Diastereoselective Synthesis of Substituted 2,3,4,5-Tetrahydro-1*H*-1-benzazepine-5-carboxylic Esters by a Tandem Reduction-Reductive Amination Reaction

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An efficient, diastereoselective synthesis of substituted and unsubstituted 2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylic esters has been developed based on the tandem reduction-reductive amination reaction. Catalytic hydrogenation of a series of 2-(2-nitrophenyl)-5-oxoalkanoic esters initiates a reaction sequence involving (1) reduction of the aromatic nitro group, (2) condensation of the *N*-hydroxylamino (or amino) nitrogen with the side chain carbonyl, and (3) reduction of the seven-membered cyclic imine. Cyclizations that produce 2-alkyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylic esters are diastereoselective for the product having the C2 alkyl and the C5 ester groups *cis*. In these reactions, the transannular ester group exerts a strong stereodirecting effect on the reduction of the cyclic imine intermediate, though not as strong as that observed in previous closures of 2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters. This decrease in diastereoselectivity is attributed to (1) the greater distance between the ester and the imine double bond and (2) the increased conformational mobility of the larger ring, both of which diminish the stereodirecting effect of the ester. Finally, formation of the seven-membered ring is sufficiently slow that reaction with the side chain ester group competes with heterocycle formation in several of the reactions.

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Introduction.

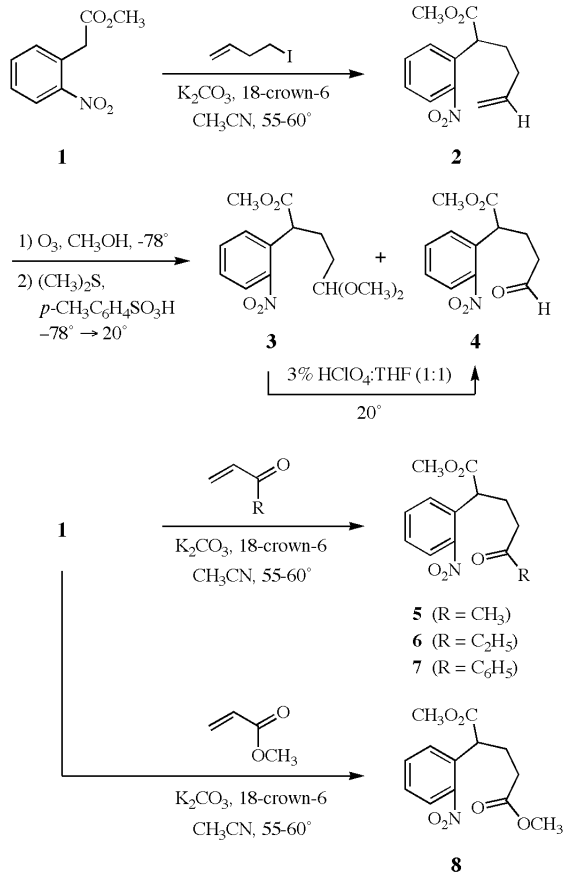
We recently reported a tandem reduction-reductive amination reaction for the diastereoselective synthesis of (±)-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters from 2-(2-nitrophenyl)-4-oxoalkanoic ester derivatives [2]. In this sequence, it was found that the side chain carboxylic ester exerted a strong stereodirecting effect on the reductive cyclization to give exclusively the *cis*-2,4-disubstituted product. The current project sought to extend this reaction to the synthesis of (±)-2-alkyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylic esters [3,4,5] with the added goal of ascertaining the ability of a similarly positioned ester group to control stereochemistry in seven-membered ring closures.

Tetrahydro-1*H*-1-benzazepine derivatives substituted at C2 and C5 have been found to selectively inhibit the V_2 receptor of the hormone arginine vasopressin. This hormone exerts its actions through three receptor subtypes with the V_2 receptor (present in the collecting duct of the kidney) controlling blood pressure, blood volume, and plasma osmolality. Thus, inhibitors of the arginine vasopressin V_2 receptor may have applications in the treatment of disorders such as diabetes, congestive heart failure, and hypertension [6]. The 2-indolinones, which are also possible products from these reactions, have been investigated as drugs for managing chronic conditions involving the muscarinic M3 receptor, which most notably include obstructive pulmonary disease, bronchitis, and asthma [7].

Results and Discussion.

