Diastereoselective Synthesis of Linear-Fused Tricyclic Nitrogen Heterocycles by a Tandem Reduction-Reductive Amination Reaction

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A two-step diastereoselective synthesis of linear-fused tricyclic nitrogen heterocycles has been developed from cyclic β-ketoesters. The cyclization substrates are readily prepared by alkylation of the methyl 2-oxocycloalkanecarboxylates with 2-nitrobenzyl bromide. Hydrogenation of these substrates initiates a reaction sequence involving (1) reduction of the aromatic nitro group, (2) condensation of the resulting hydroxylamine or aniline nitrogen with the cycloalkanone and (3) reduction of the imine. The products are isolated in high yield as single diastereomers having the *trans*-fused ring junction. The observed selectivity is rationalized in terms of a steric effect imposed by the ester group in the final reductive amination step which directs the incoming hydrogen to the opposite face of the molecule. By comparison, reductive cyclizations of substrates lacking the stereodirecting ester group give mixtures of *cis* and *trans* products with a preference for the *cis*-fused heterocycle.

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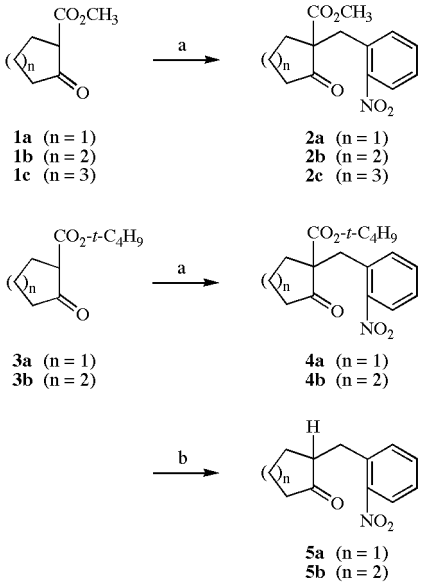
Introduction.

The search for selective chemical transformations is a continuing goal. We recently reported [2] a diastereoselective tandem reduction-reductive amination reaction for the synthesis of *cis*-substituted methyl 2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylates. In this sequence, the selectivity of the reductive ring closures was attributed to steric hindrance created by a carboxylic ester group β to the final imine intermediate which controlled the orientation of hydrogen addition. The current study extends the tandem reduction-reductive amination reaction to substrates bearing a carboxylic ester group α to the final imine and establishes the role of the ester in controlling the stereochemical outcome of the reaction. Finally, since several octahydroacridine derivatives are known to express antidepressant activity, structures prepared in this study may possess useful pharmaceutical properties [3].

Results and Discussion.

The substrates needed for our cyclization studies were prepared by alkylation of methyl 2-oxocycloalkanecarboxylates (**1a-c**) with 2-nitrobenzyl bromide [4]. Alkylation of the five- and seven-membered cyclic ketoesters **1a** and **1c** using anhydrous potassium carbonate in refluxing acetone gave **2a** and **2c** in 94% and 82% yields, respectively [5]; similar treatment of methyl 2-oxocyclohexanecarboxylate (**1b**), however, resulted in a complex mixture of products containing predominantly *O*-alkylated material. Successful conversion of **1b** to **2b** was achieved in 64% yield using potassium fluoride-on-alumina as the base in dry acetonitrile [6]. Substrates lacking the α ester group were prepared in two steps. Alkylation of *tert*-butyl 2-oxocycloalkanecarboxylates **3a** and **3b** with 2-nitrobenzyl bromide, as outlined above for the five- and six-membered cyclic systems, gave **4a** and **4b**. Ester cleavage and decarboxylation with trifluoroacetic acid then gave **5a** and **5b** in 70% and 62% overall yields, respectively [7].

