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Amino Diol Based Asymmetric Syntheses of a Fused Benzazepine as a Selective D1 Dopamine Receptor

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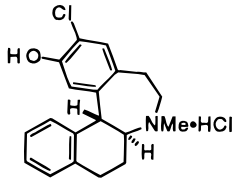
Abstract:

A six-step practical synthesis of (6a*S*,13b*R*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphtho-[2,1-*b*]azepin-12-ol, a selective D1 dopamine receptor, is developed starting from (1*S*,2*S*)-phenyl-2-amino-1,3-propanediol. An acid-promoted stereo- and regioselective cyclization of the benzazepine ring was established. Three double reactions in which two functional groups are transformed in a single step were developed. These include the double hydrolysis, the double reduction, and the cyclization and demethylation. The use of practical and economical reagents reduced the cost significantly.

Introduction

Fused benzazepines, in particular **1**, are selective D1 antagonists useful in the treatment of psychoses, depression, pain, and D1-dependent neurological disorders.[1,2] The



1, Sch 39166

original synthesis[1a] is inefficient because the cyclization step produces a 1:1 mixture of *trans* and *cis* benzazepines. The late-stage resolution drastically increases the cost of the product, and the process is very impractical for large-scale production. A slightly improved 14-step synthesis was developed starting from α-tetralone and (2-methoxy-4-chlorophenyl)magnesium bromide.[3] But a mixture of *trans* and *cis* isomers was generated in the cyclization of the seven-membered-ring step. The late-stage resolution further reduced the throughput. These shortcomings stimulated our effort towards finding an efficient, commercial process. We now report practical asymmetric syntheses of **1** starting from a commercial drug by-product.[4] A stereo- and regioselective cyclization procedure was developed to form the key seven-membered ring.

Results and Discussion

Regio- and stereoselective construction of the *trans* seven-membered ring in the benzazepines is a challenging step in any asymmetric approach. This difficulty was reflected in the reported approaches where a mixture of *trans* and *cis* isomers was generated.[1,3] To circumvent this problem, we planned to regioselectively establish the *trans* seven-membered ring first and the six-membered ring second. As shown in Scheme 1, phenyl amino diol (*S*,*S*)-**2** was selected as a starting material since it has the desired chiral centers. We envisioned an acid-promoted cyclization of the benzylic alcohol **5** to produce the more stable *trans* junctions in the seven-membered ring. A one-carbon homologation is required in order to obtain the six-membered ring. This can be achieved either before or after the seven-membered-ring formation.

Of the two variations considered, the first one began with an amide formation as shown in Scheme 1. Treatment of **2** with acid chloride **3** in the presence of NaOH produced amide **4** in 94% yield after a simple precipitation. Chlorination of 4-methoxyphenylacetic acid with commercial bleach followed by treatment with $SOCl_2$ generated the acid chloride **3** in 70% yield. Initially BH_3·Me_2S was used to reduce amide **4** to amine **5**. A more convenient method was developed using $NaBH_4$/HOAc,[5] an environmentally preferred reagent, to produce **5** in 82% yield.

Although both CF_3SO_3H and HF/BF_3 can promote the cyclization to the seven-membered ring, HF/BF_3 is the reagent of choice because it is less expensive and readily adaptable for commercial use.[6] Fortunately, only *trans* ring junction isomers were observed upon cyclization,[7] presumably due to the product stability. Two regioisomers, however, were observed with respect to the substituted phenyl ring, and this will be discussed later. N-Methylation was accomplished using CH_2O/HCO_2H to give **7** in 95% yield.[8] Conversion of alcohol **7** to its corresponding mesylate followed by treatment with NaCN in DMSO generated the

(1) (a) Berger, J. G.; Chang, W. K.; Clader, J. W.; Hou, D.; Chipkin, R. E.; McPhail, A. T. *J. Med. Chem.* **1989**, *32*, 1913. (b) Chumpradit, S.; Kung, M.; Billings, J. J.; Kung, H. F. *J. Med. Chem.* **1991**, *34*, 877. (c) Chipkin, R. E.; Iorio, L. C.; Coffin, V. L.; Mcquade, R. D.; Berger, J. G.; Barnett, A. *J. Pharmacol*. **1988**, *24*, 1093.

(2) (a) Sedvall, G.; Farde, L.; Stone-Elander, S.; Halldin, C. *In Neurobiology of Central D-1 Dopamine receptors*; Breese, G. R., Creese, I., Eds.; Plenum Press: New York, 1991; p 1. (b) Stoof, J. C.; Kebabian, J. W. *Life Sci*. **1984**, *35*, 2281.

(3) Clader, J. W. *Diastereo- and Enantiospecific Synth. of Sch 39166*. Presented at the 196th National Meeting of the American Chemical Society, Los Angeles, CA, September 1988.

(4) Commercial source was from Parke-Davis as a by-product of chloramphenicol synthesis.

(5) Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* **1976**, 763.

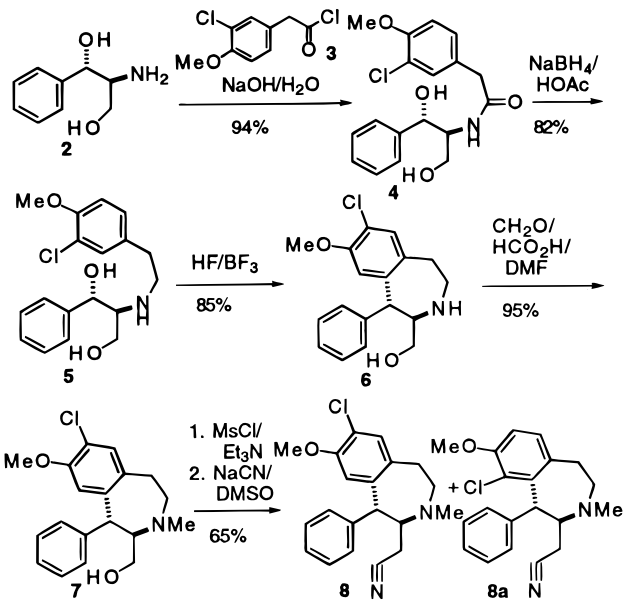
(6) Schumacher, D. P.; Murphy, B. L.; Clark, J. E.; Tahbaz, P.; Mann, T. A. *J. Org. Chem*. **1989**, *54*, 2242.

