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A General Route to the Synthesis of 1,5-Methano- and 1,5-Ethano-2,3,4,5-tetrahydro-1*H*-3-benzazepines

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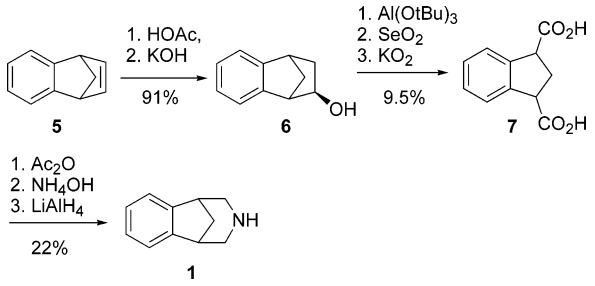
Abstract: A general approach to preparing 1,5-methano- (**1**) and 1,5-ethano-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**2**) is discussed. This strategy involves converting an indanone or tetralone (**4**) to a cyanohydrin (**3**) which is subjected to hydrogenolysis followed by lactamization and reduction to provide bicyclic aryl piperidine (**1**) and bicyclic aryl homopiperidine (**2**).

We recently desired an efficient and general route for the preparation of 1,5-methano- (**1**) and 1,5-ethano-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**2**). Both **1** and **2** have been prepared and studied as potential morphine-type analgesics; however, both were accessed by different synthetic routes and neither route was generally applicable to the respective homologue.[1,2]

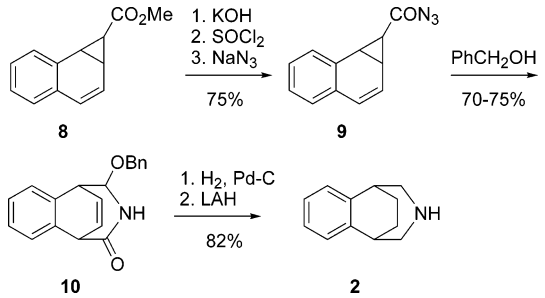
The previous preparation of **1** is shown in Scheme 1.[1] The Diels−Alder reaction between cyclopentadiene and benzyne provided benzonorbornadiene **5**.[3] Solvolysis of the alkene with acetic acid followed by saponification provided *exo*-benzonorbornenol (**6**)[4] from which sequential oxidation to the corresponding ketone,[5] diketone,[6] and finally dicarboxylic acid (**7**) proceeded in low yield. The conversion of **7** to the cyclic imide in two steps followed by reduction provided **1**. This synthesis produced **1** in nine steps and 1.2% overall yield. This benzyne Diels−Alder based approach is not well suited to the preparation of the ethylene-bridged homologue **2** as the 1,4-cyclohexadiene/benzyne cycloaddition gives an inseparable, complex mixture and proceeds in low yield.[7]

The reported synthesis of **2** is shown in Scheme 2.[2] Methyl-1-benzonorcaradienecarboxylate (**8**) was generated by heating methyl diazoacetate with an excess of naphthalene. Saponification to the acid followed by generation of the corresponding acid chloride and treatment with sodium azide provided acyl azide **9**. Heating **9** in benzyl alcohol affected rearrangement to product **10**.[8]

SCHEME 1. Mazzocchi's Strategy to Benzazepine 1[1]



SCHEME 2. Walter's Strategy to Benzazepine 2[2]



Hydrogenation of the olefin was followed by reduction using $LiAlH_4$ to give **2**. This synthesis produced **2** in seven steps and 21% overall yield. Due to the mechanistic requirement of the C3−C4 olefin of **9** for the rearrangement of **9** → **10**, this approach is not applicable to the corresponding cyclopropane acyl azide derived from indene that would be required for the synthesis of **1** via this route. Additionally, it has been reported that treatment of structurally related cyclopropane acyl azides derived from indenes under similar conditions proceeds to give the expected Curtius rearrangement products.[9]

We sought an alternative approach to both **1** and **2** that would avoid the problematic benzyne chemistry.[10] Additionally, we hoped to avoid the low-yielding, sequential oxidation process used in the Mazzochi synthesis as well as the reported improvements in this process that involve the use of heavy metals.[11] We also sought a route that would be generally applicable to this class of compounds.

