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Total Synthesis of (±)-Galanthamine from GABA through Regioselective Aryne Insertion

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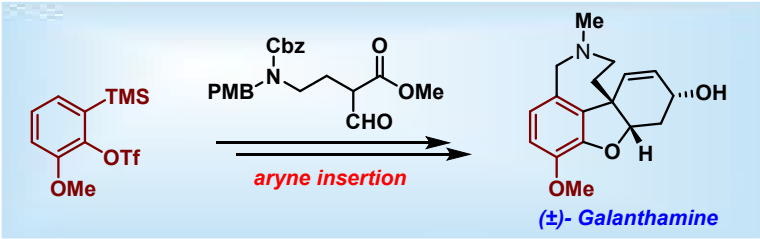

ABSTRACT: Total synthesis of (±)-galanthamine is achieved in ~5% overall yield using key regioselective aryne insertion reaction into GABA (γ-Amino butyric acid) derivative. The strategy presented involves only two sub critical temperature reactions and less than five chromatographic purifications to achieve the synthesis of galanthamine.

KEYWORDS: Galanthamine, Total synthesis, Aryne insertion, Cycloaddition, GABA.

Total synthesis of scarcely available natural products is an ongoing process in research community and has played an important role in understanding structure activity relationship (SAR) of natural products and their analogues.[1] More recently, the total syntheses of FDA approved drugs of natural product origin[2] have attracted equal attention, as many a times the supplies are inconsistent and also depleting.

(-)-Galanthamine (**1**, Figure 1), an alkaloid belonging to *Amaryllidaceae* family, with acetyl cholinesterase inhibitory activity, is one of the FDA approved drugs for symptomatic

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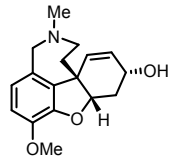
treatment of Alzheimer's disease.[3] This natural product has the ability to cross the blood-brain barrier (BBB) and is also shown to act as nicotinic acetylcholine receptor.



(-)- galanthamine (**1**)

Figure 1. Galanthamine structure.

The interesting and challenging scaffold of galanthamine has been classical target for synthetic organic chemists. Several researchers have taken up the challenge of developing synthetic routes as compiled in a review by Hudlicky *et al*[4a] and Garcia *et al*.[4b] Syntheses that appeared after the review include efforts of Banwell *et al*,[5p] Hudlicky *et al*,[5q] Nagase *et al*.[5o] Most of the reported synthesis relied on at least one of the following strategies *viz*, oxidative cyclization, chiron approach, noble metal catalyzed C-C bond formation, ring-closing metathesis and so on.

Our research group had synthesized the pruned versions of galanthamine to explore whether a simpler analogue of galanthamine will be as effective as the natural product.[6a] In this endeavour, we have also studied the literature describing total synthesis of galanthamine, for ways to optimize the yields. This effort resulted in delineating a new strategy for this "age old target" which avoids expensive metals, air sensitive reactions and also allows one to synthesize analogues. Herein we report our findings. Our retrosynthetic dissection relied on the recently developed aryne insertion reaction,[7a,b] wherein a *β*-keto ester adds onto aryne to create two C-C bonds through cyclobutene. This strategy is exploited in synthesis of several natural products with ease.[7a-h]

Thus retrosynthesis of **1** revealed the benzofuranone **2** could be achieved using Pictet-Spengler reaction and ketone-lactone condensation with ease. The required substituted benzene ring **3** in turn can be synthesized from aryne precursor **4** and GABA derivative **5**.

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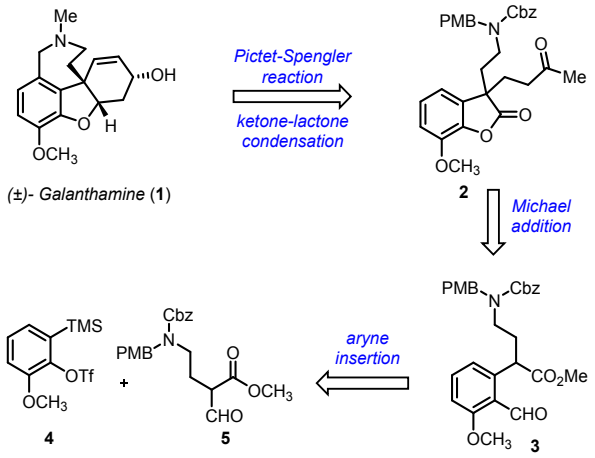