(7) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *Tetrahedron: Asymmetry* **1990**, *1*, 33.

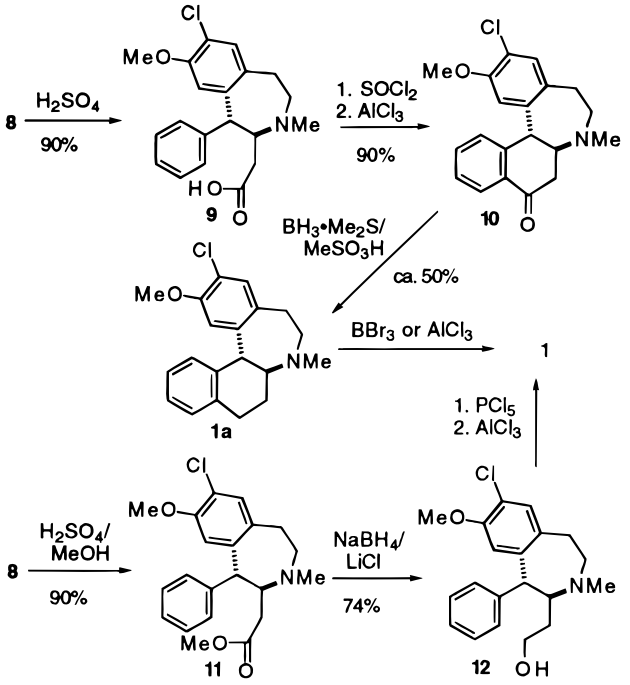
(8) (a) Eschweiler, W. *Chem. Ber*. **1905**, *38*, 880. (b) Clarke, H. T.; Gillespie, H. B.; Weisshaus, S. Z. *J. Am. Chem. Soc*. **1933**, *55*, 4571.

S1083-6160(97)00105-9 CCC: $14.00

Scheme 1



Scheme 2

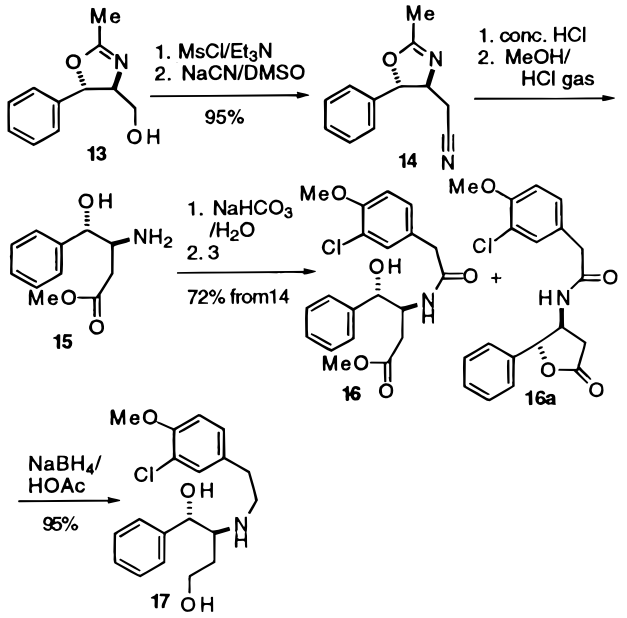


one-carbon homologated **8** in 65% overall yield with some *o*-chloro regioisomer (**8a**) as an impurity.

As shown in Scheme 2, our initial effort to form the six-membered ring started with the hydrolysis of nitrile **8** to its corresponding acid **9**. Cyclization under Friedel−Crafts acylation conditions furnished the desired six-membered ring in 90% yield. However, neither the direct hydrogenolysis nor the two-step reduction first with $NaBH_4$ and then with palladium-catalyzed hydrogenolysis worked. Reduction with a combination of BH_3·Me_2S and a strong acid[9] produced a mere 50% yield together with many impurities. Thus, we changed the strategy by switching the cyclization and the reduction order and constructing the six-membered ring *via* Friedel−Crafts alkylation. Hydrolysis of nitrile **8** to methyl ester **11** with H_2SO_4 and MeOH was accomplished in 90% yield. Reduction of ester **11** with $NaBH_4$ proceeded smoothly to give alcohol **12** in 74% yield. Conversion of alcohol **12** into its corresponding chloride with PCl_5 followed by $AlCl_3$-catalyzed cyclization at room temperature gave the six-membered ring in high yield. Unexpectedly, the methyl group was also completely removed upon heating the reaction mixture, thus eliminating one step from the synthesis. Due to strict metal and impurity specifications on the final drug substance, racemic malic acid was introduced to remove aluminum residues from the alkylation step. A simple precipitation resulted in final product in high yield and less than 25 ppm of aluminum.

(9) Kikugawa, Y.; Ogawa, Y. *Chem. Pharm. Bull.* **1979**, *27*, 2405.

