N-Phenyl-Substituted Pyrrolidines, Piperidines and Azabicyclics by a Tandem Reduction-Double Reductive Amination Reaction

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N-Phenyl-substituted pyrrolidines and piperidines have been synthesized by catalytic reduction of nitrobenzene in the presence of 4- and 5-oxoaldehydes, respectively. The process involves reduction of the aromatic nitro group to give the *N*-phenylhydroxylamine or aniline followed by reductive amination with the two carbonyl functional groups. Monocyclic systems are generally formed in high yield and are easily purified. The method has also been extended to the synthesis of fused *N*-phenylazabicyclics from 2-(3-oxopropyl)cycloalkanones. A high degree of diastereoselectivity for the *trans*-fused product is observed in substrates having an ester group α to the cycloalkanone carbonyl. Bicyclic precursors lacking this ester group give mixtures of *cis* and *trans* products. Finally, contrary to previous reports, we have demonstrated that aniline can be substituted for nitrobenzene in these reactions.

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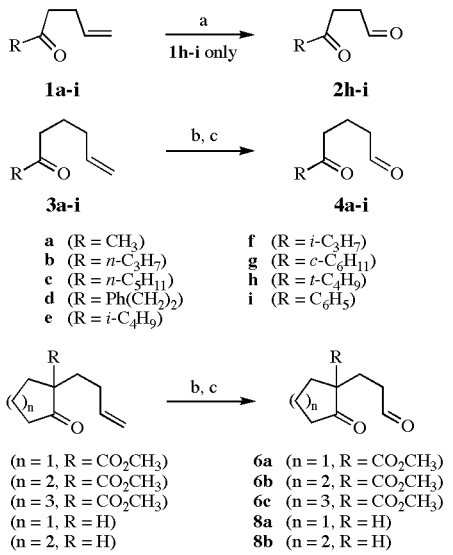
Introduction.

Pyrrolidines and piperidines are important structural components in a large number of biologically active compounds. Many synthetic procedures have been used to access these ring systems including reduction of aromatic heterocycles [2], the Hofmann-Löffler reaction [3], cyclization of hydroxylamines [4], and reductive amination [5]. This last method has typically involved reaction of 1,4- or 1,5-dicarbonyl compounds with amines or ammonium salts in the presence of borohydride reducing agents. To date, relatively little use has been made of nitro compounds as latent amines for this reaction [6]. Nitro compounds, however, have the advantage of being readily available (especially aromatic derivatives), stable and non-basic. Earlier work from this laboratory described a highly diastereoselective synthesis of substituted tetrahydroquinoline-4-carboxylate esters using a tandem reduction-intramolecular double reductive amination procedure under catalytic hydrogenation conditions [7,8]. We report here the preparation of *N*-phenyl-substituted pyrrolidines, piperidines and azabicyclics from nitrobenzene and a series of 4- and 5-oxoaldehydes using an intermolecular variant of this reaction.

Results and Discussion.

The preparation of our cyclization substrates is outlined in Scheme 1. Alkyl 3-butenyl ketones **1a-i** and alkyl 4-pentenyl ketones **3a-i** were prepared according to the method of Molander and Cameron [9]. Substrates **5a-c** for the bicyclic ring closures were prepared by alkylation of the appropriate 2-oxocycloalkane-carboxylate esters with 4-iodo-1-butene [10]; substrates **7a-b** were generated by alkylation of the corresponding cycloalkanone dimethylhydrazones followed by hydrazone exchange [9]. Since trace amounts of acid produced in the ozonolyses led to the formation of cyclic peroxides from the alkyl 3-butenyl ketones [11], reactions of **1a-i** were performed in the presence of catalytic sodium bicarbonate [9a] and the crude ozonolysates were used directly in the hydrogenation. The ozonolyses of **3a-i**, **5a-c** and **7a-b** to prepare 5-oxoaldehydes were less susceptible to cyclization and were carried out using our previously described procedure [7,12].

Scheme 1 [a]



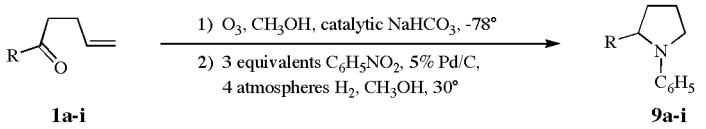
[a] Conditions: (a) (i) O_3, CH_3OH, catalytic $NaHCO_3$, −78°; (ii) $(CH_3)_2S$, −78° → 20°; (b) (i) O_3, CH_3OH, −78°; (ii) $(CH_3)_2S$, *p*-$CH_3C_6H_4SO_3H$, −78° → 20°; (c) 3% aqueous $HClO_4$:THF (1:1).

The results of our tandem reduction-double reductive amination synthesis of *N*-phenyl-substituted pyrrolidines and piperidines are given in Tables 1 and 2, respectively. The reaction involves reduction of the aromatic nitro group followed by reductive amination, first to the less hindered aldehyde and then to the ketone. The sequence generally proceeds in good yield (60-80%) for the closure of both five- and six-membered rings. In all runs, the reaction was found to work best when at least 25 weight percent (relative

to the dicarbonyl substrate) of 5% palladium-on-carbon was used [7]. This quantity of catalyst was sufficient to reduce the excess nitrobenzene and promote the cyclization despite deactivation by the saturated amine products [13].

pyrrolidines from **1a-g** gave optimum results when they were run on the crude ozonolysate using 3 equivalents of nitrobenzene. Aniline (from excess nitrobenzene) and *N*-methylaniline (from reaction of aniline with formalde-