Scheme 1. Retrosynthetic analysis of (±)-galanthamine

Retrosynthetic analysis gave us a clue that GABA (*γ*-Amino butyric acid), an easily available and clinically used neurotransmitter, would be an ideal starting material, which on simple modifications could add on to aryne precursor **4**[7c] (Scheme 1). Aryne precursor can be prepared from Guaiacol (2-methoxyphenol) in two easy steps. The ease of availability and commercial feasibility of both the starting materials attracted our attention to focus on building galanthamine skeleton. Thus protected GABA **6**[8] was converted to corresponding ester **7** using $SOCl_2$/methanol in 94% yield. The *C*-formylation of ester **7** under $TiCl_4/NEt_3$ and methyl formate conditions provided compound **5** in 92% yield. Thus formed *β*-formyl ester **5** on treatment with the methoxy benzyne precursor **4**, in presence of CsF, provided the trisubstituted aryl intermediate **3** in 62% yield. The methoxy group on benzyne, through negative inductive effect, has provided us single regioisomer, **3**.[7c] The Baeyer-Villiger oxidation of **3** resulted in the GABA stitched catechol derivative **8** in 86% yield. The hydrolysis of O-CHO group in **8** with 2M NaOH solution gave phenol, which without purification was subjected to lactonisation using TsOH and yielded the benzofuranone **9** in 65% yield for two steps (Scheme 2).

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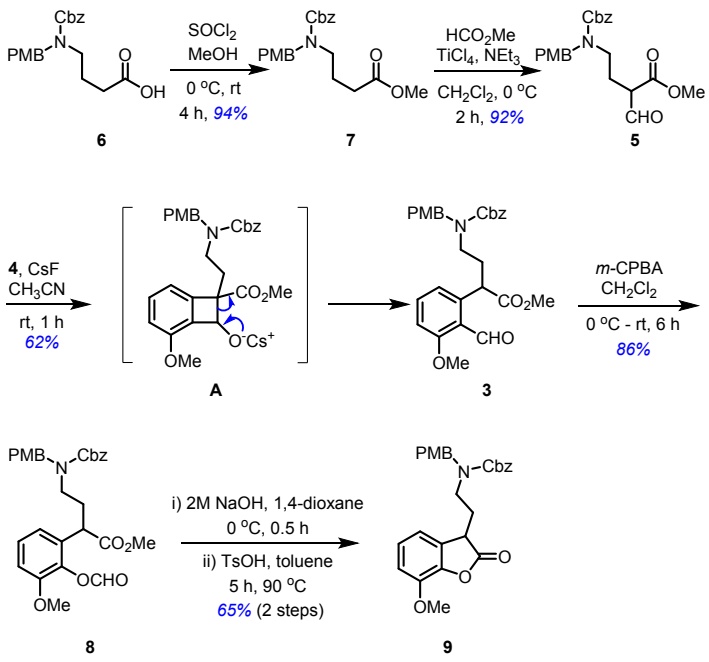

Scheme 2. Synthesis of benzofuranone **9**

Having constructed this bicyclic frame of galanthamine, the next appendage was installed through a simple Michael addition of **9** onto methyl vinyl ketone (MVK) under the influence of DIPEA to furnish the α,α-disubstituted lactone **2**. The PMB protection on amine **2** was removed by exposure to CAN resulting in 82% yield of compound **10**. The classical Pictet-Spengler reaction on **10** with paraformaldehyde was achieved in 92% yield to get the tricyclic [6,5,7] membered core of galanthamine **11**. The intramolecular ketone-lactone condensation of **11**, mediated by LDA at -78 ^{o}C, provided the tetracyclic lactol **12** in 90% yield.[5i] Reductive deoxygenation of **12** with Et_3SiH promoted by $BF_3.OEt_2$ resulted in **13** as a diastereomeric mixture, which without characterization, was subjected to *N*-methylation using HCHO/HCOOH, the O-formyl group formed during the *N*-methylation reaction was hydrolysed using potassium carbonate, and the free alcohol was oxidized with SO_3.Py condition to yield compound **14** as a single diastereomer in 65% yield for 3 steps. Compound **14** on treatment with LDA and PhSSPh followed by oxidative elimination[5o] produced the (±)-narwedine **15** which is the biogenic precursor of galanthamine, in 45% yield.[9] Diastereoselective reduction of (±)-narwedine **15** with LS-selectride furnished (±)-galanthamine (**1**) in 96% yield, whose analytical data matched with literature values (Scheme 3).