We recognized that commercially available indanone-3-carboxylic acid (**11**) should be a viable precursor to **1** through homologation with cyanide or nitromethane (Scheme 3). This strategy was initiated by converting indanone **11** to methyl ester **4a** in excellent yield.[12] Ester **4a** was treated with TMSCN (1.2 equiv) and ZnI_2 (0.01 equiv) in toluene at 50 °C for 5 h to afford silylated

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(1) For the preparation of **1**, see: Mazzocchi, P. H.; Stahly, B. C. *J. Med. Chem.* **1979**, *22*, 455.
(2) For the preparation of **2**, see: Walter, L. A.; Chang, W. K. *J. Med. Chem.* **1975**, *18*, 206.
(3) Wittig, G.; Knauss, E. *Chem. Ber.* **1958**, *91*, 895.
(4) Cristol, S. J.; Caple, R. *J. Org. Chem.* **1966**, *31*, 2741.
(5) Bartlett, P. D.; Giddings, W. P. *J. Am. Chem. Soc.* **1960**, *82*, 1240.
(6) Tanida, H.; Hata, Y. *J. Am. Chem. Soc.* **1966**, *88*, 4289.
(7) Crews, P.; Beard, J. *J. Org. Chem.* **1973**, *38*, 522 and references therein.
(8) Doering, W. von E.; Goldstein, M. J. *Tetrahedron* **1959**, *5*, 53.
(9) DeMarinis, R. M.; Bryan, W. M.; Shah, D. H.; Hieble, J. P.; Pendleton, R. G. *J. Med. Chem.* **1981**, *24*, 1432.
(10) For recent advances in benzyne-mediated protocols for the formation of benzonorbornadienes, see: Coe, J. W.; Wirtz, M. C.; Bashore, C. G.; Candler, J. *Org. Lett.* **2004**, *6*, 1589.
(11) An improvement in this oxidation strategy has been used that involved osmium-catalyzed dihdroxylation of **5**, $NaIO_4$ cleavage of the resulting diol to a dialdehyde intermediate, and reductive amination with benzylamine to close the benzazepine ring; see: Brooks, P. R.; Caron, S.; Coe, J. W.; Ng, K. K.; Singer, R. A.; Vazquez, E.; Vetelino, M. G.; Watson, H. H.; Whritenour, D. C.; Wirtz, M. C. *Synthesis* **2004**, *(11)*, 1755. For related examples, see: (a) Coe, J. W. *Org. Lett.* **2000**, *2*, 4205. (b) Bashore, C. G.; Samardjiev, I. J.; Bordner, J.; Coe, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 3268.

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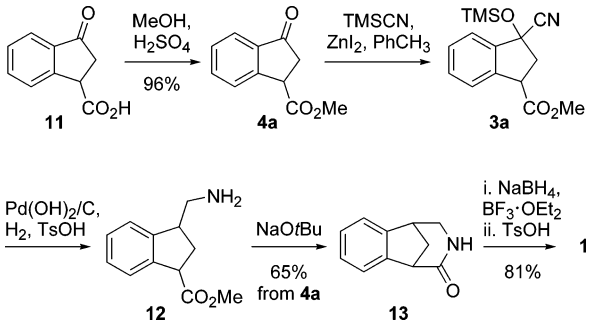
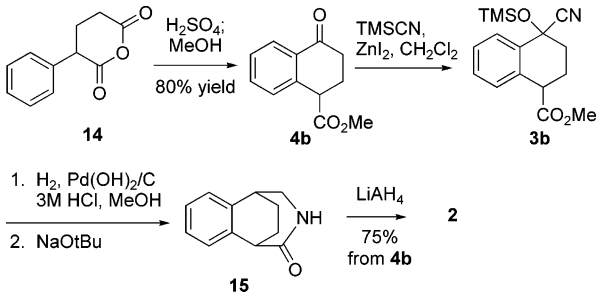
SCHEME 3. Route to 1 via Indanone-3-carboxylic Acid (11)