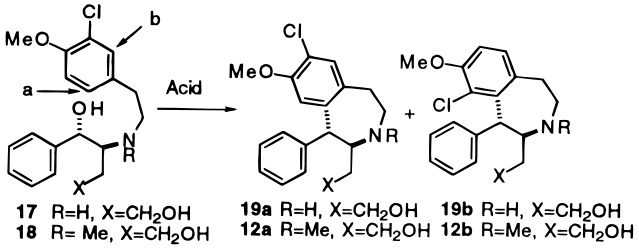
Scheme 3



The late-stage one-carbon homologation in the first approach requires two separate reduction steps to reduce amide **4** and ester **11**. Thus, we undertook another approach in which both of the carbonyl groups could be reduced in a single step. This approach begins with oxazoline **13**, a protected form of amino diol **2** and available commercially. As shown in Scheme 3, the homologation was achieved following the same procedure to produce **14** in 95% overall yield. At this point, a hydrolytic deprotection of the oxazoline ring in **14** is required to free the amino group for amide formation, and a hydrolysis of the nitrile to its corresponding ester is necessary for the ease of reduction. A double hydrolysis procedure was developed to accomplish the two transformations. Thus, treatment of **14** first with concentrated HCl and then with MeOH in the presence of gaseous HCl gave ester **15**. Adjustment of the reaction pH to between 7.5 and 8.5 followed by addition of acid chloride **3** afforded **16** and **16a** (75:25) in a combined 72% overall yield starting from **14**. $NaBH_4$ is the reagent of choice over $LiAlH_4$, BH_3·THF, $NaBH_4/AlCl_3$[10] for the simultaneous reduction of both the ester and amide functional groups. Treatment of a mixture of **16** and **16a** with $NaBH_4$ in THF followed by slow addition of HOAc reduces both carbonyl groups to give **17** in 95% yield.

(10) (a) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; Vol. I, p 581. (b) Brown, H. C.; Weissman, P. M., Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1458. (c) Kano, S.; Tanaka, Y.; Sugino, E.; Hibino, S. *Synthesis* **1980**, 695.

Table 1



17 R=H, X=CH_2OH
18 R= Me, X=CH_2OH
19a R=H, X=CH_2OH **19b** R=H, X=CH_2OH
12a R=Me, X=CH_2OH **12b** R=Me, X=CH_2OH

entry	R	X	acid	total yield, %	a:b
1	H	OH	CF_3SO_3H	90	83:17
2	H	OH	HF/BF3	90	99:1
3	Me	OH	CF_3SO_3H	84	88:12
4	H	CH_2OH	CF_3SO_3H	not determined	95:5
5	Me	CH_2OH	CF_3SO_3H	95	97:3
6	H	CH_2OH	$MeSO_3H/BF_3$	95	96:4

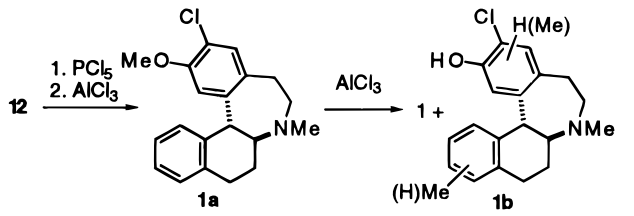
We next examined the effects of different NR and X substituents on the regioselectivity of the cyclization of the seven-membered ring using strong acids. Although the cyclization generated only the *trans* isomer, it contained two regioisomers with respect to the substituted aryl group. Presumably, a spiro-fused intermediate is involved in the cyclization because the para position is activated by the methoxy group.[11] Two factors were found to influence the ratio of **a**:**b**, the nature of the acid and the R and X groups. Of these two factors, the acid exerted greater effect as shown by entries 1 and 2 in Table 1. The ratio of **a**:**b** improved from 83:17 to 88:12 when the size of R increased from H to Me. The combined effect of NMe and CH_2OH gave the best ratio of 97:3 using CF_3SO_3H. The starting material with the N−H group (**17**) was selected for the synthesis simply because it offers easier purification. Among the acids listed in Table 1, $MeSO_3H/BF_3$ was the final reagent of choice because of its price and ease of operation. $MeSO_3H$ alone does not promote the cyclization at a detectable rate. Introduction of BF_3 to the reaction mixture at 10 °C immediately induces cyclization.

An impurity was detected in the final product when PhCl was used as a solvent for the final alkylation and demethylation. Our results in Table 2 indicated that, the higher the reaction temperature, the lower the levels of the impurity. Two recrystallizations from MeOH/*t*-BuOMe still generated unacceptable levels of this impurity. NMR and mass spectra indicated the presence of an extra methyl group in the impurity. We suspected that the impurity was generated from the $AlCl_3$-catalyzed intermolecular alkylation between **1** and MeCl formed during demethylation. Apparently, higher temperatures boiled most of the MeCl off and therefore reduced the impurity level. Replacement of PhCl with toluene reduced the impurity to less than 0.2%. Fortunately, intermolecular alkylation between the chloride derivative of **12** and toluene did not occur. A final crystallization produced **1** in >99% chemical purity and 99.9% ee.

In summary, we have developed and optimized a chiral pool-based synthesis of **1**. The stereochemistry of the fused

(11) Majetich, G.; Hicks, R.; Zhang, Y.; Tian, X.; Feltman, T. L.; Fang, J.; Duncan, S., Jr. *J. Org. Chem.* **1996**, *61*, 8169.

Table 2



entry	solvent	temp °C	impurity 1b, %
1	PhCl	65	10
2	PhCl	75	4
3	PhCl	85	2
4	PhCl	110	2
5	PhMe	85	<0.2

benzazepine was achieved by the regio- and enantioselective cyclization of a readily available inexpensive chiral alcohol. In the course of this study, we have developed three double reactions: the double hydrolysis, the double reduction, and the $AlCl_3$-catalyzed alkylation and demethylation.

Experimental Section

General Procedures. The ^1H NMR and ^{13}C NMR spectra were taken in $CDCl_3$, and all reactions were carried out under nitrogen unless otherwise noted. Melting points were not corrected. Starting materials and reagents were purchased commercially and used without further purification.