Scheme 1 [a]

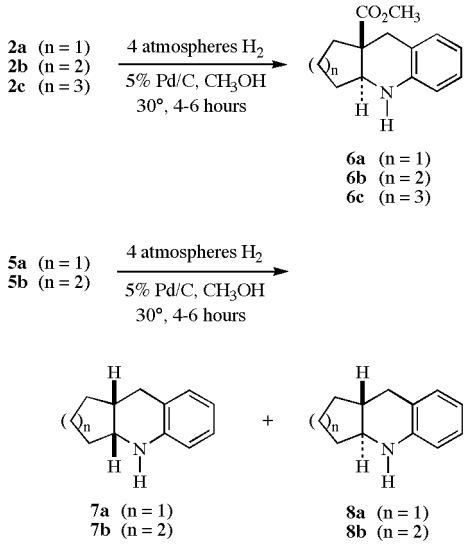


[a] Conditions: (a) For **1a** and **1c**: 2-nitrobenzyl bromide, anhydrous potassium carbonate, acetone, 56°; For **1b**: 2-nitrobenzyl bromide, potassium fluoride-on-alumina, CH_3CN, 25°; (b) CF_3CO_2H, 25°.

Treatment of the 2-nitrobenzyl-substituted ketoesters **2a-c** under catalytic hydrogenation conditions (4 atmospheres of hydrogen, 5% palladium-on-carbon, methanol, 30°, 4-6 hours) gave, in each case, a single product in 78-91% yield. X-ray crystallographic analysis of these products allowed assignment of the structures as **6a-c**, respectively. In each product, the ring junction formed in the final reductive amination step had the *trans* geometry, even in the 6-6-5 fused structure where some of the *cis* product would be expected [8].

To assess the importance of the ester group in directing the stereochemical outcome of the reaction, five- and six-membered cyclic substrates lacking the ester were subjected to the same catalytic reduction conditions. The cyclopentanone substrate **5a** gave an 86% yield of the fused-ring product as two isomers, **7a** and **8a**, in a ratio of 3.8:1; the six-ring substrate **5b** gave an 80% yield of **7b** and **8b** in a ratio of 1.7:1. These mixtures were easily separated by preparative thin layer chromatography, and structure elucidation was carried out using a combination of COSY-45 [9] and NOESY [10] techniques. Analysis of the spectra for the major products showed a correlation between the signals for the bridgehead protons indicating a *cis* ring junction [11]. The minor isomers lacked this correlation and were assigned as the *trans*-fused structures.

Scheme 2



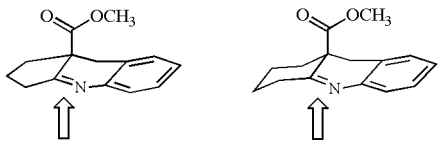
Prior to this study, only the octahydroacridine system had been reported in the literature [3,12]. Analogues varying the size of the saturated ring have not previously been described. *Cis*- and *trans*-1,2,3,4,4a,9,9a,10-octahydroacridine have been prepared by three synthetic routes [13]. In the first [12c], treatment of 1,2,3,4-tetrahydroacridine under catalytic hydrogenation conditions (1 atmosphere of hydrogen, Pd-Pt-C, methanol, 25°) gave the *cis* octahydroacridine in 93% yield. In an alternative procedure [3], reduction of 1,2,3,4-tetrahydroacridine with 95% formic acid at 170-175° followed by boiling with concentrated hydrochloric acid [14] gave a 2.7:1 mixture of *trans*:*cis* octahydroacridines in 71% yield. Finally, a 3.2:1 *trans*:*cis* mixture of octahydroacridines was formed in 96% yield by ring expansion of 4a-methoxyaminocyclohex[*a*]indan during reduction with lithium aluminum hydride [12f]. In the current study, substrates **2a-c**, bearing an ester group α to the ketone, gave exclusively the *trans*-fused heterocycle while **5a-b**, lacking the ester, gave mixtures of *cis* and *trans* products with a preference for the *cis*-fused system.

The mechanism of the reaction involves (1) reduction of the aromatic nitro group, (2) condensation of the resulting hydroxylamine or aniline [15] with the cycloalkanone, and (3) reduction of the imine. The product from cyclization of the reduced nitrogen intermediate with the ester group was not detected. The diastereoselectivity in the ring closures of **2a-c** is rationalized in terms of a steric effect imposed by the ester group which directs the incoming hydrogen to the opposite face of the molecule giving the *trans* ring junction (see Scheme 3). We have noted similar selectivity in other reductive cyclizations [2,15] when an ester group was located α or β to a reducing imine or enamine.

