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Galanthamine analogs: 6*H*-benzofuro[3a,3,2,-*e*,*f*][1]benzazepine and 6*H*-benzofuro[3a,3,2-*e*,*f*][3]benzazepine

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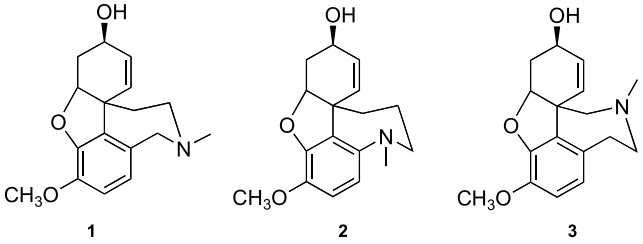
Abstract—The known cholinesterase inhibitory capability of the *Amarylidaceae* alkaloid galanthamine prompted preparation of analogs in which the position of the nitrogen within the azepine ring is altered. The analogs 6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepine and 6*H*-benzofuro[3a,3,2-*e*,*f*][3]benzazepine were prepared in 19 and 2.5%, respectively, following Kametani and Shimizu approaches, respectively. The aniline derivative 6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepine failed to undergo most of the reactions typical for galanthamine. Thus, it neither oxidized to the analogous narwedine, nor epimerized to the analogous epigalanthamine, nor reduced to the lycoramine analog, under the conditions used for galanthamine.

1. Introduction

The *Amarylidaceae* alkaloid galanthamine (**1**), available in the form of its hydrobromide salt as the drug Nivalin, has been identified as a cholinesterase inhibitor. It is widely used in Europe, especially in neuromuscular diseases such as myasthenia gravis,[4] as well as in antagonism of skeletal neuromuscular blockade (e.g., by curare),[2] drug-induced respiratory depression (e.g., by narcotics)[3] and central anticholinergic effect induced by scopolamine.[15] The positive results obtained by the use of Nivalin to treat patients suffering from Alzheimer's dementia[5] have prompted the suggestion that galanthamine (**1**) and/or its congeners may be active in the treatment of this disorder. As part of a program directed towards the preparation of analogs of **1** the synthesis of compounds in which the position of the azepine nitrogen is altered was targeted. Thus, the syntheses of the [1]benzazepine analog **2** and of the [3]benzazepine analog **3** were undertaken. The recent publication[9] of the synthesis of **3** prompts us to report our results for **2** and **3**.



2. Results

Our preparation of the [1]benzazepine **2** followed the classic Kametani synthesis of galanthamine,[6] utilizing the oxidative cyclization of the bromo-protected bisphenol **13** (Scheme 1). The acid chloride **8** and the aniline **12**, both required for preparation of the precursor to **13**, were prepared as follows. Starting from commercially available *p*-hydroxyphenylpropionic acid (**4**) the benzyl protected analog (**7**) was prepared by esterification of **4** with methanolic hydrochloric acid to give the methyl ester **5** (in 95% yield) followed by benzylation to give **6** (in 92% yield) and saponification (90% yield). Treatment of **7** with thionyl chloride afforded the required acid chloride **8** in quantitative yield. Synthesis of the aniline **12** was accomplished by formylation of commercially available 3-hydroxy-4-methoxyaniline (**9**) with ethyl formate (85% yield) to give the formanilide **10** and O-protection by benzylation with benzyl bromide to afford **11** in 85% yield. Bromination of **11** with *N*-bromoacetamide in chloroform