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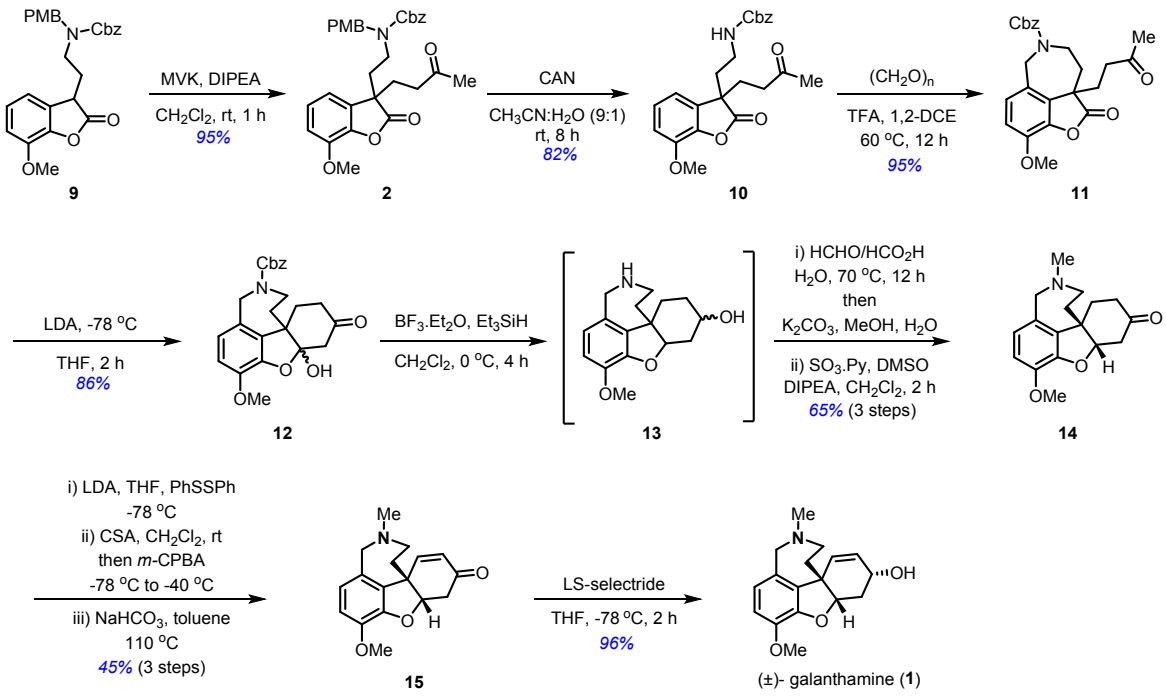
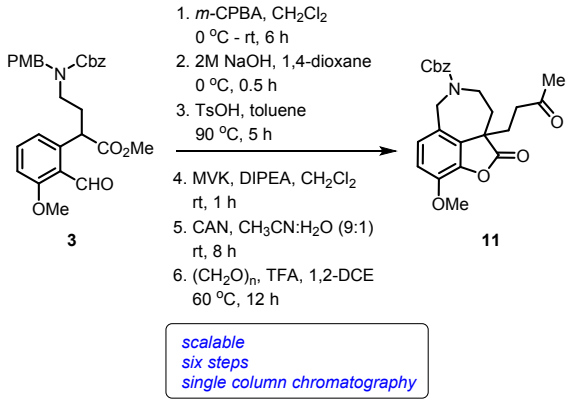


Scheme 3. Total synthesis of (±)-galanthamine

Another interesting feature of our synthetic route is the synthesis of **11** from **3** was achieved in six-consecutive steps involving only one chromatographic purification. This has added to the operational simplicity without any effect on the overall yield of the product. The conditions used are mild, temperatures are moderate and purifications are minimal (Scheme 4).



Scheme 4. Practical simplicity for synthesis of **11** from **3**

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In conclusion, synthesis of (±)-galanthamine (**1**), is achieved from GABA and aryne precursor involving only two sub-critical temperature reactions and in less than five chromatographic purifications in overall ~5% yield. This approach avoids expensive metals, air sensitive reactions and also allows one to synthesize analogues.

EXPERIMENTAL SECTION

General information: Unless otherwise noted, all reagents were used as received from commercial suppliers. All reactions were performed under nitrogen atmosphere and in a flame-dried or oven-dried glassware with magnetic stirring. All solvents were dried before use following the standard procedures. Reactions were monitored using thin-layer chromatography (SiO_2). TLC plates were visualized with UV light (254 nm), iodine treatment or using ninhydrin stain. Column chromatography was carried out using silica gel (100-200 mesh) packed in glass columns. NMR spectra were recorded at 300, 400, and 500 MHz (H) and at 75, 100, and 125 MHz (C), respectively. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 and C: δ = 77.0 ppm) as internal standard, and coupling constants (J) are given in Hz. HRMS were recorded using ESI-TOF techniques.

Methyl 4-(((benzyloxy)carbonyl)(4-methoxybenzyl)amino)butanoate (7):

To *N*-protected γ-Amino butyric acid (GABA) **6** (25.0 g, 70 mmol, 1.0 equiv) in MeOH (200 mL) was added $SOCl_2$ (6.1 mL, 84 mmol, 1.2 equiv) at 0 ^oC. The reaction was stirred for 1 h at same temperature and monitored by TLC. After disappearance of starting material, MeOH was removed under reduced pressure, and residue was extracted with EtOAc (3 x 100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution. The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure to give crude which was purified by silica gel column chromatography (Hexane/EtOAc, 4:1) to afford **7** as a pale yellow oil (24.5 g, 94% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.25 (m, 5H), 7.12 (dt, J = 31.7, 15.9 Hz, 2H), 6.85 (d, J = 21.9 Hz, 2H), 5.17 (s, 2H), 4.43 (s, 2H), 3.77 (s, 3H), 3.62 (dd, J = 16.2, 11.3 Hz, 3H), 3.26 (d, J = 22.6 Hz, 2H), 2.27 (d, J = 30.9 Hz, 2H), 1.83 (dd, J = 15.9, 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 158.8, 156.0, 136.5, 129.5, 129.1, 128.5, 128.3, 127.8, 127.7, 113.7, 67.0, 55.0, 51.3, 49.6, 49.3, 45.8, 44.9, 31.0, 23.1, 22.7; IR (neat): υ_{max} 2949, 1735, 1694, 1612, 1585, 1511, 1455, 1433, 1416, 1300, 1243, 1173, 1030, 736, 697 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{25}NO_5Na$ $[M+Na]^+$: 394.1630; found: 394.1626.