The preference for the *cis*-fused products from substrates **5a-b** is rationalized by analyzing molecular models. In the final imine reduction, the bridgehead α carbon is substituted by a sterically small hydrogen. In the expected conformation, the fused cycloalkane ring tilts away from this hydrogen creating a molecular cavity that restricts access to the bottom face of the molecule. Thus, hydrogen is delivered predominantly from the top side to give the *cis*-fused product (see Scheme 3).

Scheme 3

Hydrogen Addition with Ester



Hydrogen Addition without Ester

In summary, we have developed a simple, high-yield synthesis of linear-fused tricyclic nitrogen heterocycles based on a tandem reduction-reductive amination reaction. The current synthesis is more versatile than earlier syntheses in permitting variation of the ring sizes in the final heterocyclic targets. The transformation shows a high degree of *trans* diastereoselectivity when there is a large ester group α to the imine intermediate in the final ring closure. Without this stereodirecting group, the reaction gives mixtures of *cis* and *trans* products. We are continuing to explore this process with the goal of preparing enantiomerically pure products.

EXPERIMENTAL

All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates. Preparative separations were performed using flash column chromatography [16] on silica gel (grade 62, 60-200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies no. 5) or thin layer chromatography on 20-cm x 20-cm silica gel GF plates; band elution was monitored using a hand-held ultraviolet lamp. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and were referenced to polystyrene. ^{1}H and ^{13}C nuclear magnetic resonance 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 experiments were performed on a 400 MHz instrument. High resolution mass spectra (electron impact/direct probe) were obtained at 70 electron volts.

Commercial reagents and solvents were used as received. Potassium carbonate was ground to a fine powder, dried under vacuum at 120° for 24 hours and stored in an oven at 120°. Potassium fluoride-on-alumina was prepared according to the procedure of Yadav and co-workers [6] using neutral alumina (60-325 mesh) obtained from Fisher Scientific. Compounds **3a** and **3b** were prepared according to the method of Taylor and co-workers [7].

Representative Procedure for the Alkylation of Alkyl (±)-2-Oxocycloalkanecarboxylates: Methyl (±)-1-[(2-Nitrophenyl)-methyl]-2-oxocyclopentanecarboxylate (**2a**).

The procedure of Barco and co-workers [5] was adapted. To a solution of 1.42 g (10.0 mmole) of **1a** and 2.59 g (12.0 mmole) of 2-nitrobenzyl bromide [4] in 50 mL of dry acetone was added 5.52 g (40.0 mmole) of anhydrous potassium carbonate. The suspension was stirred and heated under reflux for 3 hours, then cooled, filtered and concentrated. The resulting light yellow oil was flash chromatographed on a 30 cm x 2.5 cm silica gel column eluted with increasing concentrations of ether in hexane. The major band gave 2.60 g (9.39 mmole, 94%) of **2a** as a light yellow oil that crystallized upon standing at 0°, mp 30-31°; ir: 1756, 1728, 1530, 1355 cm^{-1}; ^{1}H nmr: δ 7.90 (d, 1H, J = 8.1), 7.50 (t, 1H, J = 7.6), 7.40 (m, 2H), 3.74 (ABd, 1H, J = 14.3), 3.71 (s, 3H), 3.43 (ABd, 1H, J = 14.3), 2.50-2.37 (complex, 2H), 2.19 (m, 1H), 2.02-1.77 (complex, 3H); ^{13}C nmr: δ 213.9, 171.3, 150.4, 132.9, 132.8, 131.9, 128.0, 124.8, 61.2, 52.8, 38.1, 34.7, 33.4, 19.5; hrms: m/z Calcd. for $C_{14}H_{15}NO_5$: 277.0950; Found: 277.0949.

Anal. Calcd. for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.42. Found: C, 60.82; H, 5.49.

Methyl (±)-1-[(2-Nitrophenyl)methyl]-2-oxocycloheptanecarboxylate (**2c**).