The cyclization substrates required for this study were prepared in 1-3 steps from methyl 2-nitrophenylacetate (**1**) (Scheme 1). Alkylation [8] of **1** with 4-iodo-1-butene [9] furnished alkene **2** in 60% yield. Ozonolysis of alkene **2** followed by reductive workup in the presence of catalytic acid afforded acetal **3** which was hydrolyzed with 3%

Scheme 1

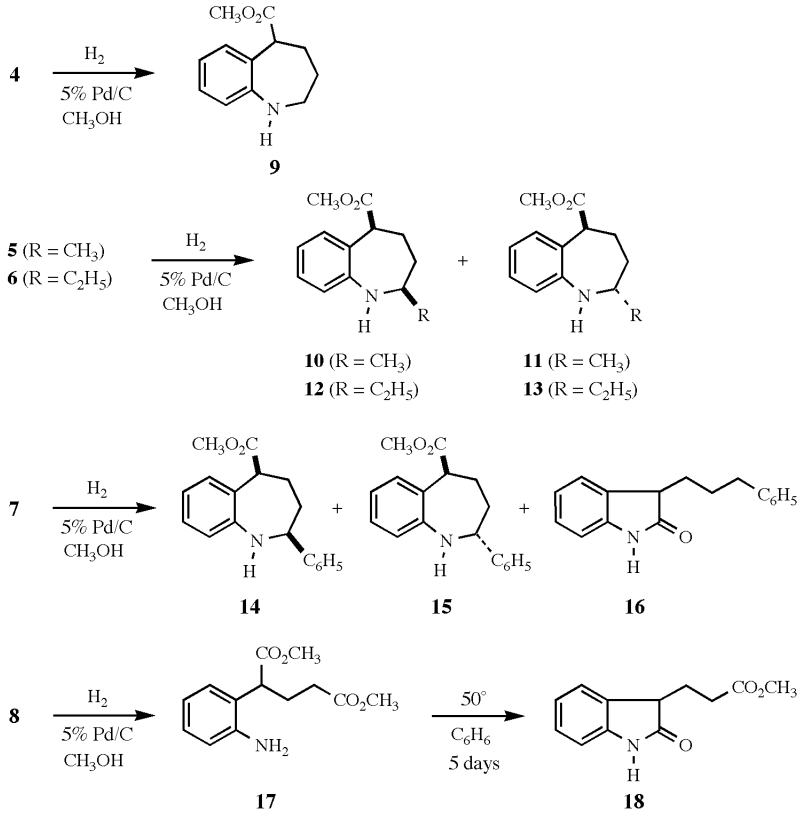


aqueous perchloric acid in tetrahydrofuran [10] to give nitro aldehyde **4** in 93% yield. Substrates **5**-**8** were generated by adapting the alkylation procedure above [8] for the conjugate addition of the methyl 2-nitrophenylacetate anion to methyl vinyl ketone, ethyl vinyl ketone, phenyl vinyl ketone [11] and methyl acrylate, respectively. The addition products were isolated in 71-94% yields.

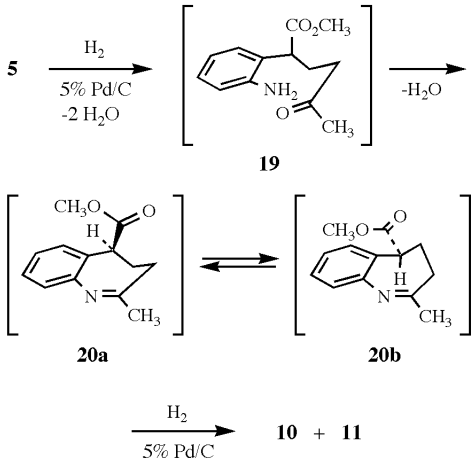
The results of our study are summarized in Scheme 2. Reduction of nitro aldehyde **4** under 4 atmospheres of hydrogen in methanol at 30° using 20 weight percent of 5% palladium-on-carbon gave methyl 2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (**9**) in 60% yield. Similar reduction of nitro ketones **5** and **6** produced mixtures of the *cis*- and *trans*-2-alkyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylic esters in 98% and 76% yields, respectively. The ratio of *cis*:*trans* products **10**:**11** from **5** was 10:1; the ratio of *cis*:*trans* products **12**:**13** from **6** was 8.5:1. Reduction-reductive amination of the phenyl-substituted substrate **7** gave *cis*- and *trans*-2-phenyl-2,3,4,5-tetrahydrobenzazepines **14** and **15** in a ratio of 5:1, but only 20% yield; the major product was indolinone **16** in 32% yield. Finally, attempted reduction-lactamization of nitro diester **8** under hydrogenation conditions gave the uncyclized amino diester **17** in 97% yield. All products were easily separated and purified by chromatographic methods.

