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An Eleven-step Synthesis of Galanthamine from Commercially Available Materials

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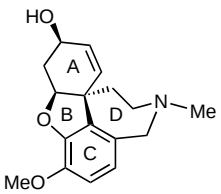
Keywords: galanthamine, Heck cyclisation, Mitsunobu reaction, narwedine, reductive amination

Narwedine, an immediate precursor to the therapeutically valuable alkaloid (–)-galanthamine, has been synthesised by engaging an iodinated isovanillin derivative in an intermolecular Mitsunobu reaction with a 2-cyclohexen-1-ol derivative. The resulting aryl ether participated in an exceptionally efficient intramolecular Heck reaction to give, after hydrolysis of the primary cyclisation product, a tetracyclic lactol. This last compound is an advanced intermediate associated with the Magnus synthesis of narwedine and could be elaborated to narwedine itself under reductive amination conditions. As a result, an eleven-step synthesis of galanthamine has been established.

Introduction

(-)-Galanthamine (**1**, a.k.a. galantamine) is a key alkaloid produced by a number of plants including the common snowdrop (*Galanthus nivalis*), the related species *Galanthus woronowii* and the red spider lily (*Lycoris radiate*).[1] In some instances it co-occurs with normally trace amounts of (-)-narwedine (**2**), the *N*-demethyl analogue of which is the likely biogenetic precursor (to **1**).[2] Originally galanthamine was used as a treatment for certain paralytic and neuropathic conditions.[1] However, the discovery that it is an orally available and reversible inhibitor of acetylcholine esterase (AChE) capable of crossing the blood/brain barrier has led to its use in the symptomatic treatment of mild to moderate forms of Alzheimer's Disease (AD),[1,3] the leading cause of dementia.[4] Given the projections for the increase in the incidence of AD among ageing populations in more developed countries, the demand for reliable supplies of galanthamine is almost certain to increase.[5] At the present time it appears that the required quantities of compound **1** are obtained from a combination of cultivation (and extraction) of the producing plants[6] and by total synthesis.[7] While the precise contributions that each of these make to the total supply chain remains unclear, the continuing focus on developing more productive cultivars and more effective growing methods[6] suggest the synthetic approach is the less significant one.



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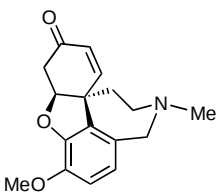

2

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Figure 1: The structures of (-)-galanthamine (1) and (-)-narwedine (2).

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This situation is a reflection, to some extent at least, of the challenges that remain in assembling the tetracyclic framework of galanthamine, especially its associated quaternary carbon center. The original synthesis of the alkaloid, reported by Barton and Kirby in 1962,[8] was a biomimetic one involving a low-yielding, intramolecular oxidative phenolic coupling leading to racemic narwedine [(±)-(2)] that can be diastereoselectively reduced to the congener 1 under a variety of conditions. A significant development in the area was the discovery that racemic narwedine can, through a fractional crystallisation process coupled with reversible E1cB/hetero-Michael addition reactions, be converted, in its entirety, into either of its constituent enantiomers using "seeding" quantities of either (+)- or (-)-galanthamine.[9] A modified version of the Barton/Kirby process, when linked with this dynamic kinetic resolution process, allowed Fröhlich and Jordis to develop a pilot-plant scale synthesis of (-)-narwedine. This now seems to be part of the galanthamine supply chain.[7] In 2009 Magnus and co-workers reported a seven-step synthesis of racemic narwedine,[10] perhaps the shortest/most efficient route to galanthamine described thus far. The key step involved an intramolecular alkylation of a phenol derivative. In 2000 Trost and Toste exploited an intramolecular Heck reaction for assembling the ABC-ring system and the associated quaternary carbon centre of galanthamine.[11] This work inspired a number of related approaches.[12] Other ingenious ones have also emerged in the intervening period.[13,14]

As part of our ongoing interest in developing new routes to galanthamine[13b] we have described two total syntheses to date, one involving a Pd-catalysed intramolecular Alder-ene reaction followed by a Diels-Alder cycloaddition (the second step serving to effect the *de novo* assembly of the aromatic A-ring)[13a] and the other being a chemoenzymatic approach.[15] Recently, and as part of a continuing program to identify new AChE inhibitors,[16] we reported[17] the first synthesis of the sesquineolignan simonsol C (3), a compound that bears a strong structural resemblance to narwedine. Accordingly, we sought to apply the key steps used in the assembly of the former compound, namely an intermolecular Mitsunobu reaction followed by an intramolecular Heck reaction, to a synthesis of the racemic modification of narwedine (2).[18] The successful outcome of such work is detailed below.