Keywords: Galanthamine; 6*H*-Benzofuro[3a,3,2-*e*,*f*][1]benzazepine; 6*H*-Benzofuro[3a,3,2-*e*,*f*][3]; Kametani synthesis; Shimizu synthesis.
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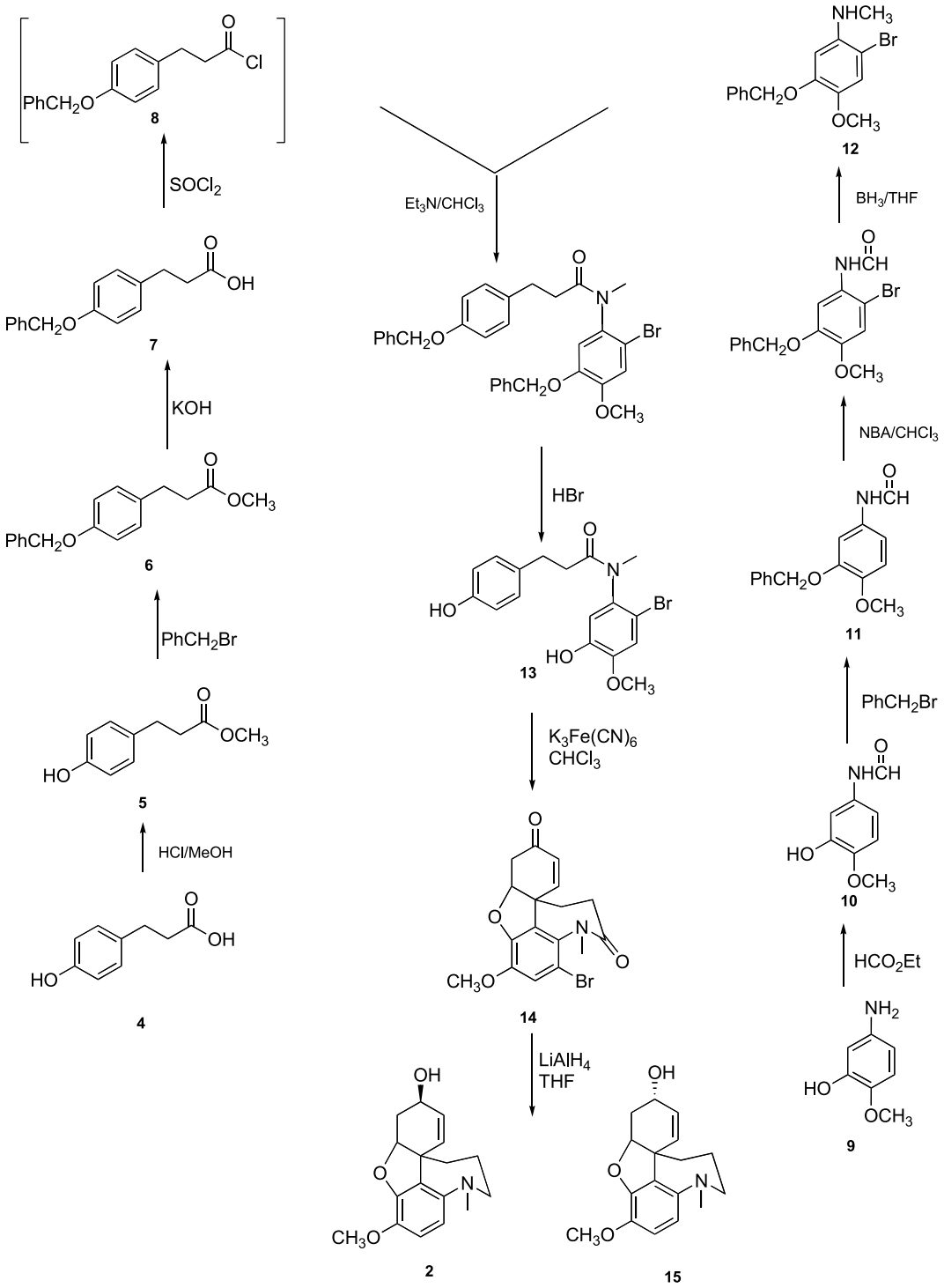
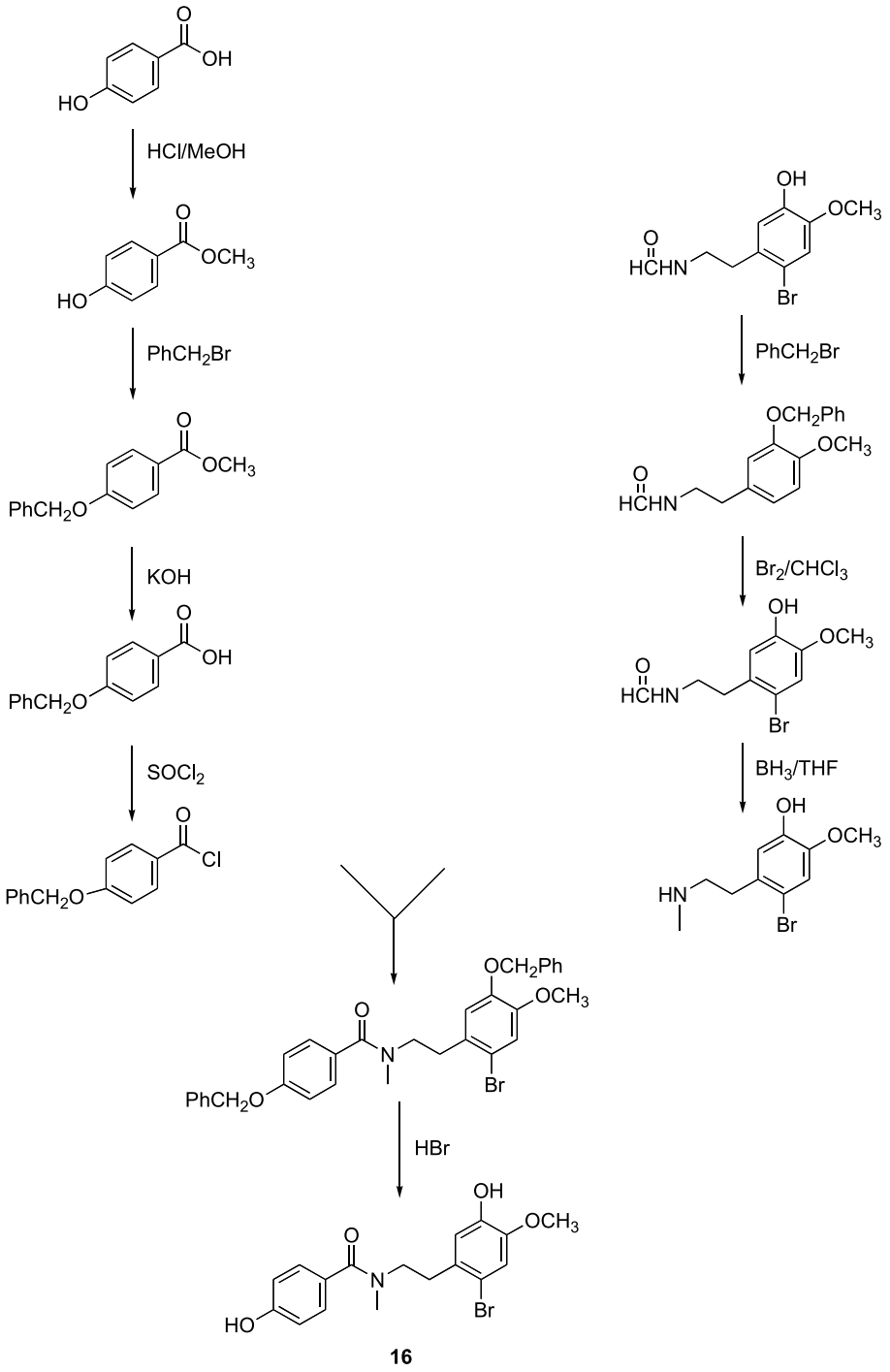


Scheme 1.

and reduction with diborane provided the required *N*-methyl-5-benzyloxy-2-bromo-4-methoxyaniline (**12**). Coupling of the acid chloride **8** with the aniline **12**, followed by debenzylation with hydrobromic acid, gave the bisphenol **13** required for cyclization in 81% yield. Oxidative cyclization by potassium ferricyanide gave the narwedine-type bromoamide **14** in 50% yield. Reduction of **14** with lithium aluminum hydride effected both reduction of the keto and amide groups to give the galanthamine analog **2** in 59% yield; it was accompanied by the epimeric alcohol **15** (7% yield). The overall yield from commercially available starting materials was 18.9%.

Attempts to prepare the [3]benzazepine **3** following an analogous route (Scheme 2) or following our improved protocol for the preparation of galanthamine[12] (Scheme 3) were unsuccessful. Thus, treatment of either bisphenol **16** or bisphenol **17** with potassium ferricyanide led to rapid consumption of the starting material and formation of multiple products; none was formed in quantities justifying

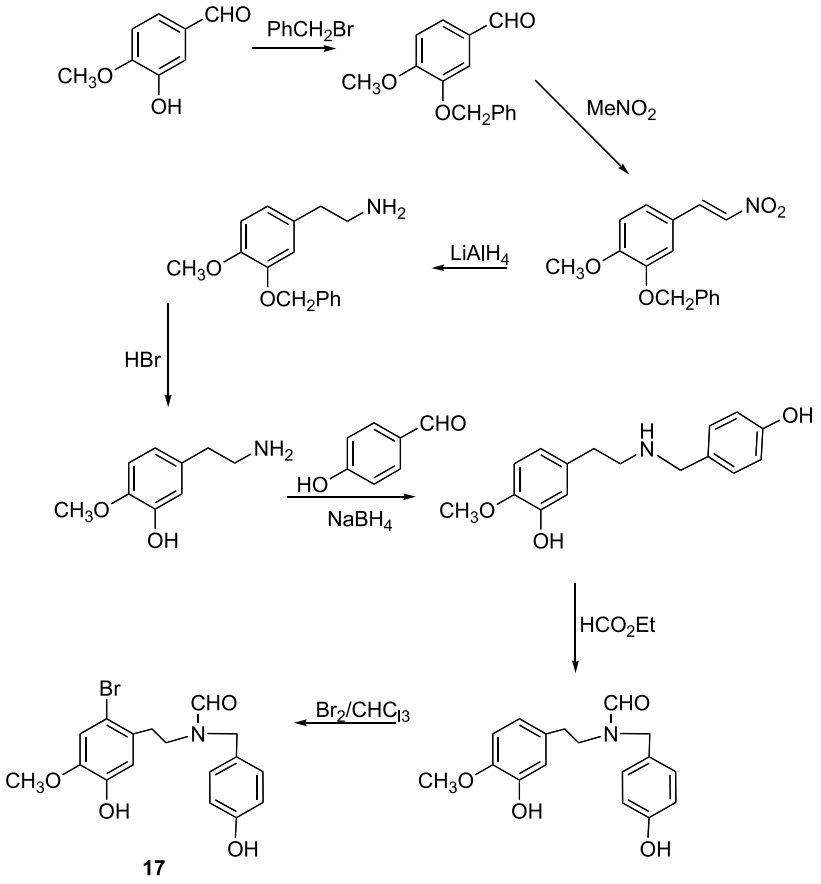


Scheme 2.