The reaction sequence to produce the 2,3,4,5-tetrahydro-1*H*-1-benzazepines likely follows the same path as our earlier 1,2,3,4-tetrahydroquinoline synthesis [2]—reduction of the aromatic nitro group followed by reductive amination of the *N*-hydroxylamino (or amino) group with the side chain carbonyl (Scheme 3). Diastereoselection in the tetrahydroquinoline ring closures occurs during hydrogenation of the final cyclic imine intermediate. In this step, steric shielding of the top face of the imine by the transannular ester group serves to direct the incoming hydrogen to the opposite side of the molecule giving a *cis* relationship between the C2 alkyl and the C4 ester groups. The reactions to produce 2-alkyl (or phenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylic esters show a similar preference for the *cis* products [12], but to a lesser degree than in the tetrahydroquinolines. Two major factors likely contribute to this reduced diastereoselectivity. First, the C5 ester in **20a** is further away from the imine double bond and thus exerts less influence in the final reduction step. Second, the more flexible seven-membered cyclic imine can place the ester group in a pseudo-equatorial position (as in **20b**) where it would be unable to block the top face of the imine double bond. Thus, formation of at least minor quantities of the *trans* products would be expected.

Scheme 2



Scheme 3



While cyclizations in the tetrahydroquinoline series [2] did not give any appreciable side reactions, closure of the seven-membered rings was sufficiently slow to allow competing processes to occur [13]. This was apparent in the cyclization of **7** where reduction of the phenyl-conjugated ketone [14] forced reaction of the *N*-hydroxylamino (or amino) nitrogen with the side chain ester to give indolinone **16** in preference to tetrahydrobenzazepines **14** and **15**. The use of lower hydrogen pressure (1.5 atmospheres) and temperature (20°) did not significantly alter this result. These findings stand in contrast to a related eight-membered ring closure, performed under identical conditions in ethanol, which showed a marked temperature dependence, with phenyl ketone reduction favored at 45-50° and reductive cyclization favored at 20° [15].

Catalytic hydrogenation of nitro diester **8** using our standard protocol gave the uncyclized amino diester **17** in nearly quantitative yield. This result matches an earlier report [4b] that also described the isolation of an amino ester from a nitro ester substrate under catalytic hydrogenation conditions. Closure to the lactam, in this case, required additional heating in 1:1 ethanol:water. The current system has two esters positioned to generate either a five-membered or a seven-membered lactam upon cyclization with the amino group. Mild heating of **17** at 50° in benzene for 5 days gave the expected [13,16] five-membered lactam **18** as the only product in 76% yield.

In conclusion, an efficient synthesis of 2,3,4,5-tetrahydro-1*H*-1-benzazepine derivatives has been developed using a tandem reduction-reductive amination strategy. Cyclizations that produce 2-alkyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylic esters gave products having the C2 alkyl and the C5 ester groups predominantly *cis*, though selectivity was not as good as in analogous closures to tetrahydroquinolines. Despite this reduced diastereoselectivity, most of the *cis*-2,5-disubstituted products were easily isolated in good to excellent yields. Finally, attempted reduction-lactamization of a nitro diester cyclization substrate gave the amino diester, which required further heating for ring closure.

EXPERIMENTAL

Commercial reagents and solvents were used as received. Potassium carbonate was ground into a fine powder, dried under vacuum for 24 hours at 120°, and stored in an oven at 120° until needed. Methyl (2-nitrophenyl)acetate (**1**) was prepared as described previously [2]. Commercially available 4-bromo-1-butene was converted to the iodide by treatment with sodium iodide in acetone [9]. Phenyl vinyl ketone was prepared by the method of Reich and co-workers [11].

All reactions were run under dry nitrogen in oven-dried glassware. The sodium bicarbonate (saturated) and sodium chloride (saturated) used in various work-up procedures were aqueous solutions. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech no. 21521) with ultraviolet detection. Preparative separations were performed by one of the following methods: (1) flash column chromatography [17] on silica gel (grade 62, 60-200 mesh) containing ultraviolet-active phosphor (Sorbent Technologies, UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20-cm x 20-cm silica gel GF plates (Analtech, no. 02015). Band elution for both methods was monitored using a hand-held ultraviolet lamp. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and referenced to polystyrene. ^{1}H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, using tetramethylsilane as an internal standard; coupling constants (J) are given in Hz. High-resolution mass spectra (electron impact/direct probe) were obtained at 70 electron volts.

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.

Methyl (±)-2-(2-Nitrophenyl)-5-hexenoate (**2**).