This compound (2.49 g, 8.17 mmole, 82%) was isolated as a light yellow solid, mp 72-73°; ir: 1739, 1716, 1530, 1353 cm^{-1}; ^{1}H nmr: δ 7.86 (d, 1H, J = 8.0), 7.48 (t, 1H, J = 7.6), 7.37 (t, 1H, J = 7.6), 7.24 (d, 1H, J = 7.6), 3.84 (ABd, 1H, J = 14.3), 3.67 (s, 3H), 3.36 (ABd, 1H, J = 14.3), 2.62 (m, 1H), 2.48 (m, 1H), 1.80-1.57 (complex, 7H), 1.38 (m, 1H); ^{13}C nmr: δ 208.2, 172.1, 150.8, 133.1, 132.2, 131.9, 127.8, 124.8, 63.7, 52.4, 41.8, 35.1, 31.9, 29.7, 25.8, 24.2; hrms: m/z Calcd for $C_{16}H_{19}NO_5$: 305.1263; Found: 305.1260.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.95; H, 6.23. Found: C, 63.18; H, 6.34.

tert-Butyl (±)-1-[(2-Nitrophenyl)methyl]-2-oxocyclopentanecarboxylate (**4a**).

This compound (2.81 g, 8.81 mmole, 88%) was isolated as a light yellow oil; ir: 1750, 1727, 1530, 1355 cm^{-1}; ^{1}H nmr: δ 7.89 (d, 1H, J = 8.0), 7.55-7.35 (complex, 3H), 3.68 (ABd, 1H, J = 14.2), 3.39 (ABd, 1H, J = 14.2), 2.41 (m, 2H), 2.09 (dd, 1H, J = 18.8, 8.5), 2.04-1.70 (complex, 3H), 1.41 (s, 9H); ^{13}C nmr: δ 214.5, 170.1, 150.8, 133.0, 132.7, 132.3, 127.8, 124.7, 82.4, 61.8, 38.0, 34.2, 33.5, 27.8, 19.6; hrms: m/z Calcd. for $C_{17}H_{21}NO_5$: 319.1419; Found: 319.1419.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.95; H, 6.58. Found: C, 63.76; H, 6.49.

Representative Procedure for the Alkylation of Alkyl (±)-2-Oxocyclohexanecarboxylates: Methyl (±)-1-[(2-Nitrophenyl)-methyl]-2-oxocyclohexanecarboxylate (**2b**).

Attempts to prepare this compound from **1b** as described above resulted predominantly in *O*-alkylation. The synthesis was accomplished using the general procedure of Yadav and co-workers [6]. To a solution of 1.56 g (10.0 mmole) of **1b** and 2.59 g (12.0 mmole) of 2-nitrobenzyl bromide in 30 mL of dry acetonitrile was added 4.80 g of potassium fluoride-on-alumina (30.0 mmole of potassium fluoride) and the mixture was stirred at room temperature for 24 hours. At this time, a second charge of 1.20 g of potassium fluoride-on-alumina (7.5 mmole of potassium fluoride) was added and the reaction was stirred for an additional 24 hours. The suspension was filtered, concentrated under vacuum and flash chromatographed on a 40 cm x 2.5 cm silica gel column eluted with increasing concentrations of ether in hexane. Band 3 gave 1.86 g (6.39 mmole, 64%) of **2b** as a light yellow solid, mp 89-90°; ir: 1738, 1716, 1530, 1354 cm^{-1}; ^{1}H nmr: δ 7.86 (d, 1H, J = 8.0), 7.47 (t, 1H, J = 7.6), 7.37 (t, 1H, J = 7.6), 7.25 (d, 1H, J = 7.7), 3.80 (ABd, 1H, J = 14.3), 3.64 (s, 3H), 3.33 (ABd, 1H, J = 14.3), 2.47 (m, 2H), 2.32 (dq, 1H, J = 13.0, 2.8), 2.00 (m, 1H), 1.72 (m, 1H), 1.70-1.40 (complex 3H); ^{13}C nmr: δ 206.5, 171.2, 150.7, 133.4, 132.1, 131.5, 127.8, 124.8, 61.6, 52.5, 41.1, 36.0, 35.4, 27.3, 22.5; hrms: m/z Calcd. for $C_{15}H_{17}NO_5$: 291.1106; Found: 291.1104.