cyanohydrin **3a** as a 2:1 mixture of diastereomers after aqueous workup.[13] The crude cyanohydrin was subjected to hydrogenolysis using Pearlman's catalyst and *p*-toluenesulfonic acid (1.5 equiv) to provide **12** as a 10:1 mixture of diastereomers.[14,15] There were two critical factors for the success of the hydrogenolysis. First, the excess cyanide needed to be removed prior to the hydrogenolysis step, and this was accomplished with the aqueous workup. Second, it was crucial to use excess acid (>1 equiv) to facilitate the hydrogenolysis of **3a**. Under these acidic conditions, the nitrile was reduced relatively rapidly and 1 equiv of acid was needed to prevent deactivation of the catalyst with the resulting free amine. Additionally, the reduction of the benzylic alcohol was sluggish and did not proceed to completion unless excess acid was employed. The observed increase in diastereoselectivity during the hydrogenolysis is consistent with initial elimination of the benzyl alcohol to an indene intermediate that is reduced from the least hindered face providing the cis isomer as the major product.[16] Removal of the catalyst by filtration followed by treatment of the filtrate containing **12** with sodium *tert*-butoxide at room temperature led to formation of **13**, which was isolated by recrystallization in 65% yield from **4a**. A minor side product that formed during the lactam cyclization was the amino acid hydrolysis product of **12**, which failed to cyclize to **13** under all conditions examined. Lactam **13** was reduced with borane (generated in situ), and the tosylate salt of **1** was isolated in 81% yield.[17] In summary, this route produced **1** in five synthetic steps and 51% overall yield.[18]

Utilizing the same strategy, the ethylene bridge homologue (**2**) was prepared from tetralone-4-carboxylate

SCHEME 4. Route to 2 via Tetralone-4-carboxylate Methyl Ester



methyl ester **4b** (Scheme 4).[19] 2-Phenylglutaric anhydride (**14**) was heated in sulfuric acid producing tetralone-4-carboxylate,[20] and this mixture was conveniently converted to ester **4b** in 80% yield by pouring the resulting acidic mixture into cold methanol and warming to room temperature. Ester **4b** was treated with TMSCN and ZnI_2 to give silylated cyanohydrin **3b** as a 1.2:1 mixture of diastereomers.[21] Hydrogenolysis of the crude cyanohydrin **3b** using Pearlman's catalyst and 3 M HCl (aq) provided the corresponding primary amine which, after filtration to remove the catalyst, was treated with sodium *tert*-butoxide to give **15**.[22] Lactam **15** was reduced with lithium aluminum hydride and **2** was isolated in 75% yield from **4b**. This route produced **2** in five steps and 60% overall yield.

In summary, we have provided a new, common strategy for the preparation of **1** and **2**. This strategy involves homologating readily available indanone and tetralone starting materials to their corresponding cyanohydrins. Hydrogenolysis of the cyanohydrin intermediates with concomitant reduction of the nitrile followed by lactamization and reduction of the resulting lactams provides the desired bicyclic aryl piperidine **1** and bicyclic aryl homopiperidine **2**. This sequence represents an efficient, high-yielding, general route to both of these benzazepine structures.

Experimental Section

3-Oxoindan-1-carboxylic Acid Methyl Ester (4a). A solution of 10.0 g of 3-oxoindan-1-carboxylic acid (56.8 mmol, 1.0 equiv) and 0.25 mL of concentrated sulfuric acid in 20 mL of methanol was heated to reflux for 4 h. The reaction mixture was then cooled to room temperature and diluted with 100 mL of methyl *tert*-butyl alcohol. The organic solution was washed twice with 60 mL of a saturated aqueous sodium bicarbonate solution and once with 50 mL of a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated. The product, 3-oxoindan-1-carboxylic acid methyl ester, crystallized as a white solid upon concentration (10.4 g, 96%): mp 46−47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 4.29 (dd, J = 8.0, 3.4 Hz, 1H), 3.76 (s, 3H), 3.13 (dd, J = 19.1, 3.4 Hz, 1 H), 2.86 (dd, J =

(12) House, H. O.; Sauter, F. J.; Kenyon, W. G.; Riehl, J.-J. *J. Org. Chem.* **1968**, *33*, 957.