The general procedure of Makosza and Tyrala [8] was used. A 250-mL, three-necked, round-bottomed flask equipped with an addition funnel, a reflux condenser, and a magnetic stir bar was charged with 100 mL of dry acetonitrile, 11.6 g (84 mmole) of anhydrous potassium carbonate, and 12 mg of 18-crown-6. Stirring was initiated and 1.95 g (10.0 mmole) of **1** was added dropwise over 10 minutes. The resulting blue solution was stirred for 10 minutes and 2.27 g (12.5 mmole) of 4-iodo-1-butene was added dropwise. The mixture was warmed to 55-60° and the reaction was allowed to proceed until thin layer chromatography indicated complete consumption of **1** (18 hours). After cooling to room temperature, the crude reaction mixture was diluted with ether, vacuum filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography on a 30 cm x 2.5 cm silica gel column eluted with 5-15% ether in hexanes to give 1.49 g (60%) of **2** as a light yellow oil; ir: 1734, 1528, 1358 cm^{-1}; ^{1}H nmr: δ 7.88 (dd, 1H, J = 8.1, 1.4), 7.55 (m, 2H), 7.42 (ddd, 1H, J = 8.8, 7.0, 1.8), 5.77 (ddt, 1H, J = 17.7, 9.8, 6.5), 5.02 (m, 1H), 4.97 (m, 1H), 4.20 (t,

1H, J = 7.2), 3.67 (s, 3H), 2.28 (m, 1H), 2.07 (m, 2H), 1.95 (m, 1H); ^{13}C nmr: δ 173.1, 149.3, 137.0, 133.5, 133.0, 129.9, 128.1, 124.7, 115.6, 52.3, 45.4, 32.0, 31.6.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.41; H, 6.01; N, 5.75.

Methyl (±)-2-(2-Nitrophenyl)-5-oxopentanoate (**4**).

A solution of 1.20 g (4.82 mmole) of **2** in 125 mL of methanol was cooled to –78° and treated with ozone until thin layer chormatography indicated complete consumption of the starting material. Excess ozone was purged with a stream of dry nitrogen and the reaction was quenched at –78° by addition of 5.08 g (84.9 mmole) of dimethyl sulfide and 200 mg of *p*-toluenesulfonic acid. The resulting solution was warmed to room temperature and stirred for 8 hours, then concentrated under reduced pressure. The crude reaction mixture was diluted with ether, washed with sodium bicarbonate and sodium chloride, and dried (magnesium sulfate). Vacuum filtration and concentration under reduced pressure gave the dimethyl acetal **3** containing 5-10% of aldehyde **4**. This mixture was dissolved in 25 mL of tetrahydrofuran, cooled to 0°, and 25 mL of 3% aqueous perchloric acid was added dropwise with stirring [10]. The solution was stirred at 0° for 1 hour and at room temperature for 4 hours, then extracted with dichloromethane (three times). The combined organic extracts were washed with sodium bicarbonate (two times) and sodium chloride, dried (magnesium sulfate), vacuum filtered, and concentrated under reduced pressure to yield 1.14 g (94%) of **4**, which was used without further purification; ir: 1737, 1527, 1353 cm^{-1}; ^{1}H nmr: δ 9.76 (s, 1H), 7.91 (dd, 1H, J = 8.1, 1.4), 7.61 (ddd, 1H, J = 8.0, 7.5, 1.4), 7.49 (dd, 1H, J = 8.0, 1.4), 7.45 (ddd, 1H, J = 8.0, 7.5, 1.4), 4.21 (t, 1H, J = 7.2), 3.67 (s, 3H), 2.53 (m, 3H), 2.18 (m, 1H); ^{13}C nmr: δ 200.8, 172.5, 149.3, 133.3, 132.9, 129.9, 128.5, 124.9, 52.4, 45.3, 41.6, 25.1.

Representative Procedure for Conjugate Addition Reactions: Methyl (±)-2-(2-Nitrophenyl)-5-oxohexanoate (**5**).