isolation and identification. Use of the dibrominated bisphenol intermediate in our modified[13] Shimizu synthesis[10] (Scheme 4) afforded the product **3** in 11% yield. The oxidative cyclization precursor **25** was obtained by formylation (46% yield) of the product obtained from reductive amination of 3-bromo-4-hydroxybenzaldehyde (**24**)[7] (prepared in 83% yield by bromination of commercially available 4-hydroxybenzaldehyde **23**) with 2-bromo-5-hydroxy-4-methoxyphenethylamine (**22**). The latter[1] was prepared by bromination of commercially available 3-hydroxy-4-methoxyphenylacetic acid (**18**) to afford the known[11] 2-bromo-5-hydroxy-4-methoxphenylacetic acid **19** (96% yield), followed by esterification and in situ conversion to the amide **21** (82% yield) and borane reduction (93% yield). The overall yield of **3** from commercially available starting materials was only 2.5%.

3. Discussion

We had previously determined that the yield in the oxidative cyclization step in the synthesis of galanthamine could be substantially improved by enhancing both the chloroform solubility and the steric hindrance to chelation of the



Scheme 3.

oxidative cyclization substrate.[13] A further example of the important role of molecular distribution properties is provided by comparison of our results to those of Poschalko et al.[9] Thus, while we were unable to isolate any meaningful amounts of cyclized product by attempted oxidation of the precursor **17** in chloroform, the cyclization product was obtained in 19–25% yield when the reaction was carried out in toluene.[9] Moreover, whereas the galanthamine precursor, 1,7-dibromo-*N*-formyl-*N*-nornarwedine had been obtained in 38–43% yield from the dibromo bisphenol,[13] the analogous 10-aza-compound **26**, the precursor of the [3]benzazepine analog **3**, was obtained in only 11%. Thus, although the oxidative cyclization process has been successfully applied to the synthesis of carbocyclic galanthamine analogs,[14] the results of our preparation of **2** and **3** confirm that this cyclization is highly sensitive to molecular features.

Altering the position of the nitrogen atom has striking effects on reactivity. Specifically, attempts to oxidize **2** to the narwedine analog **29** using manganese dioxide produced only minute amounts of **29** (Scheme 5), although treatment of galanthamine (**1**) afforded narwedine in 87% yield under the same conditions (unpublished results). Similarly, attempted epimerization of **2** to **30** (Scheme 5), under conditions that had been used successfully to convert galanthamine (**1**) to epigalanthamine failed; ^{1}H NMR (data not shown) suggested that the reaction product was the diene **31** (Scheme 5). The instability of this material precluded characterization. Preparation of the lycoramine analog **32** could not be carried out under the conditions used to convert galanthamine (**1**) to lycoramine due to the insolubility of **2** in ethanol. Attempted hydrogenation of the hydrochloride salt of **2** in ethanol produced 6-desoxylycoramine (**33**), presumably by catalytic hydrogenation of the diene **31** formed by the reaction of **2** with hydrochloric acid (Scheme 5). The lycoramine analog **32** was successfully prepared by hydrogenation of **2** in tetrahydrofuran; **33** was a byproduct (Scheme 6).