Table 1



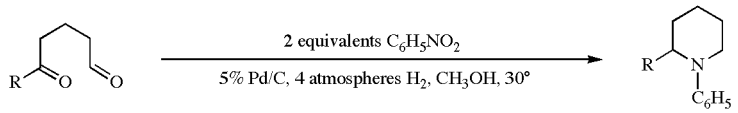
1a-i **9a-i**

Product R Yield	^{1}H NMR (deuteriochloroform) δ (ppm)	^{13}C NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})	HRMS (m/z) Calcd. Found	Molecular Formula	Analysis (%) Calcd. Found C	 H	 N
9a CH_3 74%	[22]	[22]	[22]	161.1205 161.1205	$C_{11}H_{15}N$			
9b *n*-C_3H_7 76%	7.21 (t, 2H, J = 7.3), 6.63 (t, 1H, J = 7.3), 6.55 (d, 2H, J = 7.7), 3.64 (m, 1H), 3.40 (m, 1H), 3.14 (m, 1H), 2.07-1.89 (complex, 3H), 1.81 (m, 1H), 1.69 (m, 1H), 1.43-1.26 (complex, 3H), 0.96 (t, 3H, J = 7.1)	147.3, 129.1, 115.1, 111.7, 58.3, 48.2, 35.3, 30.2, 23.5, 19.8, 14.2	1603 1507	189.1518 189.1516	$C_{13}H_{19}N$	82.54 82.66	10.05 10.12	7.41 7.27
9c *n*-C_5H_{11} 72%	7.21 (t, 2H, J = 7.3), 6.63 (t, 1H, J = 7.3), 6.55 (d, 2H, J = 7.7), 3.62 (m, 1H), 3.40 (m, 1H), 3.13 (m, 1H), 2.07-1.92 (complex, 3H), 1.81 (m, 1H), 1.72 (m, 1H), 1.42-1.20 (complex, 7H), 0.90 (t, 3H, J = 6.5)	147.3, 129.1, 115.0, 111.7, 58.6, 48.2, 33.0, 32.0, 30.2, 26.4, 23.5, 22.7, 14.1	1603 1507	217.1831 217.1829	$C_{15}H_{23}N$	82.95 82.76	10.60 10.68	6.45 6.51
9d $C_6H_5(CH_2)_2$ 68%	7.34-7.04 (complex, 7H), 6.62 (t, 1H, J = 7.3), 6.46 (d, 2H, J = 7.8), 3.67 (m, 1H), 3,42 (m, 1H), 3.14 (m, 1H), 2.68 (m, 2H), 2.09-1.92 (complex, 4H), 1.89 (m, 1H), 1.60 (m, 1H)	147.1, 141.8, 129.1, 128.4, 126.1, 125.8, 115.2, 111.7, 57.8, 48.1, 34.4, 32.9, 30.1, 23.4	1603 1507	251.1674 251.1676	$C_{18}H_{21}N$	86.06 85.87	8.37 8.42	5.58 5.59
9e *i*-C_4H_9 66%	7.21 (t, 2H, J = 7.3), 6.63 (t, 1H, J = 7.3), 6.56 (d, 2H, J = 7.8), 3.75 (m, 1H), 3.39 (m, 1H), 3.13 (m, 1H), 2.07-1.89 (complex, 3H), 1.84 (m, 1H), 1.64 (m, 1H), 1.54 (m, 1H), 1.20 (m, 1H), 1.05 (d, 3H, J = 6.4), 0.93 (d, 3H, J = 6.4)	147.2, 129.1, 115.0, 111.7, 56.8, 47.9, 41.6, 30.4, 26.2, 24.1, 23.3, 21.7	1603 1507	203.1674 203.1675	$C_{14}H_{21}N$	82.76 82.65	10.34 10.42	6.90 6.77
9f *i*-C_3H_7 61%	7.21 (t, 2H, J = 7.3), 6.65 (t, 1H, J = 7.3), 6.63 (d, 2H, J = 7.8), 3.66 (quintet, 1H, J = 3.8), 3.50 (m, 1H), 3.18 (q, 1H, J = 7.5), 2.20 (m, 1H), 2.05-1.80 (complex, 4H), 0.93 (d, 3H, J = 6.9), 0.79 (d, 3H, J = 6.9)	147.2, 129.0, 115.2, 112.3, 63.2, 49.6, 29.4, 25.6, 24.4, 19.7, 16.5	1603 1506	189.1518 189.1515	$C_{13}H_{19}N$	82.54 82.58	10.05 10.09	7.41 7.34
9g *c*-C_6H_{11} 62%	7.21 (t, 2H, J = 7.3), 6.64 (t, 1H, J = 7.3), 6.59 (d, 2H, J = 7.8), 3.61 (m, 1H), 3.47 (m, 1H), 3.13 (q, 1H, J = 8.1), 2.01-1.86 (complex, 3H), 1.84-1.57 (complex, 7H), 1.40-0.92 (complex, 5H)	148.1, 129.0, 115.1, 112.1, 63.0, 49.3, 40.4, 33.9, 30.4, 27.5, 26.7, 26.5, 26.4, 24.4	1603 1506	229.1831 229.1828	$C_{16}H_{23}N$	83.84 83.75	10.04 10.08	6.11 6.14
9h *t*-C_4H_9 54%	7.18 (t, 2H, J = 7.3), 6.76 (d, 2H, J = 7.8), 6.63 (t, 1H, J = 7.3), 3.77 (dd, 1H, J = 8.2, 1.5), 3.61 (m, 1H), 3.26 (dt, 1H, J = 9.3, 8.5), 2.14-1.72 (complex, 4H), 0.92 (s, 9H)	150.9, 128.5, 115.6, 113.6, 65.3, 52.1, 38.0, 29.7, 27.8, 24.6	1603 1502	203.1674 203.1673	$C_{14}H_{21}N$	82.76 82.54	10.34 10.45	6.90 6.86
9i C_6H_5 35%	[24]	[24]	[24]	223.1361 223.1360	$C_{16}H_{17}N$			

Overall yields were generally lower for the synthesis of pyrrolidines than for piperidines. This was due primarily to lower yields in the ozonolysis step to prepare the 4-oxoaldehydes. It was found that the reactions to prepare

hyde produced in the ozonolysis) were both easily separated from the desired heterocycles by flash chromatography. For **1h-i**, yields were slightly higher when the intermediate 4-oxoaldehydes were isolated and purified