3-Chloro-4-methoxyphenylacetyl Chloride (3). To a cooled solution of 100 mL of 11% NaOCl at 5 °C were added 100 g (590 mmol) of 4-methoxyphenylacetic acid and 24 g of 50% NaOH, the temperature being kept below 35 °C. To the mixture was added dropwise 1.0 L of 11% NaOCl. After the mixture was agitated for 2 h, the reaction was quenched with 50 g of Na_2SO_3 and acidified with H_2SO_4 to pH 1. The precipitate was filtered off and dried at 50 °C to give 87 g (70%) of 3-chloro-4-methoxyphenylacetic acid as a white solid. Mp: 97 °C (lit[12] mp 98 °C). ^1H NMR: δ 10.94 (bs, 1 H), 7.27 (d, J = 2.2 Hz, 1 H), 7.09 (dd, J = 8.3, 2.2 Hz, 1 H), 6.85 (d, J = 8.3 Hz, 1 H), 3.86 (s, 3 H), 3.51 (s, 2 H). ^{13}C NMR: δ 177.7, 154.2, 131.0, 128.6, 126.4, 122.3, 112.0, 56.1, 39.9. IR (paraffin): 2920 (s), 1710 (m), 1525 (m), 1470 (s) cm^{-1}. To a solution of 84.4 g (410 mmol) of the acid just prepared in 50 mL of CH_2Cl_2 was added at 5 °C dropwise 36 mL (498 mmol) of $SOCl_2$. The mixture was heated to reflux for 1 h and concentrated. The residual $SOCl_2$ was removed by codistillation with 2 × 20 mL of toluene to give **3** as a toluene solution.

(1*S*,2*S*)-(+)-1-Phenyl-2-((3-chloro-4-methoxyphenyl)-acetamido)-1,3-propanediol (4). To a 2 L flask were added 500 mL of water, 93.4 g of 50% NaOH, 50 g (293 mmol) of (1*S*,2*S*)-1-phenyl-1,3-propanediol **2**, and 25 mL of CH_2Cl_2. To the mixture at 20 °C was added dropwise a toluene solution of acid chloride **3** (410 mmol). After 1 h of stirring, the reaction was quenched with 200 mL of MeOH. The quenched mixture was concentrated and agitated at 5 °C for 0.5 h. The precipitate was filtered to give, after drying, 100.4 g (94.5%) of **4** as an off-white solid. $[\alpha]^{22.5}_D$: + 44.6° (4.48

(12) Munavalli, S.; Bhat, G. A.; Viel, C. *Bull. Soc. Chim. Fr.* **1966**, *10*, 3311.

mg in 2 mL of MeOH). Mp: 156−158 °C. ^{1}H NMR (DMSO-d_6): δ 7.64 (d, J = 8.7 Hz, 1 H), 7.18−7.25 (m, 6 H), 6.97−7.01 (m, 2 H), 5.52 (d, J = 4.3 Hz, 1 H), 4.86 (m, 1 H), 4.78 (t, J = 5.4 Hz, 1 H), 3.86 (bs, 1 H), 3.81 (s, 3 H), 3.20−3.62 (m, 4 H). ^{13}C NMR (DMSO-d_6): δ 172.5, 155.3, 145.6, 132.0, 131.6, 130.6, 129.3, 128.3, 127.9, 122.1, 113.9, 70.2, 61.0, 56.8, 56.4, 40.9. IR (paraffin): 3580 (m), 3280 (s), 2920 (s), 1650 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{20}ClNO_4$: C, 61.80; H, 5.76; N, 4.00. Found: C, 61.99; H, 6.13; N, 4.11.

(1*S*,2*S*)-1-Phenyl-2-(*N*-(2-(3-chloro-4-methoxyphenyl)-ethyl)amino)-1,3-propanediol (5). To a mixture of 0.5 g (1.4 mmol) of **4** and 0.27 g (7.1 mmol) of $NaBH_4$ in 5 mL of THF was added dropwise 2 mL (7.1 mmol) of HOAc over 5 min. The resulting mixture was heated to reflux for 7 h, cooled, and quenched with water. After pH adjustment to 10, the aqueous solution was extracted with EtOAc. The combined extracts were washed with brine, dried over K_2CO_3, and concentrated in vacuum to give 0.46 g (85% pure, 82% yield) of **5** as a thick oil. A small analytical sample was purified on a silica gel column, eluting with EtOAc:hexane (1:1). Mp: 62−64 °C. ^{1}H NMR: δ 7.45−7.25 (m, 5 H), 7.16 (d, J = 2.0 Hz, 1 H), 7.00 (dd, J = 8.3, 2.0 Hz, 1 H), 6.83 (d, J = 8.3 Hz, 1 H), 4.59 (d, J = 7.2 Hz, 1 H), 3.87 (s, 3 H), 3.60 (dd, J = 11.2, 3.9 Hz, 1 H), 3.36 (dd, J = 11.2, 3.9 Hz, 1 H), 2.97−2.67 (m, 8 H). ^{13}C NMR: δ 155.2, 143.1, 133.9, 131.4, 129.5, 128.9, 127.4, 123.2, 112.8, 73.2, 64.7, 59.7, 55.7, 48.1, 34.6, 12.9. IR. 3300 (s), 2920 (s), 1610 (w) cm^{-1}. HRMS: 336.1368; Calcd for $C_{18}H_{23}NO_3Cl$: 336.1366 (MH^+).