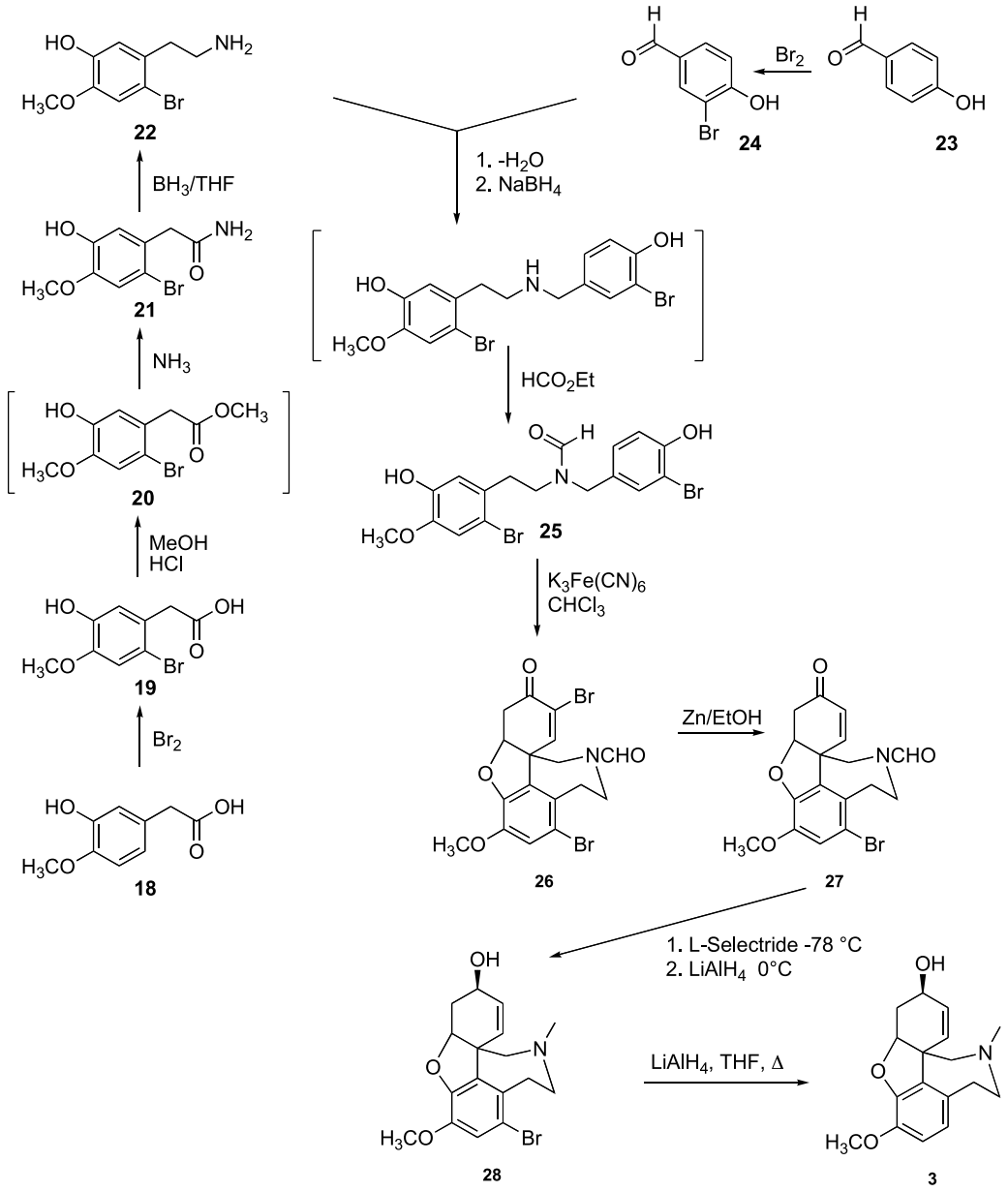
4. Conclusion

Oxidative cyclization has been utilized to prepare the [1]- and [3]benzazepine analogs of galanthamine, **2** and **3**, respectively. Despite the general structural similarity of **2**, **3**, and galanthamine (**1**), these compounds differ greatly in the reaction yields associated with the oxidative cyclization reaction as well as in their chemical reactivity.

5. Experimental

5.1. General

Melting points were determined on a Koffler hot stage. Proton magnetic resonance spectra were obtained on either a Bruker WM250 or a Varian EM390 spectrometer. Chemical shifts are relative to internal tetramethylsilane. Mass Spectra were recorded on an Applied Biosystems, Sciex



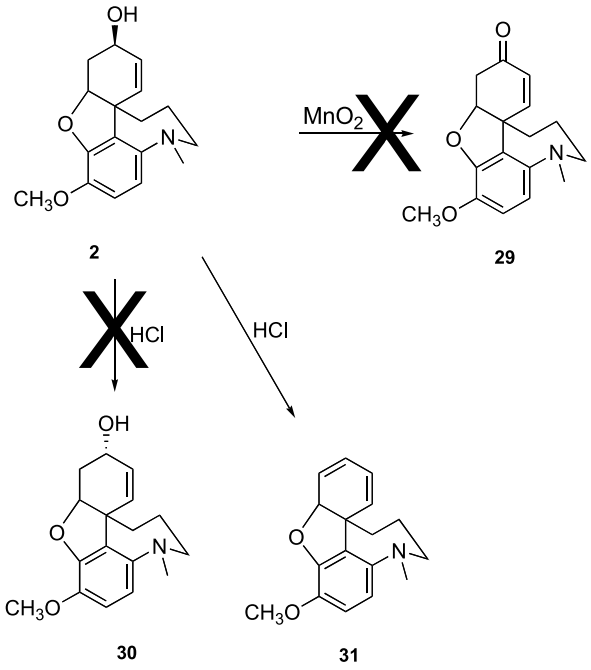
Scheme 4.

API single quadrupole mass spectrometer using atmospheric pressure chemical ionization.

5.1.1. 3-(4-Hydroxyphenyl)propionic acid methyl ester (5). After 3 h at ambient temperature a solution of 3-(4-hydroxyphenyl)propionic acid (**4**) (50 g, 0.3 mol) in 5% methanolic HCl (500 mL) was evaporated, and the residue was dissolved in EtOAc (300 mL). The solution was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and evaporated, giving a yellow oil (51.3 g, 95% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.55, 2.74 (AA′BB′, $J_{AB}=J_{AB'}=4$ Hz, CH_2CH_2), 3.60 (s, 3, $COOCH_3$), 6.67, 7.00 (AA′BB′, $J_{AB}=7.2$ Hz, $J_{AB'}=2.8$, 4 Hz, ArH), 9.18 (s, 1, OH). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67. Found: C, 66.55; H, 6.75.

5.1.2. 3-(4-Benzyloxyphenyl)propionic acid methyl ester (6). To a solution of 3-(4-hydroxyphenyl)propionic acid methyl ester (**5**) (36 g, 0.2 mol) in DMF (distilled, 275 mL) was added K_2CO_3 (165 g) followed by benzyl chloride (26 mL). After stirring for 18 h at 120 °C, this mixture was poured into ice-water (1500 mL) and concentrated HCl was added to pH 1. The solid product was removed by filtration and dried under vacuum to give 49.7 g (92% yield) of white crystals: ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.56–2.83 (AA′BB′, $J_{AB}=7.5$ Hz, $J_{AB'}=7.5$, 4 Hz, CH_2CH_2), 3.62 (s, 3, $COOCH_3$), 4.98 (s, 2, OCH_2), 6.86, 7.07 (AA′BB′, $J_{AB}=8.5$ Hz, $J_{AB'}=2.5$, 4 Hz, ArH), 7.2–7.43 (m, 5, Ph). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.56; H, 6.67. Found: C, 75.50; H, 6.74.

5.1.3. 3-(4-Benzyloxyphenyl)propionic acid (7). To a suspension of 3-(4-benzyloxyphenyl)propionic acid methyl ester (**6**) (54 g, 0.2 mol) in MeOH (500 mL) was added 0.4 N KOH (1 L), and the mixture was stirred at 60 °C until TLC showed the saponification to be complete. The volatile



Scheme 5.

solvent (MeOH) was evaporated, the pH brought to 1 with concentrated HCl, and the solution extracted with EtOAc (2×400 mL). The combined extract was dried over $MgSO_4$ and evaporated. The residue was triturated with hexane to give 46 g (90% yield) of white crystals, mp 122–123 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.60, 2.86 (AA′BB′, $J_{AB}=J_{AB'}=7.5$, 4 Hz, CH_2CH_2), 4.99 (s, 2, OCH_2), 6.86, 6.90 (AA′BB′, $J_{AB}=8.5$ Hz, $J_{AB'}=2.5$, 4 Hz, ArH), 7.2–7.4 (m, 5, Ph), 11.4 (br s, 1, COOH). Anal. Calcd for $C_{16}H_{16}O_3$: C, 75.00; H, 6.25. Found: C, 75.04; H, 6.30.

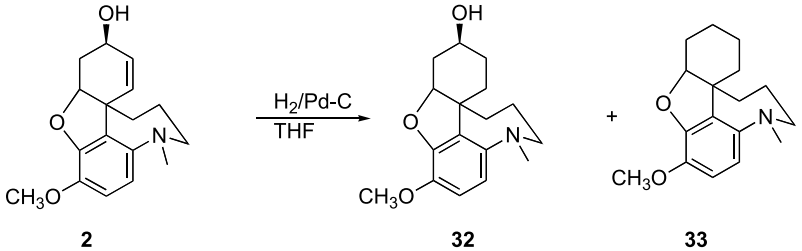
5.1.4. 3-Hydroxy-4-methoxyformanilide (10). To a suspension of 3-hydroxy-4-methoxyaniline (**9**) (20.85 g, 0.15 mol) in HCOOEt (500 mL) was added HCOOH (3 drops). The reaction mixture was refluxed for 48 h at which time TLC indicated all the starting material had been consumed. The solvent was evaporated, and the residue was dissolved in warm Me_2CO and passed through a 5×5.5 cm charcoal column (Norit). Evaporation of the solvent yielded 21.3 g of gray crystals (85%): ^{1}H NMR (250 MHz, $CDCl_3$/DMSO-d_6) exhibits the presence of two amide rotamers δ (ppm): 3.75 (s, 3, OCH_3), 6.61, 7.00 (2dd, $J=8.5$, 2.5, 1 Hz, H-6), 6.70, 7.25 (2d, $J=2.5$, 1 Hz, H-2), 6.85 (d, $J=8.5$, 1 Hz, H-5), 8.22, 8.62 (2d, $J=2$, 10, 1 Hz, CHO), 9.13 (br s, 1, OH), 9.89, 9.98 (2s, 1, NH). Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.39; N, 8.38. Found: C, 57.57; H, 5.44; N, 8.36.