Table 2



4 a-i **10 a-i**

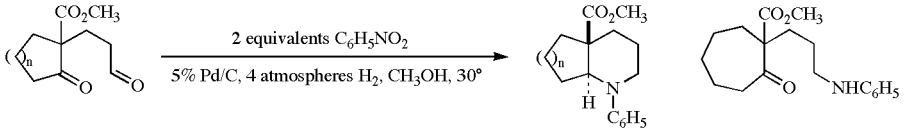
Product R Yield	^{1}H NMR deuteriochloroform δ (ppm)	^{13}C NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})	HRMS (m/z) Calcd. Found	Molecular Formula	Analysis (%) Calcd. Found C	H	N
10a CH_3 79%	[22]	[22]	[22]	175.1361 175.1359	$C_{12}H_{17}N$			
10b *n*-C_3H_7 78%	7.22 (t, 2H, J = 7.2), 6.88 (d, 2H, J = 7.8), 6.75 (t, 1H, J = 7.2), 3.79 (m, 1H), 3.33 (dt, 1H, J = 11.1, 4.0), 2.98 (m, 1H), 1.81-1.40 (complex, 10H), 0.86 (t, 3H, J = 7.2)	151.2, 129.0, 118.0, 116.3, 55.5, 43.6, 29.5, 27.7, 25.5, 20.1, 19.3, 14.2	1601 1501	203.1764 203.1767	$C_{14}H_{21}N$	82.76 83.98	10.34 10.30	6.90 6.83
10c *n*-C_5H_{11} 72%	7.22 (t, 2H, J = 7.3), 6.88 (d, 2H, J = 7.8), 6.74 (t, 1H, J = 7.3), 3.76 (sextet, 1H, J = 4.0), 3.33 (dt, 1H, J = 11.4, 4.0), 2.98 (m, 1H), 1.77-1.38 (complex, 8H), 1.23 (m, 6H), 0.84 (t, 3H, J = 6.8)	151.2, 129.0, 118.0, 116.3, 55.8, 43.7, 31.9, 27.7, 27.2, 26.6, 25.5, 22.6, 19.3, 14.0	1603 1502	231.1987 231.1987	$C_{16}H_{25}N$	83.12 82.94	10.82 10.79	6.06 6.16
10d $C_6H_5(CH_2)_2$ 74%	7.27-7.09 (complex, 7H), 6.80 (d, 2H, J = 7.8), 6.74 (t, 1H, J = 7.2), 3.81 (m, 1H), 3.36 (dt, 1H, J = 12.5, 3.6), 3.01 (m, 1H), 2.65-2.45 (complex, 2H), 1.84 (m, 2H), 1.79-1.57 (complex, 6H)	151.3, 142.4, 129.4, 128.7, 128.6, 126.1, 118.5, 116.2, 55.3, 44.0, 33.4, 29.7, 28.0, 25.7,19.8	1603 1502	265.1828 265.1831	$C_{19}H_{23}N$	86.04 85.77	8.68 8.73	5.28 5.38
10e *i*-C_4H_9 66%	7.22 (t, 2H, J = 7.2), 6.88 (d, 2H, J = 7.8), 6.74 (t, 1H, J = 7.2), 3.91 (m, 1H), 3.34 (dt, 1H, J = 11.0, 3.7), 2.98 (m, 1H), 1.84-1.40 (complex, 7H), 1.26 (m, 2H), 0.85 (d, 6H, J = 6.5)	151.0, 129.0, 117.9, 116.3, 53.4, 43.2, 36.0, 27.7, 25.4, 25.1, 23.9, 21.8, 19.2	1603 1503	217.1831 217.1830	$C_{15}H_{23}N$	82.95 82.91	10.60 10.66	6.45 6.47
10f *i*-C_3H_7 56%	7.22 (t, 2H, J = 7.2), 6.88 (d, 2H, J = 7.8), 6.74 (t, 1H, J = 7.2), 3.91 (m, 1H), 3.34 (dt, 1H, J = 11.0, 3.7), 2.98 (m, 1H), 1.84-1.40 (complex, 7H), 0.85 (d, 6H, J = 6.5)	151.5, 129.1, 116.9, 115.5, 62.3, 43.6, 26.8, 25.1, 24.3, 20.4, 20.3, 19.9	1603 1503	203.1674 203.1672	$C_{14}H_{21}N$	82.76 82.94	10.34 10.29	6.90 6.85
10g *c*-C_6H_{11} 56%	7.18 (t, 2H, J = 7.3), 6.82 (d, 2H, J = 7.9), 6.64 (t, 1H, J = 7.3), 3.49 (m, 2H), 3.08 (m, 1H), 1.90 (m, 1H), 1.85-1.52 (complex, 12H), 1.13 (m, 2H), 0.90 (m, 2H)	151.4, 129.1, 116.2, 114.7, 60.7, 42.6, 36.3, 30.6, 30.5, 29.9, 26.5, 26.4, 24.8, 24.2, 20.0	1600 1503	243.1987 243.1988	$C_{17}H_{25}N$	83.95 83.74	10.29 10.40	5.76 5.63
10h *t*-C_4H_9 [a]								
10i C_6H_5 [b]								

[a] Heterocycle **10h** was not observed. Product **11** was isolated. [b] Heterocycle **10i** was not observed. Products **14** and **15** were isolated.

prior to reductive cyclization. The synthesis of piperidines was carried out in two stages. Ozonolysis of **3a-i** in methanol followed by reductive workup and treatment with *p*-toluenesulfonic acid gave the keto acetals derived from the expected 5-oxoaldehydes. These compounds were more easily purified and stored than the dicarbonyl compounds. Prior to reductive cyclization, treatment of each keto acetal with 3% perchloric acid:tetrahydrofuran (1:1) regenerated the 5-oxoaldehyde [7,12]. Reaction of these keto aldehydes with 2 equivalents of nitrobenzene under catalytic hydrogenation conditions then afforded the piperidine derivatives. Again, the final products were readily purified by flash chromatography. In accordance with expected steric effects, ketones flanked by bulky 2° and 3° alkyl groups gave lower cyclization yields than ketones substituted with 1° groups.