(13) (a) Gassman, P. G.; Talley, J. J. *Tetrahedron Lett.* **1978**, *19*, 3773. (b) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *Chem. Commun.* **1973**, 55. (c) Lidy, W.; Sundermeyer, W. *Chem. Ber.* **1973**, *106*, 587.

(14) Ratio determined by HPLC and GC−MS. The major component was determined to be the *cis*-isomer as it is rapidly consumed in the subsequent cyclization, whereas the minor isomer is consumed more slowly.

(15) The diastereoselectivity approaches 1:1 upon increased reaction time, suggesting acid-catalyzed isomerization of the ester.

(16) Support for this presumed intermediate has been reported in similar systems; see: Trivedi, B. K.; Blankley, C. J.; Bristol, J. A.; Hamilton, H. W.; Patt, W. C.; Kramer, W. J.; Johnson, S. A.; Bruns, R. F.; Cohen, D. M.; Ryan, M. J. *J. Med. Chem.* **1991**, *34*, 1043.

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(18) For an alternative synthesis of benzazepine **1**, see: Singer, R. A.; McKinley, J. D.; Barbe, G.; Farlow, R. A. *Org. Lett.* **2004**, *6*, 2357.

(19) For an alternative synthesis of tetralone **4b**, see: Oh, S.-H.; Sato, T. *J. Org. Chem.* **1994**, *59*, 3744.

(20) Horning, E. C.; Finelli, A. F. *J. Am. Chem. Soc.* **1949**, *71*, 3204.

(21) The solvent change to methylene chloride was made to expedite removal upon workup. The reaction works in identical yield and diastereoselectivity when run in toluene.

(22) Both *p*-toluenesulfonic acid and 3 M HCl could be used in this reaction without noticeable differences in the overall yield. Use of aqueous HCl for the conversion of **3a** → **12** in Scheme 3 was efficient for the hydrogenolysis but led to increased hydrolysis of the ester.

19.1, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 204.4, 172.5, 151.3, 136.5, 135.2, 129.1, 126.7, 124.1, 52.9, 43.8, 39.7; IR (neat, cm^{-1}) 2954, 1710, 1602, 1462, 1435, 1403, 1319, 1241, 1206, 1168, 1092, 1044, 1014, 986, 881, 837, 760, 686, 580, 538.

3-Cyano-3-trimethylsilanyloxyindan-1-carboxylic Acid Methyl Ester (3a). To a solution of 3.80 g of 3-oxoindan-1-carboxylic acid methyl ester (20.0 mmol, 1 equiv) in 6 mL of toluene and 2 mL of acetonitrile was added 192 mg of zinc iodide (0.600 mmol, 0.03 equiv) followed by 3.47 mL of trimethylsilyl cyanide (26.0 mmol, 1.3 equiv). The reaction mixture was heated to 50 °C for 5 h. The reaction mixture was then cooled to room temperature and diluted with 12 mL of toluene and 8 mL of a saturated aqueous sodium bicarbonate solution. After the mixture was stirred for 1 h, the layers were separated. The organic layer was washed with another 8 mL of a saturated aqueous sodium bicarbonate solution followed by 8 mL of a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give 3-cyano-3-trimethylsilanyloxyindan-1-carboxylic acid methyl ester as an oil (5.61 g, 97%). The silylated cyanohydrin product was obtained as a mixture of two diastereomers in a 2:1 ratio: ^{1}H NMR (400 MHz, $CDCl_3$) (major isomer) δ 7.54−7.50 (m, 1H), 7.42−7.38 (m, 3H), 4.14 (t, J = 7.7 Hz, 1H), 3.78 (s, 3H), 3.01 (dd, J = 13.3, 7.5 Hz, 1H), 2.79 (dd, J = 13.3, 7.5 Hz, 1H), 0.26 (s, 9H); (minor isomer) δ 7.59−7.55 (m, 1H), 7.48−7.44 (m, 3H), 4.29 (t, J = 7.5 Hz, 1H), 3.78 (s, 3H), 3.03 (dd, J = 13.7, 7.5 Hz, 1H), 2.70 (dd, J = 13.7, 7.5 Hz, 1H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) (unassigned) δ 172.3, 172.0, 142.3, 142.1, 140.1, 138.8, 130.8, 130.5, 129.1, 128.9, 125.8, 125.6, 124.7, 124.3, 120.8, 120.6, 75.4, 75.3, 52.7, 52.7, 47.4, 46.8, 45.6, 45.3, 1.4, 1.3; IR (neat, cm^{-1}) 2956, 1739, 1477, 1436, 1253, 1197, 1169, 1135, 1092, 1033, 1011, 880, 843, 756, 623. Anal. Calcd for $C_{15}H_{19}NO_3Si$: C, 62.25; H, 6.62; N, 4.84. Found: C, 62.20; H, 6.53; N, 4.92.