5.1.5. 3-Benzloxy-4-methoxyformanilide (11). To a mixture of 3-hydroxy-4-methoxyformanilide (**10**) (16.7 g, 0.1 mmol) and K_2CO_3 (75 g) in DMF (100 mL) was added benzyl chloride (12 mL, 0.107 mol), and the mixture was stirred for 8 h at 120 °C. After cooling to room temperature, the reaction mixture was poured into ice-water, the pH was adjusted to 1 with concentrated HCl and the resultant solid was collected by filtration. After drying the brown powder weighed 21 g (82% yield): ^{1}H NMR (250 MHz, $CDCl_3$) exhibits the presence of two amide rotamers δ (ppm): 3.81, 3.84 (2s, 3, OCH_3), 5.06, 5.10 (2s, 2, OCH_2), 6.50–6.70 (m, 3, ArH), 7.20–7.38 (m, 5, Ph), 7.40, 8.17 (br s, d, $J=0.5$, 1 Hz, NH), 8.35, 8.43 (2d, $J=10$, 2, 1 Hz, CHO). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.04: H, 5.84; N, 5.45. Found: C, 70.12; H, 5.88; N, 5.40.

5.1.6. *N*-Methyl-2-bromo-5-benzyloxy-4-methoxyaniline (12). To a solution of 3-benzyloxy-4-methoxyformanilide (**11**) (25.7 g, 0.1 mol) in dry THF (600 mL) at 0 °C was added *N*-bromoacetamide (15.2 g, 0.11 mol) in several portions. After stirring overnight, the solvent was evaporated, and the residue was dissolved in $CHCl_3$ (500 mL). This solution was washed twice with H_2O (100 mL), dried over $MgSO_4$, and evaporated. Chromatography on SiO_2 (2% MeOH in $CHCl_3$) afforded 29 g (86%) of the intermediate bromo formamide as an off-white powder: ^{1}H NMR (90 MHz, $CDCl_3$) δ (ppm): 3.80 (s, 3, OCH_3), 5.08 (s, 2, OCH_2), 6.95 (s, 1, H-3), 7.20–7.45 (m, 6, Ph and NH), 8.07 (s, 1, H-6), 8.35 (d, $J=2$, 1 Hz CHO).

A solution of the above product (16.8 g, 0.05 mol) in THF (100 mL) was cooled to 0 °C, and 1 M $BH_3\cdot$THF (100 mL, 0.1 mol) was added. After refluxing for 30 min, the reaction mixture was cooled to 0 °C, and the excess BH_3 was decomposed by the addition of H_2O followed by 10% NaOH. Stirring was continued for 30 min, EtOAC (200 mL) was added, and the layers were separated. The organic layer was evaporated, and the aqueous layer was washed with EtOAc (200 mL). The combined organic phase was dried and evaporated to give **12** as an off-white semisolid, after drying under high vacuum (14.6 g, 91% yield): ^{1}H NMR (90 MHz, $CDCl_3$) δ (ppm): 2.65 (s, 3, NCH_3), 3.68 (s, 3, OCH_3), 3.65–3.95 (br s, 1, NH), 5.03 (s, 2, OCH_2), 6.20 (s, 1, H-6), 6.97 (br s, 1H-3), 7.12–1.40 (m, 5, Ph). Anal. Calcd for $C_{15}H_{16}BrNO_2$: C, 55.92; H, 5.01; N, 4.35. Found: C, 55.94; H, 5.02; N, 4.27.

5.1.7. *N*-Methyl-3-(4-hydroxphenyl)propion-(2-bromo-5-hydroxy-4-methoxy)anilide (13). A solution of 3-(4-benzyloxyphenyl)propionic acid (**7**) (25.6 g, 0.1 mol) in $SOCl_2$ (75 mL) was refluxed for 2 h. The excess $SOCl_2$ was removed at reduced pressure; the residue was dissolved in



Scheme 6.

$CHCl_3$ (pentene stabilized) and the solvent evaporated. After drying under high vacuum for 2 h, 27.5 g (100% yield) of the product **8** was obtained. A portion (14 g, 0.051 mol) was dissolved in $CHCl_3$ (150 mL) (pentene stabilized) and the solution was added to a solution of *N*-methyl-2-bromo-5-benzyloxy-4-methoxyaniline (**12**) (16.1 g, 0.05 mol) in $CHCl_3$ (pentene stabilized, 200 mL), followed by Et_3N (56 g) in $CHCl_3$ (50 mL). After stirring for 1 h, TLC showed the starting material to be consumed. The reaction mixture was then washed with 1% HCl, followed by H_2O, dried and evaporated to give a brown oil (23.8 g, 85% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.05–2.30 (AA′, 2, CH_2CO), 2.65–2.87 (BB′, 2, CH_2CH_2CO), 3.10 (s, 3, NCH_3), 3.80 (s, 3, OCH_3), 4.95 and 5.00 (2s, 4, CH_2O), 6.55 (s, 1H-3), 6.80–7.10 (AA′BB′, 4, ArH), 7.25 (s, H-6), 7.20–2.50 (m, 10, Ph).

To a solution of this oil (14 g, 0.025 mol) in EtOH (75 mL) was added 48% HBr (150 mL) and the mixture was stirred for 2 h at 60 °C. The reaction mixture was treated with charcoal and allowed to come to room temperature. The residue obtained after filtration through a pad of Celite and evaporation of the solvent was dissolved in EtOAc (200 mL), and the solution was washed with H_2O, dried over $MgSO_4$ and evaporated. The product (7.7 g, 81% yield) was obtained as an off-white semicrystalline solid after purification by column chromatography using SiO_2 and 2% MeOH in $CHCl_3$ on the eluent: ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.27, 2.83 (AA′BB′, $J_{AB}=8.5$, 4 Hz, CH_2CH_2), 3.13 (s, 3, NCH_3), 3.89 (s, 3, OCH_3), 5.60–6.50 (br s, 2, OH), 6.28 (s, 1H-3), 6.70, 6.88 (AA′BB′, $J_{AB}=9$ Hz, $J_{AB'}=2$, 4 Hz, ArH), 7.03 (s, 1, H-6). Anal. Calcd for $C_{17}H_{18}BrNO_4$: C, 53.68; H, 4.74; N, 3.68. Found: C, 53.78; H, 4.82; N, 3.62.

