Hz, 3 H), 1.38–1.47 (m, 1 H), 1.66–1.85 (m, 4 H), 1.95 (td, *J* = 11.3, 2.5 Hz, 1 H), 2.21 (dd, *J* = 14.9, 7.9 Hz, 1 H), 2.34 (dd, *J* = 13.6, 8.2 Hz, 1 H), 2.65–2.76 (m, 3 H), 2.94 (dd, *J* = 13.6, 2.1 Hz, 1 H), 3.28 and 3.53 (AB q, *J* = 13.1 Hz, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 7.12–7.30 (m, 10 H).

^{13}C NMR: δ = 14.2, 31.2, 37.5, 38.0, 38.7, 42.0, 52.4, 58.5, 60.2, 63.1, 125.8, 126.8, 128.0, 128.2, 129.0, 129.0, 138.2, 140.2, 173.0.

Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.58; H, 8.32; N, 3.99. Found: C, 78.26; H, 8.42; N, 3.86.

***cis*-Isomer**
IR (neat): 1740 cm^{-1} (C=O).

^1H NMR: δ = 1.30 (t, *J* = 7.1 Hz, 3 H), 1.53–1.72 (m, 2 H), 1.89–2.25 (m, 4 H), 2.33–2.62 (m, 4 H), 2.80–2.92 (m, 2 H), 3.38 and 3.46 (AB q, *J* = 13.0 Hz, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 7.05–7.37 (m, 10 H).

^{13}C NMR: δ = 14.3, 28.2, 32.4 (br), 36.0 (br), 37.5 (br), 40.4, 53.2 (br), 55.5, 60.2, 63.2, 125.5, 126.8, 128.1, 129.2, 138.9, 141.4, 172.9.

Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.58; H, 8.32; N, 3.99. Found: C, 78.25; H, 8.47; N, 3.86.

Ethyl [1-Benzyl-3-(3,4-dimethoxybenzyl)piperidin-4-yl]acetate (10e)
Chromatography: hexanes–EtOAc–Et_3N, 86:12:2; light yellow oils.

***trans*-Isomer**
IR (neat): 1730 cm^{-1} (C=O).

^1H NMR: δ = 1.24 (t, *J* = 7.1 Hz, 3 H), 1.35–1.45 (m, 1 H), 1.64–1.79 (m, 4 H), 1.93 (td, *J* = 11.3, 2.5 Hz, 1 H), 2.17 (dd, *J* = 14.9, 7.9 Hz, 1 H), 2.26 (dd, *J* = 13.8, 8.1 Hz, 1 H), 2.62–2.75 (m, 3 H),

2.86 (dd, *J* = 13.7, 2.0 Hz, 1 H), 3.30 and 3.50 (AB q, *J* = 13.1 Hz, 2 H), 3.84 (s, 6 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 6.62–6.66 (m, 2 H), 6.74 (d, *J* = 8.7 Hz, 1 H), 7.19–7.25 (m, 5 H).

^{13}C NMR: δ = 14.2, 31.3, 37.5, 37.6, 38.7, 42.0, 52.5, 55.7, 55.8, 58.5, 60.2, 63.2, 111.0, 112.0, 120.9, 126.8, 128.0, 129.0, 132.7, 138.1, 147.1, 148.6, 173.0.

Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.95; H, 8.09; N, 3.41. Found: C, 73.07; H, 8.17; N, 3.30.

***cis*-Isomer**

IR (neat): 1740 cm^{-1} (C=O).

^{1}H NMR: δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 1.52–1.68 (m, 2 H), 1.87–1.93 (m, 1 H), 2.02–2.22 (m, 3 H), 2.30–2.48 (m, 2 H), 2.53 (dd, *J* = 13.0, 3.9 Hz, 2 H), 2.74–2.84 (m, 2 H), 3.40 (s, 2 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 6.58 (dd, *J* = 8.1, 1.9 Hz, 1 H), 6.66 (d, *J* = 1.9 Hz, 1 H), 6.68 (d, *J* = 8.1 Hz, 1 H), 7.19–7.34 (m, 5 H).

^{13}C NMR: δ = 14.2, 28.1, 32.1 (br), 35.6 (br), 37.2 (br), 40.3, 52.8 (br), 55.6, 55.6, 55.7, 60.1, 63.0, 110.9, 112.2, 121.0, 126.7, 128.0, 128.9, 133.8, 138.8, 146.8, 148.5, 172.8.

HRMS: *m*/*z* [M]$^+$ calcd for $C_{25}H_{33}NO_4$: 411.2410; found: 411.2409.