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Methyl 4-(((benzyloxy)carbonyl)(4-methoxybenzyl)amino)-2-formylbutanoate (5):

$TiCl_4$ (11.78 mL, 161.72 mmol) and Et_3N (18.75 mL, 134.77 mmol) were successively added dropwise to a stirred solution of a methyl ester **7** (20.0 g, 53.90 mmol) and methyl formate (9.90 mL, 161.72 mmol) in CH_2Cl_2 (250 mL) at 0 ^oC under nitrogen atmosphere, and the mixture was stirred at the same temperature for 1 h and at room temperature for 1 h. Water was added to the mixture, which was extracted twice with EtOAc. The combined organic phase was washed with brine, dried over with Na_2SO_4, and concentrated. The obtained crude oil was purified by column chromatography to give the *α*–formylated ester **5** (both aldehyde and enol mixture 6:4) as yellow oil (19.78 g, 92% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 11.36 (t, J = 12.8 Hz, 0.5H), 9.75 – 9.10 (m, 0.2H), 7.64 (s, 0.3H), 7.47 – 6.71 (m, 9H), 5.15 (d, J = 3.1 Hz, 2H), 4.53 – 4.33 (m, 2H), 3.82 – 3.52 (m, 6H), 3.25 (d, J = 6.3 Hz, 2H), 2.61 – 2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 172.3, 169.1, 161.9, 159.1, 156.6, 129.9, 129.8, 129.4, 128.9, 128.5, 128.0, 127.9, 114.0, 113.9, 101.6, 67.3, 67.2, 55.2, 52.5, 51.3, 50.3, 47.0, 46.2, 26.5, 25.8; IR (neat): υ_{max} 3020, 1684, 1613, 1512, 1442, 1215, 1120, 1035, 741, 668 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{25}NO_6Na$ $[M+Na]^+$: 422.1580; found: 422.1577.

Methyl 4-(((benzyloxy)carbonyl)(4-methoxybenzyl)amino)-2-(2-formyl-3-methoxyphenyl)butaneate (3):

A flame-dried round bottom flask equipped with a magnetic stir bar was charged with **5** (15.0 g, 38 mmol, 1.0 equiv) in acetonitrile (200 mL). Methoxy aryne precursor **4** (15.0 g, 46 mmol, 1.2 equiv) and cesium fluoride (14.0 g, 95 mmol, 2.5 equiv) were sequentially added to the flask at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 1 h at same temperature, completion of the reaction was monitored by TLC. The mixture was extracted with water (150 mL). The aqueous layer was back-extracted with ethyl acetate (3 x 100 mL). The organic layers were combined and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and the crude was purified on silica gel column chromatography (Hexane/EtOAc, 6:4) to give insertion product **3** as yellow oil (12 g, 62% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 10.57 (d, J = 12.2 Hz, 1H), 7.49 – 6.90 (m, 9H), 6.81 (d, J = 8.2 Hz, 3H), 5.15 (s, 2H), 4.69 (s, 1H), 4.47 (d, J = 14.8 Hz, 1H), 4.37 (d, J = 15.2 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.59 (d, J = 28.9 Hz, 3H), 3.24 (d, J = 19.5 Hz, 2H), 2.31 (s, 1H), 1.93 (d, J = 36.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 173.7, 163.3, 158.9, 156.5, 156.1, 141.3, 136.8, 135.0, 130.0, 129.9, 129.4, 128.8, 128.4, 127.8, 122.5, 121.0, 120.7, 113.8, 110.5, 67.1, 55.9, 55.2, 52.2, 49.8,

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49.5, 45.0, 44.3, 43.8, 31.3, 30.8; IR (neat): υ_{max} 2986, 1737, 1449, 1373, 1233, 1100, 1044, 930, 847, 781 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{31}NO_7Na$ $[M+Na]^+$: 528.1998; found: 528.1997.