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.86; H, 5.84. Found: C, 61.97; H, 5.91.

tert-Butyl (±)-1-[(2-Nitrophenyl)methyl]-2-oxocyclohexanecarboxylate (**4b**).

This compound (2.63 g, 7.90 mmole, 79%) was isolated as a light yellow oil; ir: 1716, 1530, 1355 cm^{-1}; ^{1}H nmr: δ 7.81 (d, 1H, J = 8.0), 7.50-7.30 (complex, 3H), 3.61 (ABd, 1H, J = 14.3), 3.42 (ABd, 1H, J = 14.3), 2.52 (m, 2H), 2.31 (dq, 1H, J = 13.2, 2.9), 2.05 (m, 1H), 1.77-1.56 (complex, 4H), 1.35 (s, 9H); ^{13}C nmr: δ 207.1, 170.0, 150.9, 136.0, 133.6, 132.0, 127.5, 124.5, 82.6, 62.6, 41.1, 36.6, 34.8, 27.7, 27.3, 22.6; hrms: m/z Calcd. for $C_{18}H_{23}NO_5$: 333.1576; Found: 333.1574.

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.86; H, 6.91. Found: C, 64.63; H, 6.86.

Representative Ester Cleavage-Decarboxylation: (±)-2-[(2-Nitrophenyl)methyl]cyclopentanone (**5a**).

A solution of 2.75 g (8.62 mmole) of **4a** in 25 mL of trifluoroacetic acid was stirred at room temperature for 48 hours, then

concentrated under vacuum. The residue was diluted with ether and washed with water (two times), sodium bicarbonate (four times) and sodium chloride, dried (magnesium sulfate), and concentrated under vacuum. The brown oil was chromatographed on a 30 cm x 2.5 cm silica gel column with increasing concentrations of ether in hexane. The major band gave 1.51 g (6.90 mmole, 80%) of **5a** as a yellow oil; ir: 1740, 1530, 1355 cm^{-1}; ^1H nmr: δ 7.91 (d, 1H, J = 8.2), 7.53 (t, 1H, J = 7.6), 7.38 (d, 1H, J = 7.5), 7.37 (t, 1H, J = 7.6), 3.46 (dd, 1H, J = 13.8, 5.3), 2.82 (dd, 1H, J = 13.8, 8.5), 2.50 (m, 1H), 2.41 (dd, 1H, J = 18.4, 8.8), 2.22-1.95 (complex, 3H), 1.77 (m, 1H), 1.56 (m, 1H); ^{13}C nmr: δ 219.0, 149.7, 135.1, 132.9, 132.5, 127.4, 124.7, 50.2, 37.6, 32.3, 29.4, 20.4; hrms: m/z Calcd. for $C_{12}H_{13}NO_3$: 219.0895; Found: 219.0894.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.94. Found: C, 65.85; H, 6.02.

(±)-2-[(2-Nitrophenyl)methyl]cyclohexanone (**5b**).

This compound (1.42 g, 6.09 mmole, 78%) was isolated as a light yellow solid, mp 54-55°; ir: 1711, 1530, 1355 cm^{-1}; ^1H nmr: δ 7.91 (d, 1H, J = 8.2), 7.49 (m, 2H), 7.35 (m, 1H), 3.48 (dd, 1H, J = 16.1, 8.8), 2.72 (m, 2H), 2.52-2.22 (complex, 2H), 2.10 (m, 2H), 1.88 (m, 1H), 1.65 (m, 2H), 1.44 (m, 1H); ^{13}C nmr: δ 211.7, 149.7, 135.6, 133.4, 132.7, 127.2, 124.7, 51.5, 42.3, 34.4, 32.7, 28.1, 25.3; hrms: m/z Calcd. for $C_{13}H_{15}NO_3$: 233.1052; Found: 233.1053.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.44. Found: C, 66.65; H, 6.38.