The general procedure of Makosza and Tyrala [8] was adapted. A 250-mL, three-necked, round-bottomed flask equipped with an addition funnel, a reflux condenser, and a magnetic stir bar was charged with 100 mL of dry acetonitrile, 11.6 g (84 mmole) of anhydrous potassium carbonate, and 12 mg of 18-crown-6. Stirring was initiated and 1.95 g (10.0 mmole) of **1** was added dropwise over 10 minutes. The resulting blue solution was stirred for 10 minutes and 0.92 g (13.2 mmole) of methyl vinyl ketone was added dropwise. The mixture was warmed to 55-60°, and the reaction was allowed to proceed until thin layer chromatography indicated complete consumption of **1** (48 hours). After cooling to room temperature, the mixture was diluted with ether, vacuum filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography on a 30 cm x 2.5 cm silica gel column eluted with 5-15% ether in hexanes to give 2.40 g (91%) of **5** as a light yellow oil; ir: 1744, 1716, 1530, 1358 cm^{-1}; ^{1}H nmr: δ 7.89 (dd, 1H, J = 8.1, 1.5), 7.60 (ddd, 1H, J = 8.2, 7.4, 1.6), 7.51 (dd, 1H, J = 8.0, 1.5), 7.44 (ddd, 1H, J = 8.1, 7.3, 1.5), 4.16 (t, 1H, J = 7.3), 3.66 (s, 3H), 2.60-2.42 (complex, 3H), 2.12 (s, 3H), 2.11 (m, 1H); ^{13}C nmr: δ 207.3, 172.6, 149.5, 140.4, 133.2, 129.9, 128.3, 124.7, 52.3, 45.1, 41.1, 29.9, 26.6.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.87; H, 5.66; N, 5.28. Found: C, 58.80; H, 5.72; N, 5.33.

Methyl (±)-2-(2-Nitrophenyl)-5-oxoheptanoate (**6**).

This compound (2.62 g, 94%) was isolated as a light yellow oil; ir: 1744, 1716, 1530, 1356 cm^{-1}; ^{1}H nmr: δ 7.89 (dd, 1H, J = 7.9, 1.4), 7.60 (ddd, 1H, J = 7.9, 7.2, 1.4), 7.51 (dd, 1H, J = 7.9, 1.6), 7.43 (ddd, 1H, J = 8.2, 7.2, 1.6), 4.19 (t, 1H, J = 7.0), 3.66 (s, 3H), 2.46 (m, 3H), 2.39 (q, 2H, J = 7.4), 2.13 (m, 1H), 1.04 (t, 3H, J = 7.4); ^{13}C nmr: δ 210.1, 172.7, 149.4, 140.9, 133.2, 130.0, 128.3, 124.7, 52.3, 45.2, 39.7, 35.9, 26.7, 7.7.

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.09; N, 5.02. Found: C, 60.14; H, 6.15; N, 5.04.

Methyl (±)-2-(2-Nitrophenyl)-5-oxo-5-phenylpentanoate (**7**).

This compound (3.18 g, 90%) was isolated as a light yellow oil; ir: 1736, 1687, 1530, 1353 cm^{-1}; ^{1}H nmr: δ 7.91 (m, 3H), 7.57 (m, 3H), 7.44 (m, 3H), 4.32 (t, 1H, J = 7.4), 3.67 (s, 3H), 3.07 (m, 2H), 2.64 (m, 1H), 2.30 (m, 1H); ^{13}C nmr: δ 198.8, 172.7, 149.4, 136.6, 133.3, 133.2, 133.1, 130.0, 128.6, 128.3, 128.0, 124.8, 52.3, 45.4, 36.3, 27.2.

Anal. Calcd. for $C_{18}H_{17}NO_5$: C, 66.06; H, 5.20; N, 4.28. Found; C, 65.92; H, 5.24; N, 4.31.

Dimethyl (±)-2-(2-Nitrophenyl)pentanedioate (**8**).

This compound (1.99 g, 71%) was isolated as a light yellow oil; ir: 1739, 1530, 1357 cm^{-1}; ^{1}H nmr: δ 7.91 (dd, 1H, J = 8.1, 1.6), 7.60 (ddd, 1H, J = 7.9, 7.3, 1.6), 7.49 (dd, 1H, J = 7.9, 1.6), 7.44 (ddd, 1H, J = 8.1, 7.3, 1.6), 4.27 (t, 1H, J = 7.3), 3.67 (2 s, 6H), 2.54 (m, 1H), 2.37 (m, 2H), 2.19 (m, 1H); ^{13}C nmr: δ 172.9, 172.5, 149.4, 133.2, 132.9, 130.0, 128.4, 124.9, 52.4, 51.7, 45.2, 31.6, 27.9.

Anal. Calcd. for $C_{13}H_{15}NO_6$: C, 55.52; H, 5.34; N, 4.98. Found: C, 55.37; H, 5.40; N, 5.05.

Methyl (±)-2,3,4,5-Tetrahydro-1*H*1-benzazepine-5-carboxylate (**9**).