(1*S*,2*S*)-7-Chloro-8-methoxy-1-phenyl-2,3,4,5-tetrahydro-2-(hydroxymethyl)-1*H*-3-benzazepine (6). To a 500 mL plastic bottle at −78 °C were added carefully 40 mL of precooled HF and 4.1 g (12.2 mmol) of **4**. Appropriate protective measures should be taken when handling HF. This mixture at −78 °C was bubbled gently with BF_3 gas for about 15 min. The resulting mixture was agitated with the temperature between −30 and −10 °C for 5 h and diluted with 25 mL of CH_2Cl_2. The reaction was quenched into 200 mL of ice, the pH was adjusted to 12 carefully with aqueous NaOH, and the mixture was extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give 3.5 g (82%) of **5**. The minor regioisomer was separated after one-carbon homologation (see **8** and **8a**). ^{1}H NMR: δ 7.38−7.0 (m, 6H), 7.09 (s, 1H), 3.96 (d, J = 6.2 Hz, 1 H), 3.74 (s, 3 H), 3.68−3.55 (m, 1 H), 3.52−3.35 (m, 2 H), 3.15−2.70 (m, 5 H), 2.70−2.50 (m, 1 H). ^{13}C NMR: δ 155.0, 142.4, 140.9, 132.4, 129.7, 128.7, 127.6, 121.0, 115.6, 110.9, 62.5, 59.3, 55.5, 54.0, 42.0, 34.2. MS: calcd for $C_{18}H_{21}ClNO_2$ 318, found 318 (MH^+).

(1*S*,2*S*)-7-Chloro-8-methoxy-1-phenyl-2,3,4,5-tetrahydro-2-(hydroxymethyl)-3-methyl-1*H*-3-benzazepine (7). To a solution of 3.5 g (11 mmol) of **6** in 14 mL of DMF were added 1.6 mL (1.69 mmol) of aqueous paraformaldehyde and 2.09 g (44 mmol) of aqueous formic acid. The mixture was heated to 110 °C for 4.5 h and then cooled to −5 °C. The pH was adjusted to 10 with 3.5 g of 50% NaOH. Insoluble material was filtered off, and the filtrate was extracted with EtOAc. The combined extracts were washed with brine and concentrated in vacuum to give 3.5 g of crude **7**, which was carried directly to next step. A small analytical sample was purified on a silica gel column, eluting with hexanes/EtOAc (7:3). $[\alpha]^{22.5}_D$: + 27.0° (4.0 mg in 2 mL of EtOH). Mp: 50−52 °C. ^{1}H NMR: δ 7.34−7.14 (m, 5 H), 6.55 (s, 1 H), 3.76 (s, 3 H), 3.72−3.52 (m, 1 H), 3.51 (s, 1 H), 3.50 (dd, J = 6.8, 1.1 Hz, 1 H), 3.22−2.85 (m, 5 H), 2.60 (dm, J = 14.9 Hz, 1H), 2.29 (s, 3 H). ^{13}C NMR: δ 153.39, 141.13, 139.45, 133.42, 131.52, 128.49, 127.97, 126.50, 120.05, 114.85, 65.46, 60.42, 56.03, 53.52, 49.00, 43.14, 32.57, 23.01. IR: 3380, 2920, 1610 cm^{-1}. HRMS: calcd for $C_{19}H_{23}ClNO_2$ 332.1417, found 332.1419 (MH^+).

(1*S*,2*S*)-7-Chloro-8-methoxy-1-phenyl-2,3,4,5-tetrahydro-2-(cyanomethyl)-3-methyl-1*H*-3-benzazepine (8). To a solution of 1.0 g (3.0 mmol) of **7** in 4 mL of THF at 5 °C were added 0.5 mL (3.6 mmol) of Et_3N and 0.28 mL (3.6 mmol) of MsCl. The mixture was stirred at 5 °C for 1 h and quenched into 10 mL of saturated $NaHCO_3$. The pH was adjusted to 10 with 50% NaOH, and the mixture was extracted with EtOAc. The combined extracts were washed with brine, dried over K_2CO_3, and concentrated to give 0.96 g of crude mesylate. To a mixture of 0.13 g (2.6 mmol) of NaCN in 3 mL of DMSO at 70 °C was added dropwise 0.9 g of the above mesylate in 1 mL of toluene. The mixture was heated at 70 °C for 1.5 h, cooled to 25 °C, quenched into 10 mL of $NaHCO_3$, extracted with EtOAc, washed with brine, dried over K_2CO_3, and concentrated to give 0.96 g of crude **8**. The crude **8** was slurried with MeOH and filtered to give 0.63 g (65.5% from **7**) of pure **8**. Mp: 123 °C. $[\alpha]^{24}_D$: + 63.1° (10.94 mg in 2 mL of MeOH). ^{1}H NMR: δ 7.33−7.10 (m, 5 H), 7.14 (s, 1 H), 6.87 (s, 1H), 4.48 (d, J = 5.0 Hz, 1 H), 4.10−4.02 (m, 1 H), 3.91 (s, 3 H), 2.45 (s, 3 H), 2.82−2.35 (m, 5 H), 2.18 (dd, J = 10.3, 10.1 Hz, 1 H). ^{13}C NMR: δ 156.6, 142.4, 140.4, 136.5, 134.5, 130.9, 130.2, 128.9, 123.2, 121.6, 118.6, 62.2, 57.5, 55.1, 49.9, 46.5, 35.2, 13.6. IR: 2940 (s), 2230 (w) cm^{-1}. Anal. Calcd for $C_{20}H_{21}ClN_2O$: C, 70.48; H, 6.17; N, 8.22. Found: C, 70.43; H, 6.18; N, 8.18. **8a** (*ortho* to the chloro regioisomer from the cyclization step and isolated from the methanol filtrate *via* a silica gel column, eluting with hexanes/EtOAc (1:1)): ^{1}H NMR: δ 7.30−7.09 (m, 5 H), 7.98 (d, J = 8.2 Hz, 1 H), 6.82 (d, J = 8.2 Hz, 1 H), 5.31 (d, J = 4.9 Hz), 4.24−4.20 (m, 1 H), 3.92 (s, 3 H), 2.80−2.35 (m, 5 H), 2.53 (s, 3 H), 2.17−2.04 (m, 1 H). ^{13}C NMR: δ 155.49, 140.14, 138.72, 135.81, 129.90, 129.22, 128.43, 127.11, 125.88, 120.09, 111.13, 60.86, 55.73, 48.70, 48.65, 44.69, 34.58, 12.15.