Representative Procedure for the Tandem Reduction-Reductive Amination: Methyl (±)-(3a*S**,9a*S**)-2,3,3a,4,9,9a-Hexahydro-1*H*-cyclopenta[*b*]quinoline-9a-carboxylate (**6a**).

To a solution of 1.00 g (3.61 mmole) of **2a** in 150 mL of methanol was added 200 mg of 5% palladium-on-carbon, and the mixture was shaken under 4 atmospheres of hydrogen at 30° for 4 hours. The solvent was removed, the residue was diluted with ether, and the suspension was filtered through a pad of Celite topped with a layer of magnesium sulfate to separate the catalyst. Concentration under vacuum gave a yellow oil that was flash chromatographed on a 25 cm x 2 cm silica gel column eluted with 5% ether in hexane. The major band afforded 0.73 g (3.14 mmole, 87%) of **6a** as a white solid, mp 117-118°; ir: 3366, 1722 cm^{-1}; ^1H nmr: δ 7.03 (d, 1H, J = 7.7), 7.00 (t, 1H, J = 7.7), 6.74 (t, 1H, J = 7.5), 6.63 (d, 1H, J = 7.8), 4.02 (br s, 1H), 3.56 (s, 3H), 3.36 (ABd, 1H, J = 15.7), 3.25 (t, 1H, J = 9.1), 2.78 (ABd, 1H, J = 15.7), 2.23 (m, 1H), 2.02 (m, 3H), 1.88 (m, 1H), 1.52 (m, 1H); ^{13}C nmr: δ 175.0, 145.1, 129.8, 126.5, 123.3, 119.1, 116.8, 62.4, 51.6, 50.4, 39.1, 34.6, 27.6, 21.2; hrms: m/z Calcd. for $C_{14}H_{17}NO_2$: 231.1259; Found: 231.1258.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.73; H, 7.36; N, 6.06. Found: C, 72.86; H, 7.33; N, 5.99.

Methyl (±)-(8a*S**,10a*S**)-5,6,7,8,8a,9,10,10a-Octahydroacridine-8a-carboxylate (**6b**).

This compound (0.77 g, 3.13 mmole, 91%) was isolated as a white solid, mp 133-134°; ir: 3389, 1728 cm^{-1}; ^1H nmr: δ 6.98 (t, 1H, J = 7.6), 6.91 (d, 1H, J = 7.5), 6.63 (t, 1H, J = 7.5), 6.55 (d, 1H, J = 7.9), 3.66 (br s, 1H), 3.54 (s, 3H), 3.10 (ABd, 1H, J = 15.6), 3.07 (dd, 1H, J = 11.9, 4.3), 2.68 (ABd, 1H, J = 15.6), 2.26 (dq, 1H, J = 13.3, 1.9), 2.10 (qd, 1H, J = 12.4, 4.3), 1.85 (m, 1H), 1.78 (m, 1H), 1.64 (m, 1H), 1.50-1.31 (complex, 2H), 1.22 (m, 1H); ^{13}C nmr: δ 174.1, 144.0, 129.1, 126.9, 120.5, 117.8, 115.5, 58.1, 51.4, 43.7, 40.3, 35.8, 28.1, 24.9, 22.7; hrms: m/z Calcd. for $C_{15}H_{19}NO_2$: 245.1416; Found: 245.1416.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.76; N, 5.71. Found: C, 73.66; H, 7.78; N, 5.68.

Methyl (±)-(5a*S**,10a*S**)-5,5a,6,7,8,9,10,10a,11-Octahydro-6*H*-cyclohepta[*b*]quinoline-10a-carboxylate (**6c**).