To a solution of 570 mg (2.27 mmole) of **4** in 200 mL of methanol was added 125 mg of 5% palladium-on-carbon and the mixture was hydrogenated in a stainless steel hydrogenation vessel under 4 atmospheres of hydrogen for 3 hours at 30°. The crude reaction mixture was concentrated, diluted with ether, and vacuum filtered through a pad of Celite 545® topped with a layer of magnesium sulfate to remove the catalyst. Concentration of the filtrate produced a light yellow oil that was purified by preparative thin layer chromatography eluted with increasing concentrations of ether in hexanes (25-50%) to give 280 mg (60%) of **9** as a light yellow oil; ir: 3366, 1730 cm^{-1}; ^{1}H nmr: δ 7.10 (td, 1H, J = 7.7, 1.6), 7.03 (ddd, 1H, J = 7.5, 1.9, 1.0), 6.87 (td, 1H, J = 7.5, 1.2), 6.75 (d, 1H, J = 7.7, 1.2), 3.86 (dd, 1H, J = 7.4, 2.2), 3.72 (br s, 1H), 3.70 (s, 3H), 3.11 (ddd, 1H, J = 12.8, 7.9, 3.2), 2.96 (ddd, 1H, J = 12.8, 8.0, 3.3), 2.20 (m, 1H), 1.93-1.76 (complex, 3H); ^{13}C nmr: δ 174.4, 149.9, 130.4, 130.1, 127.7, 121.0, 120.2, 51.8, 50.2, 48.0, 28.5, 28.2; hrms: m/z Calcd. for $C_{12}H_{15}NO_2$: 205.1103; Found: 205.1101.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32; N, 6.83. Found: C, 70.39; H, 7.39; N, 6.75.

Reductive Cyclization of **5**.

To a solution of 1.00 g (3.77 mmole) of **5** in 200 mL of methanol was added 200 mg of 5% palladium-on-carbon and the mixture was hydrogenated as described for the preparation of **9**. The crude product was purified by preparative thin layer chromatography eluted with 25-50% ether in hexanes to give two major bands. Band 1 (fastest moving) gave **11**; band 2 gave **10**.

Methyl (±)-(2*S**,5*S**)-2-Methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (**11**).

This compound (70 mg, 9%) was isolated as a light yellow oil that crystallized on standing at 0°. The crystals were triturated at 0° with 1% ether in petroleum ether to give a white solid, mp 45-47°; ir: 3353, 1735 cm^{-1}; ^1H nmr: δ 7.07 (td, 1H, J = 7.5, 1.4), 6.94 (dd, 1H, J = 7.6, 1.4), 6.85 (td, 1H, J = 7.5, 1.2), 6.73 (dd, 1H, J = 7.6, 1.2), 3.84 (dd, 1H, J = 8.5, 2.0), 3.75 (s, 3H), 3.33 (br s, 1H), 3.05 (m, 1H), 2.15 (m, 1H), 1.88 (m, 2H), 1.51 (m, 1H), 1.20 (d, 3H, J = 6.4); ^{13}C nmr: δ 175.3, 148.3, 129.7, 128.8, 127.4, 121.0, 120.3, 52.5, 51.8, 48.9, 36.2, 27.5, 23.3; hrms: m/z Calcd. for $C_{13}H_{17}NO_2$: 219.1259; Found: 219.1257.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.42; H, 7.82; N, 6.31.

Methyl (±)-(2*R**,5*S**)-2-Methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (**10**).

This compound (740 mg, 90%) was isolated as a white solid, mp 102-104° (ether-petroleum ether); ir: 3359, 1737 cm^{-1}; ^1H nmr: δ 7.10 (td, 1H, J = 7.5, 1.6), 7.03 (dd, 1H, J = 7.4, 1.6), 6.87 (td, 1H, J = 7.4, 1.3), 6.74 (dd, 1H, J = 7.5, 1.3), 3.84 (dd, 1H, J = 6.0, 2.3), 3.65 (s, 3H), 3.27 (br s, 1H), 2.91 (m, 1H), 2.42 (m, 1H), 1.69 (m, 3H), 1.21 (d, 3H, J = 6.5); ^{13}C nmr: δ 173.7, 148.6, 131.2, 130.3, 127.9, 121.2, 120.8, 53.6, 51.8, 50.3, 34.9, 28.1, 24.0; hrms: m/z Calcd. for $C_{13}H_{17}NO_2$: 219.1259; Found: 219.1258.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.45; H, 7.84; N, 6.29.

Reductive Cyclization of **6**.