Ethyl {1-Benzyl-3-[3-(ethoxycarbonyl)but-3-enyl]piperidin-4-yl}acetate (10g)

Chromatography: hexanes–EtOAc–Et_3N, 96:2:2; pale yellow oils.

***trans*-Isomer**

IR (neat): 1730 (C=O), 1660 cm^{-1} (C=C).

^{1}H NMR: δ = 1.24 (t, *J* = 7.1 Hz, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.32–1.45 (m, 3 H), 1.46–1.77 (m, 4 H), 1.98–2.25 (m, 4 H), 2.52 (dd, *J* = 15.0, 4.3 Hz, 1 H), 2.76–2.81 (m, 1 H), 2.83–2.88 (m, 1 H), 3.45 and 3.51 (AB q, *J* = 13.2 Hz, 2 H), 4.07–4.21 (m, 4 H), 5.75 (dt, *J* = 15.6, 1.4 Hz, 1 H), 6.89 (dt, *J* = 15.6, 6.9 Hz, 1 H), 7.20–7.37 (m, 5 H).

^{13}C NMR: δ = 14.2, 29.2, 29.5, 31.3, 37.1, 38.4, 39.8, 53.1, 58.0, 60.1, 60.3, 63.2, 121.4, 126.9, 128.1, 129.0, 138.2, 148.7, 166.5, 173.0.

HRMS: *m*/*z* [M]$^+$ calcd for $C_{23}H_{33}NO_4$: 387.2410; found: 387.2406.

***cis*-Isomer**

IR (neat): 1730 (C=O), 1660 cm^{-1} (C=C).

^{1}H NMR: δ = 1.22 (t, *J* = 7.1 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.19–1.36 (m, 1 H), 1.51–1.62 (m, 4 H), 1.85–2.27 (m, 5 H), 2.22 (d, *J* = 7.6 Hz, 2 H), 2.46 (br, 1 H), 2.64 (br, 1 H), 3.30 and 3.51 (AB q, *J* = 13.1 Hz, 2 H), 4.05–4.19 (m, 4 H), 5.72 (d, *J* = 15.6 Hz, 1 H), 6.89 (dt, *J* = 15.4, 7.0 Hz, 1 H), 7.17–7.32 (m, 5 H).

^{13}C NMR: δ = 14.1, 24.8 (br), 28.2, 29.7, 35.2 (br), 36.3 (br), 37.1, 52.9 (br), 55.1, 60.0, 60.1, 63.0, 121.2, 126.8, 128.0, 128.7, 138.8, 149.0, 166.5, 172.8.

Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.27; H, 8.59; N, 3.62. Found: C, 71.43; H, 8.61; N, 3.31.

Ethyl {1-[2-(3,4-Dimethoxyphenyl)ethyl]-3-ethylpiperidin-4-yl}acetate (10h)

Chromatography: hexanes–EtOAc–Et_3N, 84:14:2; pale yellow oil; ratio *cis*/*trans* 37:63.

IR (neat): 1730 cm^{-1} (C=O).

^{1}H NMR: δ = 0.86–0.94 (m, 3 H), 1.05–1.46 (m, 6 H), 1.26 (t, *J* = 7.1 Hz, included in m at δ = 1.05–1.46), 1.51–1.81 (m, 3 H), 1.93–2.08 (m, 1 H), 2.17–2.64 (m, 6 H), 2.67–2.79 (m, 2 H), 2.95–3.04 (m, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 6.72–6.81 (m, 3 H).

^{13}C NMR: δ = 10.5 (*trans*), 11.5 (*cis*), 13.8, 20.0 (br, *cis*), 23.2, 28.2, 31.3, 32.8, 32.9, 34.0 (br, *cis*), 34.6 (br, *cis*), 36.7 (*trans*), 38.0, 39.4 (*cis*), 41.4 (*trans*), 51.5 (br, *cis*), 53.0, 54.7, 55.1, 55.2, 58.0, 59.6, 60.5, 60.6, 110.6 (*cis*), 110.6 (*trans*), 111.4, 119.9, 132.6 (*trans*), 132.7 (*cis*), 146.6 (*cis*), 146.7 (*trans*), 148.2 (*cis*), 148.2 (*trans*), 172.5 (*trans*), 172.6 (*cis*).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{21}H_{33}NO_4$: 363.2410; found: 363.2408.

Ethyl {3-Benzyl-1-[2-(3,4-dimethoxyphenyl)ethyl]piperidin-4-yl}acetate (10j)

Chromatography: hexanes–EtOAc–Et_3N, 78:20:2; colorless oil; ratio *cis*/*trans* 22:78.

IR (neat): 1730 cm^{-1} (C=O).