This compound (0.66 g, 2.56 mmole, 78%) was isolated as a white solid, mp 130-131°; ir: 3400, 1728 cm^{-1}; ^1H nmr: δ 6.97 (m, 2H), 6.63 (t, 1H, J = 7.5), 6.53 (d, 1H, J = 8.2), 3.60 (br s, 1H), 3.55 (s, 3H), 3.10 (dd, 1H, J = 10.5, 2.2), 3.06 (ABd, 1H, J = 15.5), 2.81 (ABd, 1H, J = 15.5), 2.39 (qm, 1H, J = 10.5), 2.05 (m, 1H), 1.90-1.49 (complex, 6H), 1.46 (m, 2H); ^{13}C nmr: δ 175.1, 144.4, 129.0, 126.7, 121.1, 117.8, 114.8, 61.7, 51.4, 46.6, 40.4, 36.1, 32.6, 27.6, 25.7, 22.6; hrms: m/z Calcd. for $C_{16}H_{21}NO_2$: 259.1572; Found: 259.1570.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.11; N, 5.41. Found: C, 74.25; H, 8.18; N, 5.29.

Cyclization of **5a**.

The reductive ring closure of **5a** was carried out as described for the synthesis of **6a** above. Preparative thin layer chromatography using 5-10% ether in hexanes gave two bands. Band 1 (fastest moving) contained product **7a**; band 2 contained **8a**.

(±)-(3a*R**,9a*R**)-2,3,3a,4,9,9a-Hexahydro-1*H*-cyclopenta[*b*]-quinoline (**7a**).

This compound (268 mg, 1.55 mmole, 68%) was isolated as a light yellow oil; ir: 3400 cm^{-1}; ^1H nmr: δ 6.97 (m, 2H), 6.60 (t, 1H, J = 7.2), 6.47 (d, 1H, J = 8.2), 3.65 (td, 1H, J = 5.6, 4.3), 3.60 (br s, 1H), 2.85 (dd, 1H, J = 15.8, 5.9), 2.45 (dd, 1H, J = 15.8, 6.0), 2.25 (m, 1H), 1.95-1.72 (complex, 3H), 1.58 (m, 2H), 1.42 (m, 1H); ^{13}C nmr: δ 144.6, 129.1, 126.7, 121.2, 116.7, 113.2, 55.5, 37.3, 34.8, 29.8, 29.7, 22.1; hrms: m/z Calcd. for $C_{12}H_{15}N$: 173.1205; Found: 173.1203.

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.24; H, 8.67; N, 8.09. Found: C, 82.98; H, 8.60; N, 8.13.

(±)-(3a*S**,9a*R**)-2,3,3a,4,9,9a-Hexahydro-1*H*-cyclopenta[*b*]-quinoline (**8a**).

This compound (72 mg, 0.42 mmole, 18%) was isolated as a light yellow oil; ir: 3366 cm^{-1}; ^1H nmr: δ 6.99 (d, 1H, J = 7.2), 6.98 (t, 1H, J = 7.4), 6.66 (t, 1H, J = 7.4), 6.55 (d, 1H, J = 7.8), 3.89 (br s, 1H), 2.94 (td, 1H, J = 10.5, 6.8), 2.90 (dd, 1H, J = 15.8, 5.1), 2.62 (dd, 1H, J = 15.8, 12.1), 1.99 (m, 2H), 1.91-1.71 (complex, 3H), 1.46 (ddd, 1H, *J* = 22.1, 10.8, 8.4), 1.27 (m, 1H); ^{13}C nmr: δ 145.7, 130.1, 126.6, 122.7, 118.0, 115.4, 58.9, 41.7, 34.0, 30.8, 29.0, 21.2; hrms: m/z Calcd. for $C_{12}H_{15}N$: 173.1205; Found: 173.1204.

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.24; H, 8.67; N, 8.09. Found: C, 83.06; H, 8.64; N, 8.18.

Cyclization of **5b**.

The reductive ring closure of **5b** was carried out as described for the synthesis of **6a** above. Preparative thin layer chromatography using 5-10% ether in hexanes gave two bands. Band 1 (fastest moving) contained product **7b**; band 2 contained **8b**.

(±)-(4a*R**,9a*R**)-1,2,3,4,4a,9a,10-Octahydroacridine (**7b**).