The results of reactions to prepare *N*-phenylazabicyclic compounds are summarized in Tables 3 and 4. Cyclization of **6a** and **6b** bearing an ester group α to the ring ketone gave the *trans*-fused bicyclic products as single diastereomers in 70-75% yield. This diastereoselectivity can be attributed to a steric effect where the ester shields one side of the structure during the final reduction and directs the incoming hydrogen to the opposite face of the molecule. Reaction of **8a** and **8b**, which lack the ester group, gave mixtures of *cis*- and *trans*-fused products. Structures for the bicyclic compounds were assigned using a combination of COSY-45 [14] and NOESY [15] spectra.

Table 3



6a-c **16a-b** **17**

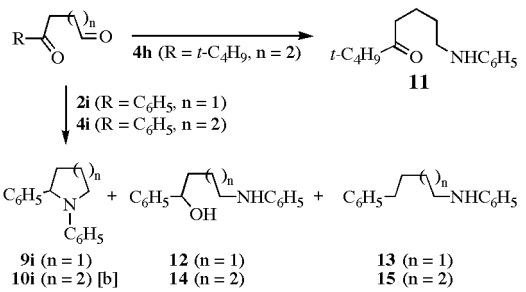
Product n Yield	^{1}H NMR (deuteriochloroform) δ (ppm)	^{13}C NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})	HRMS (m/z) Calcd. Found	Molecular Formula	Analysis (%) Calcd. Found C	H	N
16a 1 72%	7.28 (t, 2H, J = 7.7), 7.13 (d, 2H, J = 7.4), 7.04 (d, 1H, J = 7.3), 3.72 (s, 3H), 3.22 (dddd, 1H, J = 11.2, 4.5, 2.1, 1.0), 2.81 (ddd, 1H, J = 14.8, 12.1, 3.6), 2.56 (m, 2H), 2.25 (m, 1H), 1.99 (m, 1H), 1.88-1.44 (complex, 6H), 1.22 (td, 1H, J = 11.2, 4.5)	175.6, 152.1, 128.4, 123.8, 123.5, 72.8, 55.4, 53.4, 51.3, 35.0, 34.9, 28.0, 24.6, 19.6	1736	259.1572 259.1570	$C_{16}H_{21}NO_2$	74.13 74.33	8.11 8.18	5.41 5.29
16b 2 75%	7.26 (t, 2H, J = 7.7), 7.15 (d, 2H, J = 7.3), 7.07 (t, 1H, J = 7.3), 3.75 (s, 3H), 3.15 (dddd, 1H, J = 11.1, 4.3, 2.6, 1.6), 2.98 (td, 1H, J = 11.3, 3.7), 2.42 (dd, 1H, J = 12.4, 4.1), 2.32 (dm, 1H, J = 13.2), 2.11 (m, 1H), 1.98 (m, 1H), 1.77-1.58 (complex, 3H), 1.47 (m, 1H), 1.35-1.06 (complex, 5H)	175.2, 151.3, 128.2, 125.9, 124.1, 69.7, 55.5, 51.2, 48.9, 37.8, 37.1, 27.5, 25.7, 24.5, 22.4	1738	273.1729 273.1731	$C_{17}H_{23}NO_2$	74.73 74.91	8.42 8.47	5.13 5.03
17 82%	7.16 (t, 2H, J = 7.3), 6.68 (t, 1H, J = 7.3), 6.58 (d, 2H, J = 7.5), 3.72 (bs, 1H), 3.70 (s, 3H), 3.10 (t, 2H, J = 6.9), 2.65 (m, 1H), 2.49 (m, 1H), 2.19-2.03 (complex, 2H), 1.79-1.40 (complex, 10H)	209.6, 172.9, 148.2, 129.2, 117.1, 112.6, 62.6, 52.2, 44.0, 42.1, 33.0, 32.9, 29.8, 25.6, 24.8, 24.6	3406 1739 1707	303.1834 303.1831	$C_{18}H_{25}NO_3$	71.29 71.01	8.25 8.19	4.62 4.80

Attempted cyclization of substrate **6c** gave only **17** resulting from reduction of the nitro group and a single reductive amination with the side chain aldehyde; none of the bicyclic product was observed. In this case, addition of the pendant aniline nitrogen to the cycloheptanone carbonyl is presumably disfavored by internal strain [16] and steric hindrance with the unsubstituted α' carbon of the seven-membered ring.

Problems were encountered in the synthesis of piperidine derivatives from *tert*-butyl- and phenyl-substituted ketones. While the *tert*-butyl pyrrolidine precursor **1h** yielded **9h** in 54% yield, ring closure was completely suppressed for piperidine precursor **4h** and 2,2-dimethyl-7-(phenylamino)-3-heptanone (**11**) was the only product isolated (Scheme 2). For substrates incorporating a phenyl ketone, as in **2i** and **4i**, carbonyl reduction [17] competed with pyrrolidine formation and was the exclusive process in attempts to prepare the piperidine (Scheme 2). The observation that these reactions successfully yield pyrrolidines but fail in the piperidine series suggests that the outcome is dictated by more than simple steric factors. Enthalpy and entropy also play a large role in determining the reaction path. While entropy is generally perceived to be more important, it has been reported [18] that enthalpy is the dominant factor in comparisons of 5- and 6-membered ring closures. Thus, a combination of steric hindrance and less favorable enthalpy slows (or prevents) piperidine formation and permits competing processes to occur.