Methyl 4-(((benzyloxy)carbonyl)(4-methoxybenzyl)amino)-2-(2-(formyloxy)-3-methoxyphenyl)butanoate (8):

The GABA inserted aryl aldehyde **3** (10.0 g, 20 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (125 mL) at 0 °C and then *m*-CPBA (~76%, 6.7 g, 30 mmol, 1.5 equiv) was added portion-wise under nitrogen atmosphere. The mixture was stirred for 5 h at room temperature and monitored by TLC. After disappearance of starting material, the reaction was quenched with sat. $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified on silica gel column chromatography (Hexane/EtOAc, 3:2) to give insertion product **8** as yellow oil (8.87 g, 86% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 23.1 Hz, 1H), 7.40 – 7.26 (m, 5H), 7.22 – 6.65 (m, 7H), 5.15 (s, 2H), 4.39 (dt, J = 23.8, 14.8 Hz, 2H), 3.84 (d, J = 21.6 Hz, 3H), 3.80 – 3.66 (m, 4H), 3.57 (d, J = 19.6 Hz, 3H), 3.17 (d, J = 6.0 Hz, 2H), 2.31 (s, 1H), 1.93 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 168.7, 158.9, 158.8, 156.5, 151.0, 137.0, 136.7, 134.6, 133.5, 131.9, 131.3, 130.2, 129.8, 129.6, 129.4, 128.8, 128.5, 128.2, 127.9, 127.9, 127.2, 120.1, 119.9, 113.9, 111.8, 111.3, 107.4, 77.3, 77.0, 76.8, 67.3, 56.0, 55.7, 55.4, 55.2, 52.2, 49.7, 44.9, 44.0, 42.4, 42.2, 30.2, 29.7; IR (neat): υ_{max} 3020, 2404, 2356, 1738, 1692, 1606, 1512, 1473, 1216, 1172, 1116, 912, 740, 669 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{32}NO_8$ $[M+H]^+$: 522.2128; found: 522.2107.

Benzyl (2-(7-methoxy-2-oxo-2,3-dihydrobenzofuran-3-yl)ethyl)(4-methoxybenzyl)carbamate (9):

To a solution of **8** (8.0 g, 15.35 mmol, 1.0 equiv) in 1,4-dioxane (60 mL) was added 2M NaOH solution (40 mL) at 0 °C and the resulting mixture was stirred at same temperature for 0.5 h. The reaction mixture was neutralized by the addition of 2N HCl and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to give a crude oil, which was used for the next step without any further purification. To a solution of crude oil in anhydrous toluene (100 mL) was added TsOH (0.26 g, 1.53 mmol, 0.1 equiv) at room temperature. The mixture was stirred at 90 °C for 5 h, quenched by the addition of saturated aqueous solution of $NaHCO_3$ at 0 °C, and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and the crude was purified on silica gel

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column chromatography (Hexane/EtOAc, 1:1) afforded **9** as a pale yellow oil (4.6 g, 65% yield (2 steps)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 5H), 7.23 – 6.86 (m, 4H), 6.86 – 6.51 (m, 3H), 5.21 – 5.11 (m, 2H), 4.53 (d, J = 15.2 Hz, 1H), 4.29 (d, J = 15.2 Hz, 1H), 3.93 – 3.87 (m, 3H), 3.81 – 3.75 (m, 3H), 3.70 (ddd, J = 46.5, 19.6, 6.5 Hz, 1H), 3.60 – 3.13 (m, 2H), 2.15 (d, J = 22.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 159.0, 156.3, 144.0, 141.9, 136.5, 129.5, 128.9, 128.5, 128.1, 127.9, 124.8, 116.2, 115.7, 114.0, 112.7, 67.4, 56.3, 55.3, 50.2, 49.9, 43.8, 42.9, 41.3, 29.1; IR (neat): υ_{max} 2985, 1805, 1737, 1618, 1455, 1372, 1234, 1112, 1044, 930, 846, 775 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{27}NO_6Na$ $[M+Na]^+$: 484.1736; found: 484.1727.

Benzyl (2-(7-methoxy-2-oxo-3-(3-oxobutyl)-2,3-dihydrobenzofuran-3-yl)ethyl)(4-methoxy-benzyl)carbamate (2):

To a stirred solution of **9** (4.0 g, 8.7 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (35 mL) at room temperature were added DIPEA (7.56 mL, 43.39 mmol, 5.0 equiv) followed by methyl vinyl ketone (1.07 mL, 13.1 mmol, 1.5 equiv) dropwise, the reaction mixture was stirred for 1 h at room temperature. After completion of the starting material, monitored by TLC, the reaction was quenched with water (2 mL), extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with 1N HCl (2 x 10 mL) and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and the residue was purified on silica gel column chromatography (Hexane/EtOAc, 1:1) to give product **2** as yellow oil (4.37 g, 95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 19.2 Hz, 5H), 6.99 (ddd, J = 47.1, 17.7, 10.0 Hz, 4H), 6.82 – 6.31 (m, 3H), 5.10 (q, J = 12.3 Hz, 2H), 4.39 (t, J = 17.0 Hz, 1H), 4.14 (d, J = 15.0 Hz, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.08 (s, 0.5H), 2.90 – 2.78 (m, 1.5H), 2.34 – 1.90 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 178.1, 159.1, 155.9, 144.1, 141.1, 136.5, 129.8, 129.7, 129.6, 129.4, 128.9, 128.5, 128.1, 127.9, 125.4, 115.2, 114.9, 114.0, 112.7, 56.2, 55.3, 50.2, 49.8, 42.9, 42.1, 38.0, 35.7, 35.0, 32.0, 29.9; IR (neat): υ_{max} 2923, 2850, 1799, 1697, 1620, 1503, 1455, 1424, 1363, 1286, 1223, 1174, 1133, 1030, 917, 876, 818, 737, 699, 629 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{33}NO_7Na$ $[M+Na]^+$: 554.2155; found: 554.2153.