(1*S*,2*S*)-(7-Chloro-8-methoxy-1-phenyl-2,3,4,5-tetrahydro-3-methyl-1*H*-3-benzazepin-2-yl)acetic Acid (9). A mixture of 0.5 g (1.46 mmol) of **8** in 0.5 mL of concd H_2SO_4, 0.5 mL of water, and 1 mL of MeOH was heated to 70 °C for 3 h. After addition of 1 mL of concd HCl, the mixture was heated for another 40 h and quenched into 10 mL of water. After pH adjustment to 4 with H_2SO_4, the mixture was extracted with EtOAc. The combined extracts were washed and concentrated to give 0.56 g (90% pure, 90% yield) of **9**. Mp: 135−140 °C dec. ^{1}H NMR: δ 7.28−7.03 (m, 5 H), 7.13 (s, 1 H), 6.63 (s, 1 H), 4.16−4.03 (m, 2 H), 3.74 (s, 3 H), 3.17−3.14 (m, 1 H), 2.85−2.84 (m, 1 H), 2.28 (s, 3 H), 2.53−2.15 (m, 3 H). ^{13}C NMR: δ 177.8, 155.2, 141.4, 139.2, 133.5, 132.7, 129.5, 128.7, 127.6, 121.4,

116.6, 60.9, 55.6, 54.7, 48.4, 42.0, 32.8, 31.0. IR: 3380 (w), 2920 (s), 1725 (m) cm^{-1}.

(6a*S*,13b*R*)-11-Chloro-12-methoxy-6,6a,7,8,9,13b-hexahydro-7-methyl-5-oxo-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (10). A mixture of 2.0 g (5.6 mmol) of **9** and 11.2 mL (153 mmol) of $SOCl_2$ was heated to 15 °C for 15 min. Excess $SOCl_2$ was removed by codistillation with CH_2Cl_2. To the residue in 10 mL of CH_2Cl_2 at 5 °C was added 2.24 g (16.8 mmol) of $AlCl_3$. After stirring at 5 °C for 15 min, the mixture was quenched into 50 mL of ice. The precipitate was filtered off and dried to give 2.0 g (95%) of **10** as a HCl salt. ^1H NMR: δ 7.95 (d, J = 7.1 Hz, 1 H), 7.60 (dd, J = 7.4, 7.1 Hz, 1 H), 7.47 (dd, J = 7.7, 7.4 Hz, 1 H), 7.23 (s, 1 H), 7.17 (d, J = 7.7 Hz, 1 H), 5.87 (s, 1 H), 5.85 (d, J = 9.5 Hz, 1 H), 4.25 (dd, J = 13.2, 12.5 Hz, 1 H), 3.95−3.80 (m, 1 H), 3.64 (d, J = 13.2 Hz, 1 H), 3.54 (d, J = 13.2 Hz, 1 H), 3.48 (s, 3 H), 3.55−3.40 (m, 1 H), 3.15 (dd, J = 12.5, 4.4 Hz, 1 H), 2.87 (d, J = 4.7 Hz, 3 H), 3.05−2.80 (m, 2 H). IR: 3400 (s), 2920 (s), 1710 (w) cm^{-1}.

(6a*S*,13b*R*)-11-Chloro-12-methoxy-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (1a). To a mixture of 0.1 g (0.265 mmol) of **10** and 2 mL of CF_3CO_2H was added dropwise 0.08 mL of $BH_3{\cdot}Me_2S$. The resulting mixture was stirred for 30 min and quenched with 4 mL of water. The pH was adjusted to 12 with NaOH, the mixture was extracted with EtOAc, and the extract was dried over K_2CO_3 to give crude product which contains about 50% **1a** as determined by HPLC and NMR against an authentic sample.[1a]

Methyl (1*S*,2*S*)-(7-Chloro-8-methoxy-1-phenyl-2,3,4,5-tetrahydro-3-methyl-1*H*-3-benzazepin-2-yl)acetate (11). To a solution of 2.0 g (5.9 mmol) of **8** in 19 mL of MeOH and 1 mL of water was added dropwise 8 mL of H_2SO_4. The mixture was heated to 65 °C for 4 days and cooled to 0 °C. The pH was adjusted with 50% NaOH to 12, and the precipitate was filtered off, washed with water, and dried to give 1.95 g (89%) of **11**. $[\alpha]^{23.0}_D$: +13.2° (3.02 mg in 2 mL of EtOH). Mp: 110−112 °C. ^1H NMR: δ 7.30−7.10 (m, 5 H), 7.13 (s, 1 H), 6.64 (s, 1 H), 4.22 (bs, 1 H), 4.12 (dd, J = 14.0, 6.0 Hz, 1 H), 3.84 (s, 3 H), 3.66 (s, 3 H), 2.90−2.70 (m, 1 H), 2.70−2.39 (m, 4 H), 2.39 (s, 3 H), 2.20 (dd, J = 14.9, 9.3 Hz, 1 H). ^{13}C NMR: δ 173.53, 153.22, 140.70, 139.01, 134.25, 131.56, 128.19, 127.82, 126.11, 120.18, 116.12, 60.77, 56.15, 55.07, 51.64, 49.38, 45.33, 34.70, 30.32. IR: 2920 (s), 1725 (m) cm^{-1}. HRMS: calcd for $C_{21}H_{25}ClNO_3$ 374.1523, found 374.1520 (MH^+).