To a solution of 1.00 g (3.58 mmole) of **6** in 200 mL of methanol was added 200 mg of 5% palladium-on-carbon and the mixture was hydrogenated as described for the preparation of **9**. The crude product was purified by preparative thin layer chromatography eluted with 25-50% ether in hexanes to give two major bands. Band 1 (fastest moving) gave **13**; band 2 gave **12**.

Methyl (±)-(2*S**,5*S**)-2-Ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (**13**).

This compound (67 mg, 8%) was isolated as a light yellow oil that crystallized on standing at 0°. The crystals were triturated at 0° with 1% ether in petroleum ether to give a white solid, mp 46-48°; ir: 3365, 1735 cm^{-1}; ^1H nmr: δ 7.05 (td, 1H, J = 7.4, 1.5), 6.95 (dd, 1H, J = 7.6, 1.5), 6.85 (td, 1H, J = 7.4, 1.2), 6.73 (dd, 1H, J = 7.6, 1.2), 3.85 (dd, 1H, J = 8.3, 2.3), 3.74 (s, 3H), 3.42 (br s, 1H), 2.81 (m, 1H), 2.16 (m, 1H), 1.92 (m, 2H), 1.58-1.42 (complex, 3H), 0.98 (t, 3H, J = 7.4); ^{13}C nmr: δ 175.2, 148.2, 129.5, 129.1, 127.4, 120.8, 120.3, 58.3, 51.8, 49.0, 33.5, 29.5, 26.9, 10.7; hrms: m/z Calcd. for $C_{14}H_{19}NO_2$: 233.1416; Found: 233.1413.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.16; H, 8.25; N, 5.89.

Methyl (±)-(2*R**,5*S**)-2-Ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (**12**).

This compound (566 mg, 68%) was isolated as a white solid, mp 74-76° (ether-petroleum ether); ir: 3360, 1728 cm^{-1}; ^1H nmr: δ 7.11 (td, 1H, J = 7.4, 1.6), 7.03 (dd, 1H, J = 7.7, 1.6), 6.88 (td, 1H, J = 7.4, 1.2), 6.76 (dd, 1H, J = 7.7, 1.2), 3.85 (dd, 1H, J = 6.3, 2.2), 3.66 (s, 3H), 3.39 (br s, 1H), 2.65 (m, 1H), 2.42 (m, 1H), 1.79-1.63 (complex, 3H), 1.52 (quintet, 2H, J = 7.4), 0.99 (t, 3H, J = 7.4); ^{13}C nmr: δ 173.8, 148.6, 130.9, 130.5, 127.9, 121.2, 120.8, 59.7, 51.8, 50.2, 32.7, 30.1, 28.0, 10.8; hrms: m/z Calcd. for $C_{14}H_{19}NO_2$: 233.1416; Found: 233.1414.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.01. Found: C, 72.27; H, 8.23; N, 5.91.

Reductive Cyclization of **7**.

To a solution of 510 mg (1.56 mmole) of **7** in 200 mL of methanol was added 125 mg of 5% palladium-on-carbon and the mixture was hydrogenated as described for the preparation of **9**. The crude product was purified by preparative thin layer chromatography eluted with 25-50% ether in hexanes to give three major bands. Band 1 (fastest moving) gave **15**; band 2 gave **14**; band 3 gave **16**.

Methyl (±)-(2*R**,5*S**)-2-Phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (**15**).

This compound (14 mg, 3%) was isolated as a white solid, mp 68-70° (ether-petroleum ether); ir: 3349, 1733 cm^{-1}; ^1H nmr: δ 7.38-7.25 (complex, 5H), 7.12 (m, 2H), 6.92 (td, 1H, J = 7.3, 1.2), 6.74 (d, 1H, J = 7.6), 3.94 (dd, 1H, J = 5.8, 3.3), 3.85 (dd, 1H, J = 11.2, 1.7), 3.70 (s, 3H), 3.59 (br s, 1H), 2.52 (m, 1H), 2.16 (m, 1H), 1.97-1.72 (complex, 2H); ^{13}C nmr: δ 173.5, 148.4, 145.7, 131.3, 130.4, 128.7, 128.1, 127.5, 126.4, 121.6, 121.0, 63.4, 51.9, 50.1, 35.2, 28.1; hrms: m/z Calcd. for $C_{18}H_{19}NO_2$: 281.1416; Found: 281.1415.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 77.04; H, 6.83; N, 4.89.

Methyl (±)-(2*S**,5*S**)-2-Phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-carboxylate (**14**).