3-Aminomethylindan-1-carboxylic Acid Methyl Ester (12). To a solution of 5.79 g of 3-cyano-3-trimethylsilanyloxyindan-1-carboxylic acid methyl ester (20.0 mmol, 1.0 equiv) in 25 mL of methanol was added 5.71 g of *p*-toluensulfonic acid monohydrate (30.0 mmol, 1.5 equiv). The solution was stirred for 15 min, and then 4.21 g of 20% palladium hydroxide on carbon, 50% wet by weight (3.00 mmol, 0.15 equiv), was added. The reaction mixture was subjected to hydrogenolysis at 50 psi of hydrogen at 50 °C over 24 h. After this time, the reaction mixture was filtered through Celite, and typically the filtrate was used in the next step without further purification. The product could be isolated by concentrating the filtrate in vacuo. The residue was partitioned between 30 mL of methylene chloride and 20 mL of a saturated aqueous solution of sodium carbonate. The aqueous layer was extracted with another 15 mL of methylene chloride. The combined organic layers were washed with 40 mL of a saturated aqueous solution of sodium chloride. The organic solution was dried over anhydrous sodium sulfate and concentrated to afford 3-aminomethylindan-1-carboxylic acid methyl ester as an oil (3.65 g, 89%) with approximately a 10:1 ratio of diastereomers (major diastereomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 6.9, 1.6 Hz, 1H), 7.29−7.25 (m, 3H), 4.09 (t, J = 8.1 Hz, 1H), 3.80 (s, 3H), 3.31−3.24 (m, 1H), 3.14 (dd, J = 12.8, 4.7 Hz, 1H), 2.98 (dd, J = 12.8, 7.3 Hz, 1H), 2.62−2.52 (m, 1H), 2.31−2.42 (m, 1H), 1.3 (bs, 2H).

1,5-Methano-2-oxo-2,3,4,5-tetrahydro-1*H*-3-benzazepine (13). To a solution of 3-aminomethylindan-1-carboxylic acid methyl ester (assume 20.0 mmol, 1 equiv) in 50 mL of methanol (this was the crude reaction mixture from the prior step) was added 3.84 g of NaO-*t*-Bu (40.0 mmol, 2.0 equiv). The reaction mixture was heated to reflux for 2 h. The reaction was cooled to room temperature and concentrated in vacuo. The residue was partitioned between 60 mL of ethyl acetate and 40 mL of 5% aqueous solution of sodium bicarbonate. The aqueous layer was extracted twice more with 50 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated to provide a solid. The solid was recrystallized from 10 mL of toluene to obtain white crystals of 1,5-methano-2-oxo-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1.78 g, 51%): mp = 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 5.62 (s, 1H), 3.68 (dd, J = 11.2, 4.1 Hz, 1H), 3.55 (d, J = 3.7 Hz, 1H), 3.43−3.37 (m, 1H), 3.18 (d, J = 11.2 Hz, 1H), 2.52−2.45 (m, 1H), 2.32 (d, J = 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 144.7, 144.6, 128.0, 127.7, 123.2, 122.9, 49.3, 47.9, 39.1, 38.4; IR (neat, cm^{-1}) 3218, 2949, 2872, 1666, 1485, 1459, 1400, 1328, 1303, 1288, 1250, 1215, 1122, 1104, 1045, 1004, 946, 910, 756, 730, 643, 613. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 75.94; H, 6.27; N, 7.99.