Benzyl (2-(7-methoxy-2-oxo-3-(3-oxobutyl)-2,3-dihydrobenzofuran-3-yl)ethyl)carbamate (10):

To a suspension of **2** (4.0 g, 7.53 mmol) in CH_3CN : water (9:1, 40 mL) at room temperature was added portion-wise ceric ammonium nitrate (12.38 g, 22.59 mmol, 3.0 equiv), the resultant mixture was stirred for 8 h at room temperature. After consumption of starting material, the reaction was

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quenched by adding water (50 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and the crude was purified on silica gel column chromatography (Hexane/EtOAc, 1:1) to give product **10** as yellow oil (2.53 g, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.19 (m, 5H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.89 (t, *J* = 15.9 Hz, 1H), 6.84 – 6.54 (m, 1H), 5.00 (d, *J* = 11.8 Hz, 2H), 4.70 (d, *J* = 51.2 Hz, 1H), 3.92 (s, 3H), 3.12 – 2.77 (m, 2H), 2.35 – 1.93 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 206.6, 178.7, 156.0, 144.2, 141.2, 136.4, 129.8, 128.5, 128.1, 128.0, 125.5, 115.1, 112.9, 66.6, 56.2, 49.9, 38.0, 37.6, 37.2, 32.0, 29.9; IR (neat): υ_{max} 3341, 2019, 2928, 2853, 1802, 1713, 1604, 1512, 1455, 1257, 1170, 1034, 883, 844, 767, 701 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{25}NO_6Na$ $[M+Na]^+$: 434.1580; found: 434.1568.

Benzyl 7-methoxy-5-oxo-4a-(3-oxobutyl)-3,4,4a,5-tetrahydrobenzofuro[4,3-*cd*]azepine-2(1-*H*)-carboxylate (11):

To a solution of **10** (2.3 g, 5.59 mmol, 1.0 equiv) in 1,2-dichloroethane (30 mL) were added paraformaldehyde (0.83 g, 27.98 mmol, 5.0 equiv) and TFA (4.28 mL, 55.96 mmol, 10.0 equiv) at room temperature. The mixture was stirred at 60 °C for 12 h, quenched with saturated aqueous $NaHCO_3$ at 0 °C and extracted with CH_2Cl_2 (3 x 30 mL). The organics were combined and dried over Na_2SO_4. After filtration, the solvent was concentrated under reduced pressure and the crude was purified on silica gel column chromatography (Hexane/EtOAc, 3:2) which afforded **11** as a yellow oil (2.44 g, 95% yield) in 1:1 ratio of isomers; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.38 – 7.26 (m, 3.5H), 7.26 – 7.17 (m, 1.5H), 7.04 (d, *J* = 8.4 Hz, 0.5H), 6.82 (d, *J* = 8.0 Hz, 0.5H), 6.80 (d, *J* = 7.4 Hz, 0.5H), 6.72 (d, *J* = 8.4 Hz, 0.5H), 5.11 (d, *J* = 12.3 Hz, 0.5H), 5.01 (td, *J* = 12.4, 7.7 Hz, 1H), 4.97 – 4.89 (m, 0.5H), 4.80 (d, *J* = 15.3 Hz, 0.5H), 4.67 (d, *J* = 15.6 Hz, 0.5H), 4.43 (d, *J* = 14.8 Hz, 0.5H), 4.32 (d, *J* = 15.2 Hz, 0.5H), 4.23 (d, *J* = 15.6 Hz, 0.5H), 4.15 (d, *J* = 15.2 Hz, 0.5H), 3.93 (s, 1.5H), 3.92 (s, 1.5H), 3.55 (ddd, *J* = 26.8, 20.2, 7.5 Hz, 1H), 2.74 – 2.63 (m, 1H), 2.46 – 2.33 (m, 1H), 2.19 – 1.83 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 206.4, 178.3, 178.1, 155.3, 155.2, 143.4, 140.8, 140.8, 136.5, 129.5, 129.1, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 124.8, 124.3, 112.3, 112.0, 67.4, 67.3, 56.4, 56.3, 50.8, 50.3, 50.2, 45.6, 45.2, 37.7, 33.4, 32.4, 30.1, 27.8, 27.6; IR (neat): υ_{max} 3506, 3542, 2950, 1803, 1701, 1635, 1599, 1512, 1427, 1363, 1281, 1231, 1171, 1138, 1068, 1013, 920, 817, 738, 700 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{25}NO_6Na$ $[M+Na]^+$: 446.1580; found: 446.1573.