5.1.8. (4aα)-4a,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-12-methyl-11-oxobenzofuro[3a,3,2-*e*,*f*][1]benzazepin-6-one (14). To a well-stirred mixture of $CHCl_3$ (3000 mL), aqueous 5% $NaHCO_3$ (500 mL) and $K_3Fe(CN)_6$ (57 g, 0.173 mol) at 60 °C was added *N*-[3-(4-hydroxyphenyl)propionyl]-*N*-methyl-2-bromo-5-hydroxy-4-methoxyaniline (**13**) (11 g, 0.029 mol) in one portion. After stirring at 60 °C for 1.5 h the layers were separated, the $CHCl_3$ evaporated and the residue filtered through a 5 cm column of SiO_2 in EtOH stabilized $CHCl_3$. Evaporation of the solvent afforded 5.5 g (50%) of the product **14** (TLC pure) as a pink foam: ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.03–3.15 (m, 6H, CH_2CH_2 and $CH_2C{=}O$), 3.36 (s, 3, NCH_3), 3.88 (s, 3, OCH_3) 4.84 (m, 1, H-4), 6.00 (d, $J=9$, 1 Hz, H-8), 6.36 (dd, $J=9$, 2, 1 Hz, H-7), 7.08 (s, 1, H-2). Anal. Calcd for $C_{17}H_{16}BrNO_4$: C, 53.97; H, 4.23; N, 3.70. Found: C, 54.03; H, 4.30; N, 3.62.

5.1.9. (4aα,6β)-4a,5,9,10,11,12-Hexahydro-3-methoxy-12-methyl-6*H*-benzofuro-[3a,3,2-*e*,*f*][1]benzazepin-6-ol (2) and (4aα,6α)-4a,5,9,10,11,12-hexahydro-3-methoxy-12-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepin-6-ol (15). A solution of (4α)-4a,5,9,19,11,12-hexahydro-1-bromo-3-methoxy-12-methyl-11-oxobenzofuro[3a,3,2-*e*,*f*]-[1]benzazepin-6-one (**14**) (3.8 g, 0.01 mol) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (5 g, 0.47 mol) in THF (100 mL). The reaction mixture was refluxed for 36 h and stirred at room temperature for an additional 48 h. The excess $LiAlH_4$ was decomposed by the sequential addition of H_2O and 15% NaOH. The solids were removed by filtration and washed with EtOAc (200 mL). The combined organic phase was dried with $MgSO_4$ and evaporated. The product mixture was separated by column chromatography eluting with 0.4% EtOH in $CHCl_3$ affording 1.7 g (59%) of the 4α,6β isomer **2** and 0.2 g (7%) of the 4α,6α isomer **15**: ^{1}H NMR for **2** (250 MHz, $CDCl_3$) δ (ppm): 1.41, 1.71 (AB, 2, H-9), 1.88, 2.15 (AB, 2, H-10), 2.04, 2.68 (AB, $J=15.6$, 2 Hz, H-5), 2.35 (d, $J=11.4$, 1 Hz, OH), 2.78, 3.30 (AB, 2, H-11), 2.86 (s, 3, NCH_3), 3.80 (s, 3, OCH_3), 4.11 (m, $J=11.4$, 1 Hz, H-6), 4.58 (m, 1, H-4), 5.90 (dd, $J=10.3$, 4.8, 0.9, 1 Hz, H-7), 6.00 (dd, $J=10.3$, 0.9, 1 Hz, H-8), 6.28 (d, $J=8.75$, 1 Hz, H-1), 6.69 (d, $J=8.75$, 1 Hz, H-2): ^{1}H NMR for **15** (250 MHz, $CDCl_3$) δ (ppm): 1.49, 1.87 (AB, 2, H-9), 1.72, 2.75 (AB, 2, H-5), 1.82, 2.07 (AB, 2, H-10), 2.11 (br s, 1, OH), 2.75, 3.24 (AB, 2, H-11), 2.81 (s, 3, NCH_3), 3.78 (s, 3, OCH_3), 4.55 (m, 1, H-4), 4.59 (m, 1, H-6), 5.68 (d, $J=10.3$, 1 Hz, H-7), 6.01 (d, $J=10.3$, 1 Hz, H-8), 6.22 (d, $J=8.7$, 1 Hz, H-1), 6.64 (d, $J=8.7$, 1 Hz, H-2).

5.1.10. (4aα,6β)-4a,5,9,10,11,12-Hexahydro-3-methoxy-12-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepin-6-ol (2) hydrochloride. The free base **2** (1.7 g, 0.006 mol) was dissolved in EtOH, and ethanolic HCl was added. The solvent was evaporated, and the product was recrystallized from EtOH/Et_2O to give 1.7 g (89%) of the hydrochloride salt, mp 181.5–182.0 °C. Anal. Calcd for $C_{11}H_{22}C1NO_3 \cdot 1/4H_2O$: C, 62.20; H, 6.87; N, 4.27. Found: C, 62.23; H, 6.93; N, 4.26.

5.1.11. 2-Bromo-5-hydroxy-4-methoxyphenylacetic acid (19).[11] To a solution of 3-hydroxy-4-methoxyphenylacetic acid (**18**) (70 g, 0.386 mol) in HOAc (1000 mL) was added a solution of Br_2 (67.74 g, 0.424 mol) in HOAc (100 mL) at room temperature. The mixture was stirred overnight and the solvent evaporated. The residue was dissolved in toluene and the solvent evaporated. The residue was treated with toluene (800 mL), the mixture heated for 15 min, cooled to room temperature and the product filtered, to afford 97 g (96%) of semicrystalline solid: ^{1}H NMR (90 MHz, DMSO-d_6) δ (ppm): 3.48 (s, 2, CH_2), 3.69 (s, 3, OCH_3), 6.70 (s, 1, Ar), 6.97 (s, 1, Ar). *m*/*z* Calcd for $C_9H_9BrO_4$: 259.9685 and 261.9664. Found: 259.9691 and 261.9674.

5.1.12. 2-Bromo-5-hydroxy-4-methoxyphenylacetamide (21). Dry HCl was passed through a solution of 2-bromo-5-hydroxy-4-methoxphenylacetice acid (**19**) (97 g, 0.371 mol) in MeOH (1000 mL) at 0 °C for 30 min. The mixture was left overnight, then the solvent was evaporated, and the residue (**20**) was dissolved in EtOAc. The solution was washed twice with water, aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and the solvent was evaporated. The ester was dissolved in MeOH (800 mL) and NH_3 was bubbled through for 8 h at 0 °C. The reaction mixture was left in the dark for 10 days. The volatiles were removed under reduced pressure and the residue was suspended in MeOH (150 mL) and filtered, affording 79 g (82%) of amide **21**, mp 185–187: ^{1}H NMR (90 MHz, DMSO-d_6) δ (ppm): 3.25 (s, 2, CH_2); 3.75 (s, 3, OCH_3); 6.50–7.40 (m, 4, NH_2, Ar); 8.82 (s, 1, OH). *m*/*z* Calcd for $C_9H_{10}BrNO_2$: 258.9844 and 260.9824. Found: 258.9840 and 260.9827.