1,5-Methano-2,3,4,5-tetrahydro-1*H*-3-benzazepine Tosylate (1). To a solution of 1.38 g of 1,5-methano-2,3,4,5-tetrahydro-2-oxo-1*H*-3-benzazepine (8.00 mmol, 1 equiv) in 8 mL of tetrahydrofuran was added 603 mg of sodium borohydride (16.0 mmol, 2.0 equiv) followed by slow addition of 2.77 mL of boron trifluoride diethyl etherate (21.6 mmol, 2.7 equiv). Once the effervescence subsided, the reaction mixture was heated to 50 °C for 5 h. The reaction was then cooled to room temperature for addition of 10 mL of methanol (added dropwise at first) and 0.125 mL of concentrated hydrochloric acid. Heating was resumed at a reflux for 12 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue was diluted with 20 mL of 20% aqueous sodium hydroxide followed by 30 mL of methyl *tert*-butyl ether. The mixture was stirred for 30 min, and then the aqueous layer was extracted with another 30 mL of methyl *tert*-butyl ether. The combined organic layers were washed with 40 mL of a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. After concentration in vacuo, 1.67 g of *p*-toluenesulfonic acid monohydrate (8.80 mmol, 1.1 equiv) was added with 20 mL of 2-propanol. The solution was heated until homogeneous and then allowed to gradually cool to room temperature with stirring. White crystals of the tosylate salt of 1,5-methano-2,3,4,5-tetrahydro-1*H*-3-benzazepine formed which were collected by filtration (2.17 g, 81%): mp 207−208 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.69 (d, J = 7.9 Hz, 2H), 7.43−7.32 (m, 4H), 7.23 (d, J = 7.9 Hz, 2H), 3.37 (d, J = 11.2 Hz, 4H), 3.30 (bs, 2H), 3.15 (d, J = 12.4 Hz, 2H), 2.36 (s, 3H), 2.40−2.35 (m, 1H), 2.08 (d, J = 11.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 140.8, 140.5, 139.1, 127.2, 127.2, 124.3, 122.3, 45.1, 39.7, 37.3, 18.7; IR (KBr, cm^{-1}) 3438, 3021, 2958, 2822, 2758, 2719, 2683, 2611, 2424, 1925, 1606, 1497, 1473, 1428, 1339, 1302, 1259, 1228, 1219, 1176, 1160, 1137, 1122, 1087, 1078, 945, 914, 876, 847, 829, 818, 801, 710, 492. Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23; Found: C, 65.05; H, 6.48; N, 4.26.

4-Oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic Acid Methyl Ester (4b). 2-Phenylglutaric anhydride (52.2 g, 0.274 mol) and concentrated sulfuric acid (274 mL) were heated in an oil bath at 70 °C for a period of 1.5 h. The resulting mixture was allowed to cool to rt and was added to a cooled solution (ice/water bath) of MeOH (550 mL) over a period of 30 min. Upon complete addition, the mixture was allowed to warm to rt and stirred for 20 h. The mixture was poured over 1 L of ice. Brine (500 mL) and water (500 mL) were added, and the resulting mixture was extracted with EtOAc (4 × 500 mL). The combined organics were washed successively with satd $NaHCO_3$ (500 mL), water (500 mL), and brine (500 mL). The organics were dried (Na_2SO_4), filtered, and concentrated to provide 44.8 g (80%) of the title compound as a brown oil which was used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (dd, 1H, J = 7.9, 1.3 Hz), 7.48 (td, 1H, J = 7.5, 1.3 Hz), 7.35 (td, 1H, J = 7.5, 1.3 Hz), 7.29 (1H, d, J = 7.9 Hz), 3.96, (t, 1H, J = 5.0 Hz), 3.69 (s, 3H), 2.87 (ddd, 1H, J = 17.4, 11.6, 5.0 Hz), 2.60 (dt, 1H, J = 17.4, 5.0 Hz), 2.51−2.43 (m, 1H), 2.36−2.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.2, 173.3, 140.4, 133.8, 132.4, 129.4, 128.2, 127.6, 52.6, 44.6, 35.8, 26.0; GCMS *m*/*z* 204 (M^+); HRMS (ES) calcd for M + H + CH_3CN 246.1130, found 246.1131.