While the reaction chronology seems clear, the actual intermediates involved are less obvious. Earlier work by others [19] offered evidence that *N*-phenylhydroxylamine was the primary nucleophilic intermediate in reductive aminations using nitrobenzene under catalytic hydrogenation conditions; the alternative intermediate, aniline, was shown to be virtually unreactive. While the hydroxylamine is expected to be a stronger nucleophile due to the alpha effect [20], a control experiment was necessary to assess the possible role of aniline in the reaction. We therefore repeated the reaction of 4-oxopentanal and 5-oxohexanal substituting

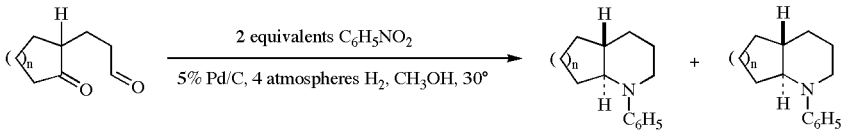
Scheme 2 [a]



9i (n = 1) **12** (n = 1) **13** (n = 1)
10i (n = 2) [b] **14** (n = 2) **15** (n = 2)

[a] Conditions: 2 equivalents $C_6H_5NO_2$, 5% Pd/C, 4 atmospheres H_2, CH_3OH, 30°; [b] Compound **10i** was not formed.

Table 4



8a-b **18a-b** **19a-b**

Product n Yield	^{1}H NMR (deuteriochloroform) δ (ppm)	^{13}C NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})	HRMS (m/z) Calcd. Found	Molecular Formula	Analysis (%) Calcd. Found C	 H	 N
18a 1 67%	7.22 (dd, 2H, J = 8.8, 7.3), 6.92 (d, 2H, J = 8.8), 6.74 (t, 1H, J = 7.3), 4.12 (dt, 1H, J = 9.6, 6.5), 3.38 (dt, 1H, J = 11.9, 3.8), 2.84 (td, 1H, J = 11.5, 3.2), 2.09 (m, 1H), 1.85-1.45 (complex, 8H), 1.30 (m, 2H)	151.1, 129.0, 117.8, 115.2, 59.7, 43.1, 37.6, 29.4, 26.1, 24.9, 21.6, 20.3	1603 1496	201.1518 201.1515	$C_{14}H_{19}N$	83.58 74.33	9.45 8.18	6.97 5.29
19a 1 19%	7.27 (t, 2H, J = 7.4), 7.10 (d, 2H, J = 7.4), 7.02 (t, 1H, J = 7.4), 3.30 (dt, 1H, J = 12.2, 3.1), 2.59 (m, 1H), 2.37 (ddd, 1H, J = 16.5, 10.5, 6.3), 1.95 (m, 1H), 1.78 (m, 3H), 1.60 m, 3H), 1.30 (m, 3H), 1.12 (m, 1H)	153.2, 128.6, 123.3, 123.1, 67.4, 57.9, 45.4, 30.3, 29.8, 28.9, 26.9, 19.9	1602 1495	201.1518 201.1516	$C_{14}H_{19}N$	83.58 74.91	9.45 8.47	6.97 5.03
18b 2 75%	7.22 (dd, 2H, J = 8.8, 7.2), 6.89 (d, 2H, J = 8.8), 6.74 (t, 1H, J = 7.2), 3.82 (dt, 1H, J = 11.9, 4.3), 3.30 (dt, 1H, J = 12.4, 3.1), 2.87 (td, 1H, J = 12.1, 2.9), 2.06 (m, 1H), 1.82 (m, 1H), 1.77-1.53 (complex, 6H), 1.47-1.12 (complex, 5H)	150.7, 129.0, 117.9, 115.8, 58.0, 42.0, 35.8, 31.9, 25.9, 25.8, 23.8, 20.8, 20.3	1603 1496	215.1674 215.1675	$C_{15}H_{21}N$	83.72 83.61	9.77 9.83	6.51 6.63
19b 2 15%	7.29 (t, 2H, J = 7.4), 7.14 (d, 2H, J = 7.4), 7.09 (t, 1H, J = 7.4), 3.12 (dm, 1H, J = 11.3), 2.71 (td, 1H, J = 11.6, 2.8), 2.34 (m, 1H), 1.91-1.58 (complex, 7H), 1.50-0.95 (complex, 6H)	152.8, 128.7, 125.6, 124.3, 65.6, 58.0, 42.5, 33.1, 32.4, 31.5, 26.5, 26.2, 25.5	1603 1495	215.1674 215.1671	$C_{15}H_{21}N$	83.72 83.57	9.77 9.79	6.51 6.46

aniline (and also *N*-phenylhydroxylamine) for nitrobenzene. In each case, the heterocyclic product was produced in a yield nearly identical to that obtained using nitrobenzene. Thus, aniline cannot be ruled out as an intermediate in this process. Furthermore, the option of using aniline in the reaction dramatically increases the number of possible substitution patterns on the aromatic reacting partner.

In conclusion, a synthesis of *N*-phenyl-substituted pyrrolidines and piperidines based on the tandem reduction-double reductive amination of nitrobenzene with 4- and 5-oxoaldehydes has been developed. The process is clean, efficient, operationally simple, and gives yields comparable to or better than other methods. The reaction has also been applied to a diastereoselective synthesis of several new azabicyclic systems. In this application, the degree of diastereoselectivity appears to depend on the steric bulk of the substituent α to the ketone involved in the final ring closure step. Finally, while the use of nitrobenzene offers several advantages in manipulating reagents, we have demonstrated that aniline can also be used in the reaction. We are currently working to extend this methodology to the synthesis of morpholine and piperazine derivatives.