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Benzyl 7-methoxy-5-oxo-4a-(3-oxobutyl)-3,4,4a,5-tetrahydrobenzofuro[4,3-*cd*]azepine-2(1*H*)-carboxylate (12):

To a stirred solution of **11** (0.2 g, 0.47 mmol, 1.0 equiv) in anhydrous THF (10 mL) at -78 °C was added LDA (2.5M, 0.2 mL, 0.47 mmol, 1.0 equiv) under argon atmosphere and the mixture was stirred at the same temperature for 0.5 h. Then another portion of LDA (2.5M, 0.1 mL, 0.24 mmol, 0.5 equiv) was added and the reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched with 1N HCl, and extracted by EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (Hexane/EtOAc, 1:1) to afford compound **12** as a foamy solid (0.172 g, 86% yield) in 2:3 ratio of isomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 3.8H), 7.24 – 7.14 (m, 1.2H), 6.87 (d, J = 8.2 Hz, 0.4H), 6.71 (d, J = 8.2 Hz, 0.4H), 6.65 (d, J = 8.2 Hz, 0.6H), 6.58 (d, J = 8.2 Hz, 0.6H), 5.11 (dd, J = 19.2, 8.9 Hz, 0.4H), 4.99 – 4.85 (m, 1.4H), 4.76 (d, J = 15.8 Hz, 0.6H), 4.64 (t, J = 12.3 Hz, 0.6H), 4.44 (br.s, 1H) 4.37 (dd, J = 14.1, 10.6 Hz, 1H), 4.13 (dd, J = 30.7, 15.5 Hz, 1H), 3.82 (s, 1.2H), 3.72 (s, 1.8H), 3.39 (t, J = 13.7 Hz, 0.4H), 3.30 (t, J = 13.5 Hz, 0.6H), 3.04 (dd, J = 20.8, 17.2 Hz, 1H), 2.84 (dd, J = 17.2, 10.7 Hz, 1H), 2.54 – 2.40 (m, 1H), 2.39 – 2.29 (m, 1.4H), 2.25 (t, J = 8.3 Hz, 0.6H), 2.08 – 1.96 (m, 1H), 1.95 – 1.85 (m, 1H), 1.77 (dd, J = 14.4, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 206.9, 155.4, 155.3, 145.5, 145.2, 144.1, 136.6, 136.4, 130.7, 130.5, 128.8, 128.4, 128.4, 128.0, 127.8, 122.4, 121.5, 111.4, 111.0, 110.2, 109.7, 67.3, 67.1, 56.0, 55.8, 51.5, 51.4, 51.0, 46.9, 46.6, 45.8, 45.2, 35.1, 34.0, 33.3, 30.4; IR (neat): υ_{max} 3329, 3020, 2352, 1805, 1689, 1510, 1432, 1218, 1163, 1073, 914, 746, 667 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{25}NO_6Na$ $[M+Na]^+$: 446.1580; found: 446.1578.

(4a*S*,8a*R*)-3-Methoxy-11-methyl-4a,5,7,8,9,10,11,12-octahydro-6*H*-benzo[2,3]benzofuro-[4,3-*cd*]azepin-6-one (14):

To a stirred solution of **12** (2.0 g, 4.72 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added Et_3SiH (7.53 mL, 47.28 mmol, 10 equiv). After stirring at 0 °C for 10 min, $BF_3{\cdot}Et_2O$ (3.48 mL, 28.368 mmol, 6 equiv) was added to it. The reaction was kept at 0 °C for 0.5 h and then allowed to reach room temperature and stirred for 3 h. The reaction was quenched with saturated Na_2CO_3 and extracted by EtOAc (3 x 25 mL). The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue **13** was used for the next step without any further purification. To a stirred solution of **13**

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(0.88 g, 1.0 equiv) in $CHCl_3$ (20 mL) was added formaldehyde (37% in water, 5.76 mL, 20 equiv) and formic acid (12.8 mL, 100 equiv). Then the reaction was heated to 60 °C and stirred overnight. The reaction was quenched with saturated Na_2CO_3 and extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was dissolved in MeOH/H_2O (6/1, 8 mL) and K_2CO_3 (0.92 g, 2 equiv) was added to it. The mixture was stirred at room temperature for 2 h, and solvent was evaporated residue was dissolved in EtOAc. The organic phase was combined, washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue (1.04 g, 3.04 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL). To the solution at 0 °C were added DMSO (1.28 mL, 18.24 mmol, 6 equiv), DIPEA (5.28 mL, 30.44 mmol, 10 equiv) and SO_3.Py (1.44 g, 9.12 mmol 3 equiv) respectively, the reaction mixture stirred for 2 h at 0 °C. After completion of starting material monitored by TLC, reaction was quenched with adding excess water, and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts was dried over Na_2SO_4 and concentrated to give a crude, which on column chromatography ($CHCl_3$/CH_3OH, 9:1) afforded **14** as a white solid (0.88 g, 65% yield (3 steps)); mp 130–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (d, J = 0.9 Hz, 2H), 4.82 (t, J = 2.9 Hz, 1H), 4.52 (d, J = 14.9 Hz, 1H), 4.05 (d, J = 14.9 Hz, 1H), 3.85 (s, 3H), 3.53 (ddd, J = 16.8, 8.3, 7.9 Hz, 2H), 3.04 (dd, J = 17.6, 3.3 Hz, 1H), 2.70 (dd, J = 17.6, 2.7 Hz, 1H), 2.59 (s, 3H), 2.38 (d, J = 2.8 Hz, 1H), 2.37 – 2.28 (m, 2H), 2.07 – 2.00 (m, 1H), 1.99 – 1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 147.3, 145.4, 131.1, 124.2, 120.5, 112.0, 88.1, 57.8, 56.0, 52.9, 47.0, 39.9, 38.2, 35.2, 33.5, 28.9; HRMS (ESI) calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1660; found: 288.1598.