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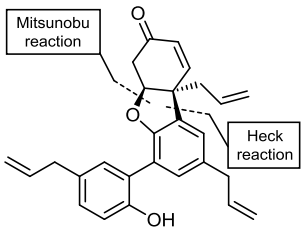

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Figure 2: The structure of simonsol C (**3**) and the two key bond-forming events used in its synthesis

Results and Discussion

In our first route to racemic narwedine (Scheme 1), the previously reported[17] allylic alcohol **4** (available in four steps from commercially available cyclohexane-1,4-dione mono-ethylene ketal) was engaged in an intramolecular Mitsunobu reaction[19] with the readily available iodinated derivative, **5**,[20] of isovanillin with the latter coupling partner serving as the nucleophile.[21] The ether **6** (73%) thus formed was subjected to an intramolecular Heck reaction under the indicated conditions[22] and thus affording the tricyclic sulfonamide **7** in essentially quantitative yield. Successive treatment of the last compound with sodium naphthalenide (to cleave the tosyl group) then a solution of sodium triacetoxyborohydride in moist acetic acid (to reduce the imine resulting from the intramolecular Schiff base condensation reaction and to hydrolyse the ketal residue) gave a rather complex mixture from which (±)-narwedine [(±)-**2**] could be isolated albeit in just 30% yield. This disappointing outcome is probably due to complications arising from premature reduction of the aldehyde residue within the substrate by $NaC_{10}H_8$. Nevertheless, the racemic narwedine generated by this means was identical, in all respects, with an authentic sample of compound **2** prepared by our earlier route.[13a]

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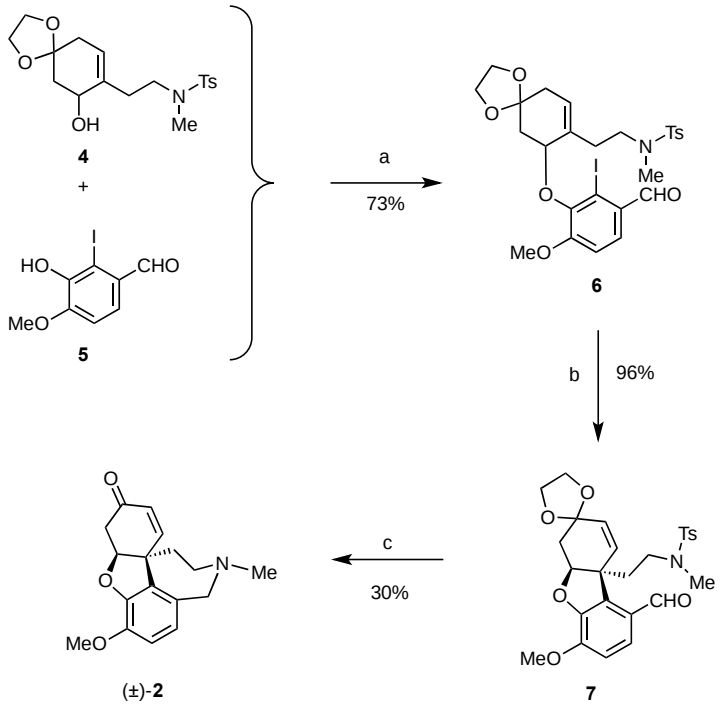

Scheme 1. A new route to (±)-narwedine [(±)-**2**]. Reagents and conditions (a) Bu_3P, TMAD, THF, 0 to 22 °C, 16 h; (b) $Pd(OAc)_2$, dppp, Ag_2CO_3, toluene, 112 °C, 3 h; (c) $NaC_{10}H_8$, THF, −78 °C, 0.2 h then AcOH, $NaBH(OAc)_3$, 18 °C, 4 h. TMAD = *N*,*N*,*N*',*N*'-tetramethylazodicarboxamide; dppp = 1,3-bis(diphenylphosphino)propane.