(1*S*,2*S*)-7-Chloro-8-methoxy-1-phenyl-2,3,4,5-tetrahydro-2-(2-hydroxyethyl)-3-methyl-1*H*-3-benzazepine (12). To a mixture of 0.8 g (2.08 mmol) of **11** in 2 mL of MeOH were added 0.48 g (12 mmol) of $NaBH_4$ and 0.26 g of LiCl. The mixture was heated to reflux for 3 h, cooled, and quenched with 5 mL of water. The pH was adjusted to 12 with NaOH, the mixture was extracted with EtOAc, and the extract was washed with brine and dried over K_2CO_3. Concentration followed by crystallization from EtOAc/hexane gave 0.58 g (74%) of **12**. Mp: 128−130 °C. $[\alpha]^{22.3}_D$: −5.8° (4.82 mg in 2 mL of MeOH). ^1H NMR: δ 7.45−7.15 (m, 6 H), 6.55(s, 1 H), 4.07 (d, J = 6.5 Hz, 1 H), 3.77 (s, 3 H), 3.85−3.65 (m, 3 H), 3.45−2.85 (m, 3 H), 2.57 (dm, J = 16.0 Hz, 1 H), 2.25 (s, 3 H), 2.00−1.85 (m, 1 H), 1.43 (dm, J = 10.9 Hz, 1 H). ^{13}C NMR: δ 153.8, 142.1, 139.9, 133.4, 131.8, 128.8, 128.3, 126.8, 120.4, 115.3, 65.2, 63.6, 57.5, 56.3, 49.6, 43.3, 32.9, 31.3. IR: 3320 (m), 2900 (s), 1600 (m), 1420 (s) cm^{-1}. Anal. Calcd for $C_{20}H_{24}ClNO_2$: C, 69.45; H, 6.99; N, 4.04. Found: C, 69.47; H, 7.31; N, 4.17.

(4*S*,5*S*)-(2-Methyl-5-phenyl-2-oxazolin-4-yl)acetonitrile (14). The same procedure for the preparation of **8** was followed. **13** (100 g) (available from Aldrich) gave 103 g (95%) of **14** with a 95% purity as determined by HPLC. ^1H NMR: δ 7.43−7.25 (m, 5 H), 5.21 (d, J = 6.6 Hz, 1 H), 4.19 (dd, J = 6.6, 6.0 Hz, 1 H), 2.71 (d, J = 6.0 Hz, 2 H), 2.14 (d, J = 1.0 Hz, 3 H). ^{13}C NMR: δ 166.2, 138.2, 128.8, 125.2, 116.6, 84.8, 70.5, 40.7, 23.7, 13.7.

Methyl (3*S*,4*S*)-(+)-4-Phenyl-3-((3-chloro-4-methoxyphenyl)acetamido)-4-hydroxybutanoate (16). A mixture of 50 g (238 mmol) of **14** and 100 mL of concd HCl was heated to 75 °C for 2 h. The mixture was distilled to a slurry and codistilled with 2 × 50 mL of toluene. To the residue was added 100 mL of MeOH, and the mixture was bubbled with gaseous HCl while the temperature was kept below 37 °C. The mixture was stirred at 25 °C for 16 h and quenched into 50 mL of THF. The pH was adjusted to 8.5 by adding 400 mL of saturated $NaHCO_3$ and 20 g of K_2CO_3. To the resulting mixture at 15 °C was added 40 mL of a 6.5 M solution of acid chloride **3** while the pH was kept between 7.5 and 8.5 with K_2CO_3. After 1 h of stirring, the precipitate was filtered and dried to give 70 g (72%) of product as a mixture of **16** and **16a**. Data for **16** are as follows. ^1H NMR: δ 7.33−7.18 (m, 5 H), 6.98 (dd, J = 8.3, 1.8 Hz, 1 H), 6.19 (d, J = 8.3 Hz, 1 H), 5.66 (d, J = 6.0 Hz, 1 H), 4.83 (d, J = 4.3 Hz, 1 H), 4.37−4.32 (m, 1 H), 3.88 (s, 3 H), 3.62 (s, 3 H), 3.34 (s, 2 H), 2.69 (dd, J = 16.1, 6.0 Hz, 1 H), 2.55 (dd, J = 16.1, 6.6 Hz, 1 H). Data for **16a** are as follows. Mp: 162−165 °C. ^1H NMR: δ 7.39−7.26 (m, 3 H), 7.14−7.10 (m, 2 H), 6.81 (s, 1 H),6.73 (s, 2 H), 5.69 (d, J = 6.0 Hz, 1 H), 5.32 (d, J = 7.1 Hz, 1 H), 5.00−4.94 (m, 1 H), 3.90 (s, 3 H), 3.23 (s, 2 H), 3.00 (dd, J = 18.0, 7.5 Hz, 1 H), 2.67 (dd, J = 18.0, 3.6 Hz, 1 H). ^{13}C NMR: δ 174.5, 170.6, 159.5, 154.5, 133.4, 130.8, 128.8, 128.5, 125.2, 112.2, 82.5, 56.1, 49.6, 42.0, 35.9. IR: 3330 (m), 2920 (s), 1775 (m) cm^{-1}. HRMS: calcd for $C_{19}H_{19}ClNO_4$ 360.1003, found 360.1005 (MH^+).