5.1.13. 2-Bromo-5-hydroxy-4-methoxyphenethylamine (22).[1] To the amide **21** (64 g, 0.246 mol) in a 2 L round-bottom flask was added slowly 1 N BH_3/THF (800 mL, 0.266 mol). The reaction mixture was refluxed for 5 h, cooled to 0 °C and concentrated methanolic HCl was added (500 mL). After stirring overnight, the solvent was evaporated, the residue redissolved in MeOH and the solvent evaporated again. This operation was repeated three times. The residue was dissolved in MeOH (500 mL) and the pH was brought to 8 by addition of MeONa in MeOH. The precipitated salt was removed by filtration and the solvent was evaporated at reduced pressure to afford 56 g (93%) of **22** as a light brown wax: ^{1}H NMR (90 MHz, DMSO-d_6) δ (ppm): 2.84 (s, 4, CH_2CH_2); 3.72 (s, 3, OCH_3); 6.78 (s, 1, Ar); 7.02 (s, 1, Ar).

5.1.14. 3-Bromo-4-hydroxybenzaldehyde (24). To a solution of 4-hydroxybenzaldehyde (**23**) (50 g, 0.409 mol) in a mixture of $CHCl_3$ (500 mL) and MeOH (50 mL) was added a solution of Br_2 (71 g, 23 mL, 0.45 mol) in $CHCl_3$ (100 mL) dropwise at room temperature. The mixture was stirred for 2 h and washed with water to neutral pH. The organic phase was dried with $MgSO_4$ and the solvent was evaporated. Recrystallization from $CHCl_3$ afforded 68.4 g (83%) of **24**, mp 118–120 °C (lit.[8] 124 °C).

5.1.15. *N*-(2-Bromo-5-hydroxy-4-methoxyphenethyl)-*N*-(3-bromo-4-hydroxybenzyl)formamide (25). A mixture of the aldehyde **24** (45.7 g, 0.227 mol) and the crude amine **22** (56 g, 0.227 mol) in anhydrous MeOH (1600 mL) and molecular sieves 4 Å (230 g) was stirred overnight at room temperature. After the sieves were removed by filtration and the mixture diluted to 3200 mL with MeOH, $NaBH_4$ (19 g, 0.5 mol) was added in six equal portions at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was treated with 15% HCl/MeOH to pH 1, and the mixture was left overnight at room temperature. The solvent was then removed under reduced pressure, the residue redissolved in MeOH, and the NaCl removed by filtration. This procedure was repeated three times. The residue was then dissolved in MeOH (700 mL) and methanolic MeONa was added until the pH was 8. The precipitated NaCl was filtered off, and the solvent was evaporated. The residue was suspended in HCOOEt (1000 mL) with NEt_3 (10 mL), and the mixture was refluxed until TLC ($CHCl_3$/MeOH/NH_4OH aqueous, 90:10:1) showed complete consumption of starting material (3 days). The solvent was removed under reduced pressure. The crude material was purified on a SiO_2 (1000 g) column (2% MeOH in $CHCl_3$) providing 48 g (46%) of the formamide **25** as a semicrystalline light yellow solid: ^{1}H NMR (90 MHz, DMSO-d_6) shows two rotamers δ (ppm): 2.50–2.95 (m, 2, $ArCH_2$); 3.22–3.55 (m, 2, $ArCH_2CH_2N$); 3.82 (s, 3, OCH_3); 4.18 and 4.45 (two-s, 2, $ArCH_2N$); 6.55–7.33 (m, 5, Ar); 8.00 and 8.28 (two-s, 1, CHO). *m/z* Calcd for $C_{17}H_{17}Br_2NO_4$: 456.9524, 458.9504, and 460.9486. Found: 456.9523, 458.9519, and 460.9482.

5.1.16. (*rac*)-(4aα)-4a,5,9,10,11,12-Hexahydro-1,7-dibromo-3-methoxy-10-formyl-6*H*-benzofuran[3a,3,2-*e*,*f*][3]benzazepin-6-one (26). To a well stirred biphase of $CHCl_3$ (3500 mL) and a solution of $K_3Fe(CN)_6$ (27.3 g, 0.083 mol) and $NaHCO_3$ (14 g, 0.17 mol) in H_2O (27.5 mL) at 60 °C in a 5 L Morton flask under N_2 was added formamide **25** (10 g, 0.022 mol) in one portion. After stirring at 60 °C for 2 h, the reaction mixture was cooled and the $CHCl_3$ layer was separated. The aqueous layer was washed with $CHCl_3$ (1000 mL). The combined organic phase was evaporated and the product was separated on 100 g of SiO_2 using 1% MeOH in $CHCl_3$ as eluant. After solvent removal under reduced pressure, 1.1 g (11% yield) of HPLC-pure product was obtained as a yellow foam: ^{1}H NMR (90 MHz, $CDCl_3$) showed two rotamers δ (ppm): 2.62–3.56 (m, 6, 3×CH_2); 3.75 (s, 3, OCH_3); 3.80–4.12 (m, 1, H-12a); 4.58–4.82 (m, 1, H-4a); 4.45 and 4.48 (two-d, J= 17, 1 Hz, H-12b); 6.75–6.90 (m, 1, H-8); 6.95 (s, 1, H-2); 8.01 and 8.05 (two-s, 1, CHO). MS (APCI-ESI) calcd for $C_{17}H_{15}Br_2NO_4$: 455/457/459. M^+-1. Found: 456/458/460; M^--1. Found: 454/456/458. High resolution mass spectra could not be obtained for this material.

5.1.17. (*rac*)-(4aα)-4a,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-10-formyl-6*H*-benzofuro[3a,3,2-*e*,*f*][3]benzazepin-6-one (27). To a solution of dibromoenone **26** (0.89 g, 0.002 mol) in EtOH (50 mL) was added 2.6 g of activated zinc powder. The mixture was refluxed until HPLC (2% MeOH in $CHCl_3$) showed completion of the reaction (overnight). The solution was filtered hot and the zinc was washed thoroughly with hot EtOH. The alcohol was evaporated and the residue was separated on a SiO_2 column (1% MeOH in $CHCl_3$) providing 0.65 g (88%) of the product **27** as a white foam: ^{1}H NMR (90 MHz, $CDCl_3$) showed two rotamers δ (ppm): 2.55–3.08 (m, 5); 3.10–3.98 (m, 2); 3.70 (s, 3, OCH_3); 4.45–4.84 (m, 2, H-4a, H-9); 5.92 and 6.02 (two-d, J=10, 1 Hz, H-7); 6.46 and 6.50 (two-d-d, J=10, 1.8, 1 Hz, H-8); 6.90 (s, 1, Ar); 8.00 and 8.18 (two-s, 1, CHO). *m/z* Calcd for $C_{17}H_{16}BrNO_4$: 377.0263 and 379.0242. Found: 377.0263 and 379.0226.