EXPERIMENTAL

Commercial reagents and solvents were used as received. All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech) using ultraviolet or iodine detection or capillary gas chromatography (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness, 50-300°) using flame ionization detection. Preparative separations were performed using flash chromatography [21] on silica gel (grade 62, 60-200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies no. 5); band elution was monitored using a hand-held ultraviolet lamp. Melting points were uncorrected. Ir spectra were run as thin films on sodium chloride disks and were referenced to polystyrene. ^{1}H and ^{13}C nmr spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, and were referenced to internal tetramethylsilane; coupling constants (J) have been given in Hz. COSY-45 and NOESY spectra were recorded at 400 MHz. High resolution mass spectra (direct probe/electron impact) were obtained at 70 electron volts.

All alkyl 3-butenyl and alkyl 4-pentenyl ketones were synthesized according to the literature method [9]. Many of the simple 5-oxoaldehydes as well as **8a** and **8b** have also been reported [9a]. Previously unknown 5-oxoaldehydes prepared as part of this study are given below along with a representative procedure.

Caution: Though we never experienced any problems, addition of 5% palladium-on-carbon to methanol can cause fires. This operation should be performed under a nitrogen atmosphere.

Representative Procedure to Prepare Previously Unreported 5-Oxoaldehydes: 5-Oxodecanal (**4c**).

A solution of 1.00 g (5.95 mmole) of **3c** in 150 mL of methanol was cooled to –78° and treated with ozone until thin layer chromatography indicated complete consumption of starting material. Excess ozone was removed on a stream of dry nitrogen and 8.00 g (6.77 mL, 109 mmole) of dimethyl sulfide was added. The reaction was warmed slowly to 0° and 250 mg of *p*-toluenesulfonic acid was added. The reaction was slowly warmed to room temperature during 2 hours and stirring was continued for 12 hours. The reaction was concentrated, diluted with ether, washed with sodium bicarbonate and sodium chloride, and dried (magnesium sulfate). Removal of the ether gave the expected keto acetal containing a small amount of the keto aldehyde.

Prior to reductive cyclization, this mixture was treated with 3% perchloric acid:tetrahydrofuran (1:1) at 0° for 1 hour and at room temperature for 12 hours, then extracted (two times) with dichloromethane [12]. The organic layer was washed with sodium bicarbonate and sodium chloride, dried (magnesium sulfate), and concentrated under vacuum to give 970 mg (5.71 mmole, 96%) of **4c** as a light yellow oil; ir: 2830, 2722, 1721 cm^{-1}; ^1H nmr: δ 9.76 (t, 1H, J = 1.4), 2.47 (m, 2H), 2.38 (t, 2H, J = 7.4), 1.90 (quintet, 2H, J = 7.1), 1.65 (m, 1H), 1.57 (quintet, 2H, J = 7.4), 1.28 (m, 5H), 0.89 (t, 3H, J = 7.1); ^{13}C nmr: δ 210.2, 201.9, 43.0, 42.8, 41.3, 31.4, 23.5, 22.4, 16.0, 13.9; hrms: m/z Calcd. for $C_{10}H_{18}O_2$: 170.1307; Found: 170.1303.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.59: H, 10.59. Found: C, 70.83; H, 10.68.

5-Oxo-7-phenylheptanal (**4d**).

This compound (938 mg, 4.60 mmole, 93%) was obtained as a light yellow oil; ir: 2824, 2728, 1722 cm^{-1}; ^1H nmr: δ 9.73 (t, 1H, J = 1.4), 7.28 (m, 2H), 7.21 (m, 3H), 2.90 (t, 2H, J = 7.3), 2.72 (t, 2H, J = 7.3), 2.45 (2 t, 4H, J = 7.1), 1.88 (quintet, 2H, J = 7.1); ^{13}C nmr: δ 209.2, 201.8, 140.9, 128.5, 128.3, 126.1, 44.2, 42.9, 41.6, 29.7, 15.9; hrms: m/z Calcd. for $C_{13}H_{16}O_2$: 204.1150; Found: 204.1149.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.47: H, 7.84. Found: C, 76.66; H, 7.90.

7-Methyl-5-oxooctanal (**4e**).

This compound (960 mg, 6.15 mmole, 95%) was obtained as a light yellow oil; ir: 2830, 2722, 1718 cm^{-1}; ^1H nmr: δ 9.76 (t, 1H, J = 1.5), 2.47 (m, 4H), 2.27 (d, 2H, J = 6.9), 2.13 (nonet, 1H, J = 6.6), 1.89 (quintet, 2H, J = 7.1), 0.91 (d, 6H, J = 6.6); ^{13}C nmr: δ 210.0, 201.9, 51.8, 43.0, 41.8, 24.6, 22.5, 15.9; hrms: m/z Calcd. for $C_9H_{16}O_2$: 156.1150; Found: 156.1148.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.23; H, 10.26. Found: C, 69.35; H, 10.30.

5-Cyclohexyl-5-oxopentanal (**4g**).

This compound (900 mg, 4.95 mmole, 89%) was obtained as a light yellow oil; ir: 2835, 2721, 1733, 1711 cm^{-1}; ^1H nmr: δ 9.76 (t, 1H, J = 1.5), 2.51 (t, 2H, J = 7.0), 2.48 (m, 2H), 2.31 (m, 1H), 1.89 (quintet, 2H, J = 7.0), 1.92 (complex, 5H), 1.40-1.17 (complex, 5H); ^{13}C nmr: δ 213.3, 202.0, 50.8, 43.0, 39.1, 28.4, 25.8, 25.6, 16.0; hrms: m/z Calcd. for $C_{11}H_{18}O_2$: 182.1307; Found: 182.1308.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.53; H, 9.89. Found: C, 72.25; H, 10.01.

Representative Reduction-Reductive Amination Procedures to Prepare Pyrrolidines: (±)-2-Methyl-1-phenylpyrrolidine (**9a**).