(4a*S*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-one (or) Narwedine (15):

To a solution of compound **14** (1.0 g, 3.48 mmol, 1.0 equiv) in anhydrous THF (10 mL) was added to LDA (2.5M, 1.35 mL, 17.4 mmol, 5.0 equiv) with stirring at -78 °C under an argon atmosphere. After 0.5 h, a solution of diphenyl disulfide (3.7 g, 17.4 mmol) in THF (15 mL) was added at -78 °C, and then the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with H_2O (10 mL), and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. To the resultant crude (mixture of α- and β-phenylsulfide) in CH_2Cl_2 (15 mL) was added (±)-camphor-10-sulfonic acid (550 mg, 2.25 mmol), and the mixture was stirred at room temperature for 10 min

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under an argon atmosphere. A solution of *m*-CPBA (65%, 590 mg, 2.25 mmol) in CH_2Cl_2 (15 mL) was added at -78 °C, and the mixture was stirred at -40 °C for 0.5 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (10 mL). The reaction mixture was poured to saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The mixture of the crude residue and $NaHCO_3$ (500 mg) in toluene (50 mL) was stirred at 110 °C for 2 h under an argon atmosphere. Saturated aqueous $NaHCO_3$ solution (10 mL) and H_2O (50 mL) were added, and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel ($CHCl_3/CH_3OH$, 9:1) to afford compound **15** as a pale yellow solid (447 mg, 45% yield); mp 184–186 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (dd, J = 10.4, 1.8 Hz, 1H), 6.68 (q, J = 8.2 Hz, 2H), 6.04 (d, J = 10.4 Hz, 1H), 4.73 (dt, J = 4.2, 2.3 Hz, 1H), 4.14 (d, J = 15.3 Hz, 1H), 3.84 (s, 3H), 3.78 (d, J = 15.4 Hz, 1H), 3.29 (t, J = 13.1 Hz, 1H), 3.15 (dd, J = 17.8, 2.3 Hz, 2H), 2.75 (dd, J = 17.8, 3.8 Hz, 1H), 2.46 (s, 3H), 2.27 (td, J = 13.6, 3.2 Hz, 1H), 1.88 (d, J = 13.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 146.9, 144.1, 130.4, 128.5, 127.1, 122.1, 111.9, 87.9, 60.3, 56.0, 53.9, 48.8, 42.0, 37.2, 32.9; HRMS (ESI) calcd for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1443; found: 286.1437.

(±)-Galanthamine (1):

To a solution of the enone (narwedine) **15** (500 mg, 1.75 mmol, 1.0 equiv) in anhydrous THF (10 mL) was added LS-Selectride (1.0 M in THF, 2.11 mL, 2.10 mmol, 1.25 equiv) at -78 °C, the resulting mixture was stirred at -78 °C to room temperature for 2 h, concentrated to give a solid, and which was purified by silica gel flash column chromatography ($CHCl_3/CH_3OH$, 9:1) to obtain compound **1** as a colorless solid (480 mg, 96% yield); mp 124–126 ºC; (The ^{1}H and ^{13}C NMR spectra were in good agreement with literature); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (d, J = 8.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.07 (dd, J = 10.3, 1.1 Hz, 1H), 6.00 (ddd, J = 10.2, 4.9, 1.0 Hz, 1H), 4.61 (s, 1H), 4.19 – 4.06 (m, 2H), 3.84 (s, 3H), 3.68 (d, J = 14.6 Hz, 1H), 3.33 – 3.21 (m, 1H), 3.05 (d, J = 14.4 Hz, 1H), 2.69 (ddt, J = 15.7, 3.1, 1.4 Hz, 1H), 2.40 (s, 3H), 2.13 – 1.99 (m, 2H), 1.71 (br s, 1H), 1.58 (ddd, J = 13.7, 3.9, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 144.0, 133.0, 129.2, 127.5, 126.8, 122.0, 111.1, 88.7, 62.0, 60.6, 55.9, 53.8, 48.2, 42.1, 33.8, 29.9; HRMS (ESI) calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1600; found: 288.1591.

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