5.1.18. (*rac*)-(4aα,6β)-4a,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-10-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][3]-benzazepin-6-ol (28). A solution of (*rac*)-(4aα)-4a,5,9,10,11,12-hexahydro-1-bromo-3-methoxy-10-formyl-6*H*-benzofuro[3a,3,2-*e*,*f*][3]benzazepin-6-one (**27**) (3.67 g, 0.0097 mol) in dry THF (150 mL) at −78 °C was stirred under dry argon for 20 min, and 1 M L-Selectride (19.5 mL, 0.0195 mol) was added dropwise. After stirring at −78 °C for 2 h, the mixture was allowed to warm up to 0 °C, and 1 M $LiAlH_4$/THF (19.5 mL, 0.0195 mol) was added dropwise. Stirring was continued overnight. Excess reducing agent was decomposed by sequential addition of H_2O (2.65 mL) and 10% NaOH (8 mL). The inorganic salts were removed by filtration, and the solution was dried with $MgSO_4$. Column chromatography on SiO_2 (2% MeOH in $CHCl_3$) provided 2.55 g (72%) of **28** as a white foam: ^{1}H NMR (90 MHz, $CDCl_3$) δ (ppm): 1.62–1.90 (m, 2), 2.01–2.25 (m, 3), 2.30 (s, 3, NCH_3), 2.35–2.75 (m, 2), 2.80–3.22 (m, 2), 3.70 (s, 3, OCH_3), 3.99–4.11 (m, 1, H-6), 4.51 (m, 1, H-4), 5.86–6.02 (m, 2, H-7, H-8), 6.79 (s, 1, H-2). *m/z* Calcd for $C_{17}H_{20}BrNO_3$: 365.0627 and 367.0606. Found: 365.0630 and 367.0619.

5.1.19. (*rac*)-(4aα,6β)4a,5,9,10,11,12-Hexahydro-3-methoxy-10-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][3]-benzazepin-6-ol (3). A solution of (*rac*)-(4aα,6β)-4a,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-10-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][3]benzazepin-6-ol **28** (2.55 g, 0.007 mol)

in dry THF (150 mL) was added to a suspension of 4 g (0.073 mol) of $LiAlH_4$ (4 g, 0.073 mol) at 0 °C, and the mixture was refluxed for 72 h. After cooling to 0 °C, the excess $LiAlH_4$ was decomposed by sequential addition of H_2O (4 mL) and 10% NaOH (12 mL). The inorganic salts were removed by filtration, the filtrate dried over $MgSO_4$, and the solvent evaporated. Column chromatography on SiO_2 (3% MeOH in $CHCl_3$) provided 1.98 g of **3**. The amine was converted to a *p*-toluenesulfonic acid salt, which was collected by filtration and recrystallized from EtOH/ether providing 2.8 g (96%) of **3**·TsOH, mp 206 °C (dec); IR (KBr): 3300, 3010, 1510, 1450, 1235, 1145, 1050, 790, 690 cm^{-1}: ^1H NMR (250 MHz, DMSO-d_6) δ (ppm): 2.04–2.29 (m, 1), 2.29 (s, 3, NCH_3), 2.80–2.97 (m, 3), 3.21–3.71 (m, 5), 3.73 (s, 3, OCH_3), 4.07–4.15 (m, 1, H-6), 4.52–4.58 (m, 1, H-4), 5.87–5.98 (m, 2, H-7, H-8), 6.67 (d, J=8.2, 1 Hz, H-2), 6.90 (d, J=8.2, 1 Hz, H-1), 7.12 (d, J=8.0, 2 Hz, H-3, H-5), 7.48 (d, J=8.0, 2 Hz, H-2, H-6), 9.66 (br s, 1, N=H). Anal. Calcd for $C_{24}H_{29}NO_6S$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.85; H, 6.39, N, 3.03.

5.1.20. (4aα)-4a,5,7,8,9,10,11,12-Octahydro-3-methoxy-12-methyl-6*H*-benzofuro-[3a,3,2-*e*,*f*][1]benzazepine (33) hydrochloride. To a solution of (4aα,6)-4a,5,9,10,11,12-hexahydro-3-methoxy-12-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepin-6-ol (**2**) (1.1 g, 3.5 mmol) in 1% ethanolic HCl (50 mL) was added Pd/C (200 mg) and the mixture was hydrogenated for 2 h at 40 psi. The catalyst was removed by filtration, and the product was crystallized from EtOH/Et_2O to afford 1.1 g (92%) of the hydrochloride salt of the product, mp 205–220° (dec): ^1H NMR (250 MHz, D_2O) δ (ppm): 1.17–1.82 (m, 7), 2.00–2.62 (m, 5), 3.23 (s, 3, NCH_3), 3.53 (t, 1, H-11a), 3.69–3.89 (m, 1, H-11e), 3.89 (s, 3, OCH_3), 4.22 (br s, 1, H-4), 4.82 (s, 4, NH+HOD), 7.01 (AB, 2, ArH). Anal. Calcd for $C_{17}H_{23}NO_2 \cdot HCl$: C, 65.91; H, 7.75; N, 4.52; Cl, 11.47. Found: C, 65.70; H, 7.86; N, 4.48; Cl, 11.48.

5.1.21. (4aα,6β)-4a,5,7,8,9,10,11,12-Octahydro-3-methoxy-6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepin-6-ol (32) hydrochloride. To a solution of (4aα,6β)-4a,5,9,10,11,12-hexahydro-3-methoxy-12-methyl-6*H*-benzofuran[3a,3,2-*e*,*f*][1]benzazepin-6-ol (**2**) (2.87 g, 0.01 mol) in THF (150 mL) was added 10% Pd/C (400 mg), and the mixture was shaken under 40 psi of H_2 for 7 h. The catalyst was removed by filtration, the solvent evaporated, and the residue purified by chromatography using 0.2–0.5% EtOH in $CHCl_3$ to afford 1.39 (46%) of **32**. The desoxy compound **33** was isolated in 26% as a byproduct. Treatment of **32** with 1% HCl in EtOH gave the hydrochloride salt. Crystallization from EtOH/Et_2O gave 1.2 g (81%) of the pure salt, mp 235 °C (dec): ^1H NMR (250 MHz, D_2O) δ (ppm): 1.60–2.63 (m), 3.27 (2, 3, NCH_3), 3.55 (t, 1, H-11a), 3.74–3.82 (m, 1, H-11e), 3.89 (s, 3, OCH_3), 4.17 (br s, 1, H-4), 4.33 (br s, 1, H-6), 4.80 (s, 1.5, NH–HOD), 7.01 (AB, 2, ArH). Anal. Calcd for $C_{17}H_{24}ClNO_3$: C, 62.67; H, 7.37; N, 4.50; Cl, 10.91. Found: C, 62.76; H, 7.46; N, 4.27; Cl, 10.85.

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