A solution of 800 mg (8.16 mmole) of **1a** [9a] in 150 mL of methanol containing 100 mg of sodium bicarbonate was ozonized at –78° until thin layer chromatography indicated complete consumption of the starting material. The crude ozonolysate was transferred directly to a stainless steel pressure vessel, 3.01 g (24.5 mmole) of nitrobenzene and 200 mg of 5% palladium-on-carbon were added (see **Caution** above), and the mixture was shaken under 4 atmospheres of hydrogen at 30° for 6 hours. The crude product was concentrated, diluted with ether and filtered through a plug of Celite topped with a layer of anhydrous magnesium sulfate to remove the catalyst. Removal of the ether afforded a light brown oil that contained the pyrrolidine along with aniline and *N*-methylaniline. The product was purified by flash chromatography on a 30 cm x 2.5 cm column eluted with 1% ether in hexane. Band 1 afforded 972 mg (6.04 mmole, 74%) of **9a**. The spectral data matched those reported previously [22]. The same procedure was used to prepare **9b-g** (see Table 1).

In the control experiments, 3.00 equivalents of aniline or *N*-phenylhydroxylamine [23] was added in place of nitrobenzene prior to hydrogenation. The yields of **9a** in these control experiments were 77% and 74%, respectively.

(±)-2-*tert*-Butyl-1-phenylpyrrolidine (**9h**).

This compound was best prepared by first isolating the **2h** from the ozonolysis (methanol, catalytic sodium bicarbonate, -78°; dimethyl sulfide workup (no acid), flash chromatography) of **1h**. The resulting 4-oxoaldehyde was dissolved in methanol and hydrogenated in the presence of 2 equivalents of nitrobenzene and 25 weight percent (based on the dicarbonyl substrate) of 5% palladium-on-carbon. The final product was purified by flash chromatography to give 400 mg (1.97 mmole, 54% overall) of **5h** as a light yellow oil. The spectral data are given in Table 1.

(±)-1,2-Diphenylpyrrolidine (**9i**).

This compound was best prepared as above by first isolating the **2i** from the ozonolysis of **1i**. The resulting 4-oxoaldehyde was dissolved in methanol and hydrogenated in the presence of 2 equivalents of nitrobenzene and 25 weight percent (based on the dicarbonyl substrate) of 5% palladium-on-carbon. The final product was purified by flash chromatography to give 224 mg (1.00 mmole, 35% overall) of **9i** as a light yellow oil that solidified on standing, mp 35-37°. The spectral data matched those reported previously [24]. The reductive cyclization also produced compounds **12** and **13**.

(±)-1-Phenyl-4-(phenylamino)butanol (**12**).

This compound (236 mg, 0.98 mmole, 33%) was obtained as a light yellow oil. The spectral data matched those reported previously [25].

N-(4-Phenylbutyl)benzenamine (**13**).

This compound (63 mg, 0.28 mmole, 9%) was obtained as a light yellow oil; ir: 3411 cm^{-1}; ^1H nmr: δ 7.28 (t, 2H, J = 7.5), 7.16 (complex, 5H), 6.68 (t, 1H, J = 7.3), 6.58 (d, 2H, J = 7.5), 3.58 (br s, 1H), 3.12 (t, 2H, J = 6.9), 2.66 (t, 2H, J = 7.3), 1.80-1.59 (complex, 4H); ^{13}C nmr: δ 148.4, 142.2, 129.2, 128.4,

128.3, 125.8, 117.1, 112.7, 43.8, 35.6, 31.4, 29.7; hrms: m/z Calcd. for $C_{16}H_{19}N$: 225.1518; Found: 225.1519.

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.33; H, 8.44; N, 6.22. Found: C, 85.12; H, 8.52; N, 6.35.

Representative Reduction-Reductive Amination Procedure to Prepare Piperidines: (±)-2-Methyl-1-phenylpiperidine (**10a**).

A solution of 550 mg (4.82 mmole) of **4a** and 1.19 g of nitrobenzene (9.65 mmole) in 125 mL of methanol was hydrogenated in the presence of 140 mg of 5% palladium-on-carbon (see **Caution** above). Workup and purification as described for **9a** gave 674 mg (3.85 mmole, 79%) of **10a** as a light yellow oil. The spectral data matched those previously reported [22]. The same procedure was used to prepare **10b-g** (see Table 2).

In the control experiments, 2.00 equivalents of aniline or *N*-phenylhydroxylamine [23] was added in place of nitrobenzene prior to hydrogenation. The yields of **10a** in these control experiments were 76% and 75%, respectively.

Attempted Reductive Cyclization of 6,6-Dimethyl-5-oxoheptanal (**4h**): 2,2-Dimethyl-7-(phenylamino)-3-heptanone (**11**).

This compound (727 mg, 3.12 mmole, 82%) was obtained as a light yellow oil that crystallized on standing at 0°, mp 26-28°; ir: 3400, 1701 cm^{-1}; ^1H nmr: δ 7.17 (t, 2H, J = 7.3), 6.68 (t, 1H, J = 7.3), 6.59 (d, 2H, J = 7.5), 3.62 (br s, 1H), 3.12 (t, 2H, J = 6.7), 2.53 (t, 2H, J = 6.7), 1.63 (m, 4H), 1.14 (s, 9H); ^{13}C nmr: δ 215.7, 148.3, 129.2, 117.1, 112.6, 44.1, 43.7, 36.0, 29.0, 26.4, 21.3; hrms: m/z Calcd. for $C_{15}H_{23}NO$: 233.1780; Found: 233.1777.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.25; H, 9.87; N, 6.01. Found: C, 77.47; H, 9.94; N, 5.95.

Attempted Reductive Cyclization of 5-Oxo-5-phenylpentanal (**4i**).

Hydrogenation of 964 mg (5.48 mmole) of **4i** as above gave a mixture of **14** and **15**. The compounds were separated on five 20 cm x 20 cm preparative thin layer chromatography plates eluted with 5-10% ether in hexane.

(±)-1-Phenyl-5-(phenylamino)pentanol (**14**).