In an effort to establish an improved procedure for closing the D-ring of narwedine the reaction sequence shown in Scheme 2 was pursued. Specifically, the previously reported[17] congener **8** of compound **4** was reacted with phenol **5** under Mitsunobu conditions and the ether **9** (76%) so formed engaged in an intramolecular Heck reaction to afford the benzofuran **10** in 90% yield. Subjection of this last compound to reductive amination conditions using methylamine and sodium triacetoxyborohydride in acetic acid/dichloromethane then gave the 2° -amine **11** in 57% yield. This modest yield, the rather complex mixture of products arising from the various attempts to carry compound **11** forward to narwedine, and the outcomes of the studies presented immediately below prompted the abandonment of this approach. Part of the difficulty associated with finishing this approach most likely arises from orchestrating the required sequence of acetal and ketal cleavage reactions. Thus, the latter functionality reacts faster than the former[17] and so introducing the unwanted possibilities of both intra- and inter-molecular reactions between a 2-cyclohexen-1-one residue and a pendant 2° -amine.

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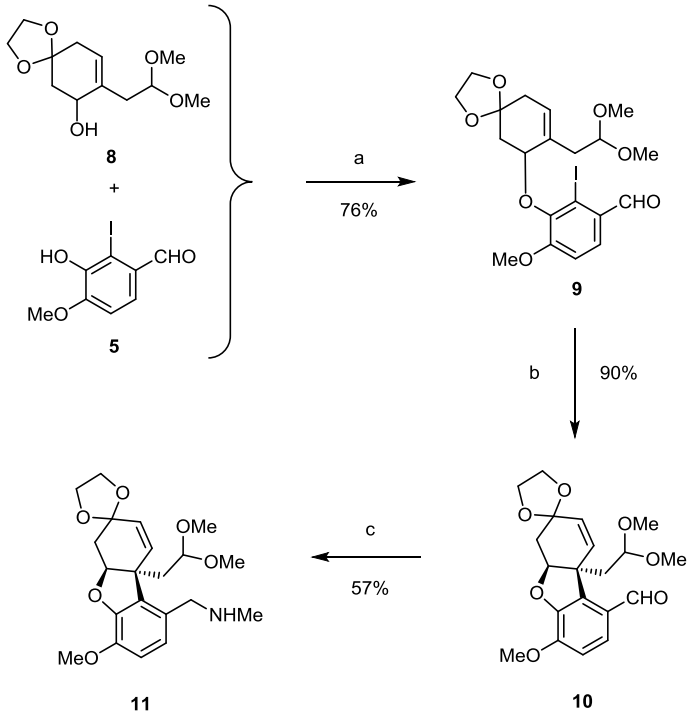

Scheme 2. Attempts to establish an improved synthesis of the D-ring. Reagents and conditions (a) Bu_3P, DEAD, THF, 0 to 22 °C, 4 h; (b) $Pd(OAc)_2$, dppp, Ag_2CO_3, toluene, 112 °C, 4 h; (c) H_2NMe, AcOH, $NaBH(OAc)_3$, DCM, 22 °C, 16 h. DEAD = diethyl azodicarboxylate.

The ultimately more effective route to racemic narwedine is shown in Scheme 3. This involved the one-pot and acid-catalysed hydrolysis of both the acetal and ketal residues within the Heck cyclisation product **10** using 1 M aqueous HCl in refluxing THF and thereby affording lactol **12** in 86% yield that was found to exist largely in one anomeric form (>10:1 mixture). This compound almost certainly arises through the initially produced hemiacetal adding in an intramolecular hetero-Michael addition reaction to the 2-cyclohexen-1-one revealed by hydrolysis of the ketal moiety. It is the key intermediate associated with the Magnus group's synthesis of (±)-narwedine.[10] In seeking to effect the conversion **12** → **2** we chose to build upon the somewhat limited amount of experimental detail provided by this group[10] and ultimately found that sequential treatment of the former compound with the hydrochloride salt of methylamine in the presence of sodium cyanoborohyride and acetic acid gave a boron complex of narwedine that could be cleaved using methanesulfonic acid in refluxing 1,4-dioxane. By such means compound **2** was obtained in 48% yield over the two operations involved. Once again, the spectral data acquired on this product matched those derived from an authentic sample. In addition, the material produced by the route described here was reduced with L-selectride[9,23] and thus providing (±)-galanthamine [(±)-**1**] in 83% yield. This material was identical, in all respects, with an authentic sample.[15]