^{1}H NMR: δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 1.41–1.51 (m, 1 H), 1.63–1.72 (m, 3 H), 1.81–1.87 (m, 1 H), 1.95–2.04 (m, 1 H), 2.15–2.31 (m, 2 H), 2.37–2.78 (m, 6 H), 2.92–2.99 (m, 2 H), 3.81–3.85 (m, 6 H), 4.10–4.19 (m, 2 H), 6.63–6.79 (m, 3 H), 7.07–7.28 (m, 5 H).

^{13}C NMR: δ = 14.1, 28.2 (*cis*), 31.5, 33.1, 35.5 (*cis*), 36.7 (*trans*), 37.7 (*trans*), 37.8, 38.6, 40.1 (*cis*), 42.0 (*trans*), 53.0, 55.1 (*cis*), 55.5, 55.7, 55.7 (*cis*), 58.5, 60.2, 60.7, 110.9, 111.6 (*trans*), 111.8 (*cis*), 120.2 (*trans*), 120.4 (*cis*), 125.6 (*cis*), 125.8 (*trans*), 128.0 (*cis*), 128.1 (*trans*), 128.8 (*trans*), 129.0 (*cis*), 132.8 (*trans*), 133.2 (*cis*), 139.9 (*trans*), 141.1 (*cis*), 147.0, 148.5, 172.8 (*cis*), 172.8 (*trans*).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{26}H_{35}NO_4$: 425.2566; found: 425.2572.

Debenzylated Piperidines 11; General Procedure

A deoxygenated mixture of **9** (1.5 mmol), 10% Pd/C (22 mg), and EtOH (7 mL) was treated with H_2 (3.45 bar) at r.t. for 48 h. The mixture was filtered through Celite, which was washed with CH_2Cl_2 (100 mL). The combined filtrate and washings were evaporated under reduced pressure and the residue was purified by flash chromatography (silica gel saturated with Et_2NH). Purification details and characterization data are provided below for the individual cases.

Ethyl (3-Isopropylpiperidin-4-yl)acetate (11c)

Chromatography: EtOAc–Et_2NH, 98:2; colorless oil; ratio *cis*/*trans* 26:74.

IR (neat): 3300 (N–H), 1735 cm^{-1} (C=O).

^{1}H NMR: δ = 0.78 (d, *J* = 7.1 Hz, 3 H, *trans*), 0.88 (d, *J* = 6.0 Hz, 6 H, *cis*), 0.92 (d, *J* = 7.0 Hz, 3 H, *trans*), 1.09–1.30 (m, 5 H), 1.23 (t, *J* = 7.1 Hz, included in m at δ = 1.09–1.30), 1.57–2.05 (m, 4 H), 2.21–3.02 (m, 6 H), 4.10 (q, *J* = 7.1 Hz, 2 H).

^{13}C NMR: δ = 14.1, 15.9, 20.0, 21.0, 21.1, 26.1, 27.3, 30.7, 32.9, 35.4, 38.5, 40.7, 45.2, 45.5, 46.5, 47.0, 47.2, 60.0, 60.1, 173.1, 173.5.

HRMS: *m*/*z* [M]$^+$ calcd for $C_{12}H_{23}NO_2$: 213.1729; found: 213.1723.

Ethyl {3-[3-(Ethoxycarbonyl)propyl]piperidin-4-yl}acetate (11f)

Chromatography: EtOAc–Et_2NH, 98:2 EtOAc–Et_2NH; pale yellow oil; ratio *cis*/*trans* 30:70.

IR (neat): 3340 (N–H), 1740 cm^{-1} (C=O).

^{1}H NMR: δ = 1.07–1.25 (m, 2 H), 1.22 (t, *J* = 7.1 Hz, 6 H), 1.27–1.76 (m, 7 H), 2.02 (dd, *J* = 14.8, 8.9 Hz, 1 H, *trans*), 2.14–2.31 (m, 3 H), 2.49–3.12 (m, 4 H), 4.09 (q, *J* = 7.1 Hz, 4 H).

^{13}C NMR: δ = 14.1, 21.9, 22.7, 26.1, 29.0, 30.4, 32.6, 34.3, 34.4, 35.2, 35.9, 37.8, 38.1, 38.8, 41.3, 44.7, 46.3, 48.4, 51.3, 60.1, 173.0, 173.4, 173.4.

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{27}NO_4$: 285.1940; found: 285.1938.

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(13) Also characteristic of the *cis*-isomers was the room temperature broadening of some of the ^{13}C NMR resonances, because of conformational interconversion between two equatorial/axial conformers, whereas the corresponding signals in the diequatorial *trans*-isomers were sharp.