This compound (936 mg, 3.67 mmole, 67%) was obtained as a light yellow oil that crystallized on standing at 0°, mp 37-38°; ir: 3400 cm^{-1}; ^1H nmr: δ 7.39-7.26 (complex, 5H), 7.16 (t, 2H, J = 7.3), 6.68 (t, 1H, J = 7.3), 6.58 (d, 2H, J = 7.6), 4.69 (dd, 1H, J = 7.4, 5.8), 3.53 (br s, 1H), 3.10 (t, 2H, J = 7.0), 1.98 (br s, 1H), 1.79 (complex, 2H), 1.63 (quintet, 2H, J = 7.3), 1.54 (m, 1H), 1.39 (m, 1H); ^{13}C nmr: δ 148.3, 144.7, 129.2, 128.5, 127.6, 125.8, 117.2, 112.7, 74.5, 43.8, 38.7, 29.4, 23.4; hrms: m/z Calcd. for $C_{17}H_{21}NO$: 255.1623; Found: 255.1620.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.49. Found: C, 79.81; H, 8.26; N, 5.62.

N-(5-Phenylpentyl)benzenamine (**15**).

This compound (105 mg, 0.43 mmole, 8%) was obtained as a light yellow oil; ir: 3404 cm^{-1}; ^1H nmr: δ 7.28 (t, 2H, J = 7.5), 7.17 (complex, 5H), 6.68 (t, 1H, J = 7.3), 6.58 (d, 2H, J = 7.5), 3.48 (br s, 1H), 3.09 (t, 2H, J = 7.1), 2.63 (t, 2H, J = 7.5), 1.66 (2 quintets, 4H, J = 7.5), 1.45 (m, 2H); ^{13}C nmr: δ 148.5, 142.5, 129.2, 128.4, 128.3, 125.7, 117.1, 112.7, 43.9, 35.8, 31.2, 29.4, 26.8; hrms: m/z Calcd. for $C_{17}H_{21}N$: 239.1674; Found: 239.1673.

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.36; H, 8.79; N, 5.86. Found: C, 85.09; H, 8.90; N, 5.77.

Representative Procedure for the Preparation of Azabicyclic Precursors where R = CO_2CH_3: Methyl (±)-2-Oxo-1-(3-oxopropyl)cyclopentanecarboxylate (**6a**).

This compound was prepared from 1.00 g (5.10 mmole) of **5a** [10] by ozonolysis, conversion to the keto acetal, purification, and hydrolysis as described for **4c**. The yield was 980 mg (4.94 mmole, 97%) of **6a** as a light yellow oil. This compound was used without further purification; ir: 2841, 2728, 1756, 1727 cm^{-1}; ^1H nmr: δ 9.75 (t, 1H, J = 1.1), 3.72 (s, 3H), 2.70 (ddd, 1H, J = 18.3, 9.5, 5.9), 2.56-2.25 (complex, 4H), 2.19 (ddd, 1H, J = 15.1, 9.3, 5.8), 2.10-1.80 (complex, 4H); ^{13}C nmr: δ 214.5, 201.0, 171.5, 58.8, 52.6, 39.4, 37.8, 34.0, 25.4, 19.5; hrms: m/z Calcd. for $C_{10}H_{14}O_4$: 198.0892; Found: 198.0893.

Methyl (±)-2-Oxo-1-(3-oxopropyl)cyclohexanecarboxylate (**6b**).

This compound (930 mg, 4.38 mmole, 92%) was isolated as a light yellow oil and used without further purification; ir: 2842, 2731, 1748, 1724 cm^{-1}; ^1H nmr: δ 9.74 (t, 1H, J = 1.2), 3.75 (s, 3H), 2.59-2.40 (complex, 5H), 2.17 (ddd, 1H, J = 14.3, 9.5, 5.6), 2.02 (m, 1H), 1.89 (m, 1H), 1.76 (m, 1H), 1.65 (m, 2H), 1.47 (m, 1H); ^{13}C nmr: δ 207.6, 201.1, 172.3, 59.9, 52.4, 40.9, 39.3, 36.6, 27.4, 26.8, 22.5; hrms: m/z Calcd. for $C_{11}H_{16}O_4$: 212.1048; Found: 212.1045.

Methyl (±)-2-Oxo-1-(3-oxopropyl)cycloheptanecarboxylate (**6c**).

This compound (950 g, 4.19 mmole, 94%) was isolated as a light yellow oil and used without further purification; ir: 2858, 2725, 1728 cm^{-1}; ^1H nmr: δ 9.74 (t, 1H, J = 1.2), 3.73 (s, 3H), 2.72-2.38 (complex, 4H), 2.27 (ddd, 1H, J = 14.1, 9.3, 5.6), 2.14 (dd, 1H, J = 13.1, 8.5), 1.94 (ddd, 1H, J = 14.1, 9.6, 5.6), 1.80-1.61 (complex, 5H), 1.53 (m, 2H); ^{13}C nmr: δ 209.3, 201.2, 172.8, 61.7, 52.3, 42.2, 39.7, 33.8, 29.8, 27.6, 25.5, 24.8; hrms: m/z Calcd. for $C_{12}H_{18}O_4$: 226.1205; Found: 226.1204.

Representative Reduction-Reductive Amination Procedure to Prepare Azabicyclics: Methyl (±)-(1*S**,6*S**)-5-Aza-5-phenylbicyclo[4.3.0]nonanecarboxylate (**16a**).

A solution of 0.98 g (4.94 mmole) of **6a** and 1.22 g (9.88 mmole) of nitrobenzene in 150 mL of methanol was hydrogenated in the presence of 200 mg of 5% palladium-on-carbon (see **Caution** above). Workup and purification as described for **9a** gave 920 mg (3.56 mmole, 72%) of **16a** as a light yellow oil. The same procedure was used to prepare **16b**, **17**, **18a-b** and **19a-b**. The spectral data for **16a-b** and **17** are given in Table 3; data for **18a-b** and **19a-b** are given in Table 4.

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