(1*S*,2*S*)-1-Phenyl-2-(N-(2-(3-chloro-4-methoxyphenyl)-ethyl)amino)-1,4-butanediol (17). To a solution of 50 g (129 mmol) of **16** and **16a** in 400 mL of THF was added 40 g (1.03 mol) of $NaBH_4$. The mixture was refluxed for 2 h, and then cooled to 10 °C. To the cooled mixture was added dropwise 51 mL of HOAc. The mixture was refluxed for 7 h, cooled, and quenched into 500 mL of water. The pH was adjusted to 12 with NaOH, and THF was removed under vacuum. The residue was extracted with EtOAc, and the extract was washed with dilute aqueous NaOH, dried over K_2CO_3, and concentrated to give 47 g (90% purity, 95% yield) of **17**. A small analytical sample was purified on a silica gel column, eluting with hexanes/EtOAc (6:4). $[\alpha]^{23.0}_D$: +20.3° (13.39 mg in 2 mL of EtOH). Mp: 45−47 °C. ^1H NMR: δ 7.40−7.26 (m, 5 H), 7.19 (d, J = 1.4 Hz, 1 H), 7.04 (dd, J = 8.3, 1.4 Hz, 1 H), 6.85 (d, J = 8.3 Hz, 1 H), 4.61 (d, J = 7.1 Hz, 1 H), 3.88 (s, 3 H), 3.85−3.55 (m, 2

H), 3.30−2.65 (m, 8 H), 1.75−1.60 (m, 1 H), 1.60−1.45 (m, 1 H). ^{13}C NMR: δ 153.40, 141.93, 132.62, 130.26, 128.42, 127.89, 127.82, 126.53, 122.18, 112.02, 74.46, 63.36, 61.43, 56.10, 47.91, 35.50, 30.76. IR: 3350 (m), 3180 (m), 2920 (s) cm^{-1}. HRMS: calcd for $C_{19}H_{25}ClNO_3$ 350.1523, found 350.1532 (MH^+).

(1*S*,2*S*)-7-Chloro-8-methoxy-1-phenyl-2,3,4,5-tetrahydro-2-(2-hydroxyethyl)-1*H*-3-benzazepine (19a). To a solution of 20 g (51.5 mmol) of **17** in 80 mL of $MeSO_3H$ at 10 °C was bubbled BF_3 for 30 min to complete the cyclization. The reaction was quenched into a mixture of 200 mL of water and 110 g of 50% NaOH solution at 10 °C. The precipitate was filtered and dried to give 52 g (yield carried over to next step) of crude product as a mixture of **19a** and **19b** (96:4) as determined by HPLC. A small analytical sample was purified on a silica gel column, eluting with hexanes/EtOAc (7:3). The data for **19a** are as follows. Mp: 138−142 °C. ^{1}H NMR: δ 7.36−7.22 (m, 3 H), 7.15 (s, 1 H), 7.16−7.19 (m, 2 H), 6.57 (s, 1 H), 3.99 (d, J = 6.3 Hz, 1 H), 3.77 (s, 3 H), 3.85−3.72 (m, 1 H), 3.70−3.55 (m, 1 H), 3.15−2.85 (m, 4 H), 2.75−2.60 (m, 1 H), 2.00−1.80 (m, 1 H), 1.57 (dd, J = 14.7, 2.7 Hz, 1 H). ^{13}C NMR: δ 153.66, 140.55, 139.38, 131.50, 128.94, 127.91, 127.84, 126.95, 120.41, 114.94, 63.03, 58.24, 56.09, 41.65, 34.75, 33.01, 23.03. IR: 3380 (w), 3180 (w), 2920 (s), 1470 (s) cm^{-1}. HRMS: calcd for $C_{19}H_{23}ClNO_2$ 332.1417, found 332.1423 (MH^+).

N-Methylation of 19 to 12. To a solution of 67.7 g of crude **19** (26 g pure, 78 mmol) in 208 mL of DMF were added 11.6 mL (155 mmol) of 37% aqueous formaldehyde and 12.2 mL (3.12 mmol) of formic acid. The mixture was heated at 100 °C for 2 h and cooled to 10 °C. To the mixture was added 100 mL of MeOH and NaOH to adjust the pH to 13. The resulting solution was heated at 65 °C for 3 h to hydrolyze formate formed. To the mixture at 15 °C was added 400 mL of water to precipitate product. The solid was filtered, slurried with water, and dried to give 32.6 g of crude **12**. Recrystallization of crude product with *i*-PrOH gave 19.4 g (80% from **17**) of pure **12**.

1. To 10 g (28.4 mmol) of **12** in 50 mL of toluene was added 2.9 g (13.9 mmol) of PCl_5. The mixture was heated to 65 °C for 1 h and cooled to 25 °C. To the mixture was added portionwise 11.5 g (84.4 mmol) of $AlCl_3$. The mixture was heated back to 65 °C for 4−5 h to complete both the cyclization and demethylation. After addition of 10 mL of MeCN, the reaction was quenched at 40 °C into a solution of 35 g of *d*,*l*-malic acid in 10 mL of MeCN and 150 mL of 4.0 N NaOH. After concentration, the precipitate was filtered, washed with water, and dried to give 7.41 g of free base. To 5 g of the free base in 50 mL of MeOH was added 14 mL of 1.25 N HCl in MeOH. The mixture was heated to reflux, treated with 1 g of Darco, filtered, concentrated, and cooled to 25 °C. To the cooled mixture was added 3 mL of *t*-BuOMe, and the resulting mixture was stirred at 10°C for 30 min. The precipitate was filtered off and dried to give 4.9 g of **1** (72% overall yield) as a white solid. The chemical and chiral purities were determined by HPLC and found to be 99.7% and 99.9%, respectively.

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Supporting Information Available

^{1}H NMR, ^{13}C NMR, and IR spectra for **3**−**12**, **14**, **16**, **16a**, **17**, and **19** and chiral HPLC chromatograms for **1** (43 pages). See any current masthead page for ordering and Internet access instructions.

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