4-Cyano-4-trimethylsilanyloxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic Acid Methyl Ester (3b). 4-Oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid methyl ester (28.0 g, 0.137 mol) was dissolved in CH_2Cl_2 (138 mL). ZnI_2 (0.22 g, 0.69 mmol) and I_2 (0.21 g, 0.82 mmol) were added, and then TMSCN (32.95 mL, 0.247 mol) was added dropwise over 15 min. The resulting mixture was heated at reflux for 20 h. The mixture

was cooled to rt, satd $NaHCO_3$ (100 mL) was added, and the resulting mixture was stirred for 30 min. The mixture was partitioned, and the organic layer was washed successively with satd $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL). The organic layer was dried (Na_2CO_3), filtered, and concentrated to afford 34.5 g (83%) of the title compound as a brown oil which was used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72−7.68 (m, 1H), 7.37−7.31 (m, 2H), 7.29−7.26 (m, 1H), 3.86−3.83 (m, 1H), 3.717/3.715 (s, 3H), 2.60−2.20 (m, 4H), 0.212/0.189 (9H); GCMS *m*/*z* 303 (M^+).

1,5-Ethano-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2). Pearlman's catalyst (20% $Pd(OH)_2$−C (50% water), 17.22 g, 12.3 mmol) was added to a solution of 4-cyano-4-trimethylsilanyloxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid methyl ester (24.8 g, 81.2 mmol) in MeOH (400 mL) and 3 M aq HCl (41 mL). This mixture was shaken under an atmosphere of hydrogen (50 psi) at 50 °C for a period of 20 h. The resulting solution was filtered through a pad of Celite and washed with MeOH (300 mL). Sodium *tert*-butoxide (27.5 g, 286 mmol) was added, and the resulting solution was stirred at rt for 20 h. The mixture was concentrated, and the residue was dissolved in EtOAc (500 mL) and water (200 mL). The layers were partitioned, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated to afford 11.2 g of 1,5-ethano-2-oxo-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**15**) as a white solid (GCMS *m*/*z* 187). Tetrahydrofuran (160 mL) was added to this white solid, and the resulting slurry was heated in an oil bath at 45 °C. A solution of $LiAlH_4$ in THF (1 M, 120 mmol, 120 mL) was added dropwise to this mixture over a period of 60 min. The resulting mixture was heated at 45 °C for 20 h. Upon cooling to rt, a solution of water (8.65 mL) in THF (50 mL) was added dropwise to the mixture over a period of 120 min and the resulting mixture was allowed to stir for 20 h. The solids were removed by filtration through a pad of Celite, and the filter cake was washed with additional THF (200 mL). The filtrate was concentrated to afford 9.32 g (90%) of the title compound as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19 (dd, 2H, J = 5.4, 3.3 Hz), 7.08 (dd, 2H, J = 5.4, 3.3 Hz), 2.99−2.95 (m, 4H), 2.81−2.76 (m, 2H), 2.04−1.99 (m, 2H), 1.87−1.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.2, 126.8, 126.6, 52.9, 41.9, 27.1; APCI MS *m*/*z* 174.2 (M + 1); HRMS (ES) calcd for M + H 174.1283, found 174.1275.

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