This compound (280 mg, 1.50 mmole, 50%) was isolated as a white solid, mp 68-69° (lit [3,12c] mp 67-68°); ir: 3400 cm^{-1};

^{1}H nmr: δ 6.94 (m, 2H), 6.56, (t, 1H, J = 7.4), 6.44 (d, 1H, J = 8.0), 3.50 (m, 1H), 3.48 (br s, 1H), 2.90 (dd, 1H, J = 16.3, 5.7), 2.53 (dd, 1H, J = 16.3, 4.1), 1.96 (m, 1H), 1.79-1.56 (complex, 4H), 1.50-1.28 (complex, 4H); ^{13}C nmr: δ 143.9, 129.7, 126.5, 119.2, 116.3, 113.2, 49.9, 32.9, 32.5, 31.7, 27.2, 24.7, 20.7; hrms: m/z Calcd. for $C_{13}H_{17}N$: 187.1361; Found: 187.1362.

Anal. Calcd. for $C_{13}H_{17}N$: C, 87.42; H, 9.09; N, 7.49. Found: C, 87.13; H, 9.01; N, 7.61.

(±)-(4a*S**,9a*R**)-1,2,3,4,4a,9,9a,10-Octahydroacridine (**8b**).

This compound (168 mg, 0.90 mmole, 30%) was isolated as a white solid, mp 80-81° (lit [3,12f] mp 80-82°); ir: 3400 cm^{-1}; ^{1}H nmr: δ 6.93 (m, 2H), 6.59 (t, 1H, J = 7.4), 6.46 (d, 1H, J = 8.0), 3.59 (br s, 1H), 2.84 (td, 1H, J = 10.3, 3.8), 2.66 (dd, 1H, J = 16.1, 5.0), 2.47 (dd, 1H, J = 16.1, 11.8), 1.87 (m, 2H), 1.75 (m, 2H), 1.52 (m, 1H), 1.42-1.24 (complex, 3H), 1.02 (m, 1H); ^{13}C nmr: δ 144.5, 129.2, 126.6, 121.5, 116.9, 113.6, 56.0, 37.6, 34.6, 33.5, 31.9, 25.9, 24.6; hrms: m/z Calcd. for $C_{13}H_{17}N$: 187.1361; Found: 187.1359.

Anal. Calcd. for $C_{13}H_{17}N$: C, 87.42; H, 9.09; N, 7.49. Found: C, 87.19; H, 9.05; N, 7.56.

Experimental X-ray Data for **6a**, **6b** and **6c**.

Intensity data were measured on a Brucker P4 diffractometer with MoK_α radiation (λ = 0.71073Å) at room temperature [17]. All non-hydrogen positions were determined using the SHELXS [18] structure solution program and refined by full matrix least squares methods on the basis of F^2 using the SHELXL97 [19] refinement program. Hydrogen atoms were placed in calculated positions using idealized geometry and constrained to those positions during final refinements. For **6a**: $C_{14}H_{17}NO_2$, formula weight 231.29, a = 6.896(8), b = 22.333(10), c = 7.914(3) Å, β = 104.37(4)°, V = 1190.5(15) Å^3, Z = 4, monoclinic space group $P2_1/c$, density(calculated) = 1.290 Mg/m^3, 2081 unique reflections, R = 0.0676. For **6b**: $C_{15}H_{19}NO_2$, formula weight 245.31, a = 9.354(1), b = 8.954(1), c = 15.796(2) Å, β = 93.33(1)°, V = 1320.8(3) Å^3, Z = 4, monoclinic space group $P2_1/c$, density(calculated) = 1.234 Mg/m^3, 2694 unique reflections, R = 0.0580. For **6c**: $C_{16}H_{21}NO_2$, formula weight 259.34, a = 11.026(2), b = 11.989(2), c = 12.188(3) Å, α = 85.49(2), β = 68.02(1), γ = 69.30(2)°, V = 1394.9(5) Å^3, Z = 4, triclinic space group P1 bar, density(calculated) = 1.235 Mg/m^3, 6150 unique reflections, R = 0.0671.

Structural and atomic parameters have been deposited with the Cambridge Crystallographic Data Center as deposition nos. 176509 (**6a**), 176510 (**6b**) and 176511 (**6c**). Copies may be obtained from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ.

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