This compound (73 mg, 17%) was isolated as a white solid, mp 82-84° (ether-petroleum ether); ir: 3343, 1732 cm^{-1}; ^1H nmr: δ 7.42-7.27 (complex, 5H), 7.10 (td, 1H, J = 7.2, 1.7), 6.99 (dd, 1H, J = 7.6, 1.7), 6.92 (td, 1H, J = 7.2, 1.3), 6.76 (dd, 1H, J = 7.6, 1.3), 3.96 (m, 2H), 3.79 (s, 3H), 3.63 (br s, 1H), 2.22 (m, 1H), 1.95 (overlapping m, 3H); ^{13}C nmr: δ 175.5, 148.1, 145.5, 134.2, 130.6, 128.8, 128.1, 127.6, 126.4, 121.7, 120.8, 62.4, 51.9, 48.6, 36.9, 27.8; hrms: m/z Calcd. for $C_{18}H_{19}NO_2$: 281.1416; Found: 281.1414.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.99; H, 6.84; N, 4.88.

(±)-3-(3-Phenylpropyl)-2-indolinone (**16**).

This compound (125 mg, 32%) was isolated as a white powder, mp 82-83° (ether-petroleum ether); lit mp 84-85° [18]; ir: 3217, 1708 cm^{-1}; ^1H nmr: δ 8.70 (br s, 1H), 7.28-7.10 (complex, 7H), 7.01 (t, 1H, J = 7.5), 6.88 (d, 1H, J = 7.5), 3.48 (t, 1H, J = 5.9), 2.61 (overlapping m, 2H), 2.00 (m, 2H), 1.78-1.60 (complex, 2H); ^{13}C nmr: δ 180.4, 141.8, 141.5, 129.6, 128.3 (2), 127.8, 125.8, 124.1, 122.3, 109.7, 45.9, 35.8, 30.1, 27.5; hrms: m/z Calcd. for $C_{17}H_{17}NO$: 251.1310; Found: 251.1307.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.27; H, 6.77; N, 5.58. Found: C, 80.96; H, 6.87; N, 5.54.

Dimethyl (±)-2-(2-Aminophenyl)pentanedioate (**17**).

To a solution of 750 mg (2.66 mmole) of **8** in 200 mL of methanol was added 180 mg of 5% palladium-on-carbon and the mixture was hydrogenated as described for the preparation of **9**. The crude product was purified by preparative thin layer chromatography eluted with 25-50% ether in hexanes to give 650 mg

(97%) of **17** as a yellow oil that darkened on exposure to air; ir: 3453, 3378, 3263, 1732 cm^{-1}; ^1H nmr: δ 7.07 (overlapping t and d, 2H, J = 7.5), 6.74 (td, 1H, J = 7.5, 1.1), 6.69 (d, 1H, J = 7.5), 4.11 (br s, 2H), 3.78 (t, 1H, J = 7.4), 3.68 (s, 3H), 3.67 (s, 3H), 2.35 (m, 3H), 2.19 (m, 1H); ^{13}C nmr: δ 174.0, 173.9, 144.9, 128.2, 127.9, 122.7, 118.9, 116.7, 52.2, 51.7, 45.4, 31.4, 25.8; hrms: m/z Calcd. for $C_{13}H_{17}NO_4$: 251.1157; Found: 251.1155.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.77; N, 5.58. Found; C, 62.47; H, 6.85; N, 5.44.

Methyl (±)-3-(2-Oxoindolin-3-yl)propanoate (**18**).

A solution of 650 mg (2.59 mmole) of **17** in 25 mL of benzene was heated at 50° until thin layer chromatography indicated complete conversion of the starting material (5 days). The solution was concentrated under reduced pressure and purified by preparative thin layer chromatography eluted with 50% ether in hexanes. The major band afforded 430 mg (76%) of **18** as a light yellow oil that crystallized upon standing. Recrystallization from ether-petroleum ether gave **18** as a white solid, mp 76-77°; lit mp 79-80° [19]; ir: 3259, 1733, 1711 cm^{-1}; ^1H nmr: δ 9.51 (br s, 1H), 7.22 (overlapping t and d, 2H, J = 7.6), 7.03 (td, 1H, J = 7.5, 1.1), 6.93 (d, 1H, J = 7.5), 3.63 (s, 3H), 3.55 (t, 1H, J = 6.2), 2.58-2.21 (complex, 4H); ^{13}C nmr: δ 180.2, 173.3, 141.7, 128.5, 128.1, 124.0, 122.3, 109.9, 51.6, 44.9, 29.9, 25.3; hrms: m/z Calcd. for $C_{12}H_{13}NO_3$: 219.0895; Found: 219.0892.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.94; N, 6.39. Found: C, 65.89; H, 6.01; N, 6.28.

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