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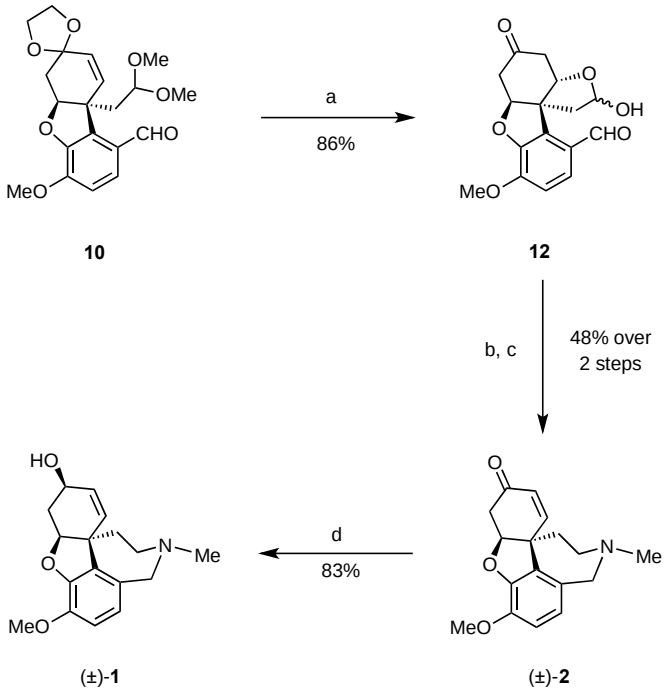

Scheme 3. A synthesis of (±)-narwedine [(±)-**2**] *via* the Magnus lactol **12**. Reagents and conditions (a) 1 M aq. HCl, THF, 60 ° C, 2 h; (b) H_3NMeCl, Et_3N, AcOH, $NaBH_3CN$, 1,4-dioxane, 22 ° C, 30 h; (c) 20% v/v aq. $MeSO_3H$, 1,4-dioxane, 101 ° C, 5 h; (d) L-selectride, THF, -78 ° C, 3 h.

Conclusion

When the five steps required to obtained compound **8** from commercially available cyclohexane-1,4-dione mono-ethylene ketal are taken into account,[17] the reaction sequence described here and leading to (±)-narwedine is ten steps in length. This compares with the seven involved in the Magnus synthesis[10] that continues to set the benchmark for efficiency in this challenging area. That said, the capacities for refinement of our approach as well as the opportunities for the generation of novel and biologically active analogues of galanthamine are areas of research that continue in our laboratories. Establishing a shorter synthesis of compound **8** is clear a priority. The present work also serves to emphasize the utility of combining the products of the intermolecular Mitsunobu reaction of 2-halogenophenols and allylic alcohols with the Heck cyclization reaction for the rapid assembly of benzofurans.[24] Efforts to extend such processes in various ways represent an ongoing focus and the results of such studies will be reported in due course.

Experimental Section

General Experimental Procedures: Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling

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constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^1H and ^{13}C NMR spectra, respectively. Infrared spectra (□$_{max}$) were recorded on a FTIR Spectrometer. Samples were analysed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on the material isolated from the indicated chromatographic fractions using an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al*.[25] with silica gel 60 (40–63 □m) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs *et al*.[26] Where necessary, reactions were performed under an nitrogen atmosphere.

(±)-*N*-(2-(9-(3-Formyl-2-iodo-6-methoxyphenoxy)-1,4-dioxaspiro[4.5]dec-7-en-8-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide (6): A magnetically stirred solution of alcohol **4**[17] (515 mg, 1.40 mmol), phenol **5**[20] (545 mg, 1.96 mmol) and tri-*n*-butylphosphine (0.50 mL, 1.96 mmol) in dry THF (25 mL) was cooled to 0 °C then treated with TMAD[19] (341 mg, 1.96 mmol). The resulting yellow solution was maintained at this temperature for 0.5 h then warmed to and maintained at room temperature for 18 h. The resulting suspension was treated with silica and the mixture thus obtained concentrated under reduced pressure. The free-flowing powder thus obtained was subjected to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 1:1 v/v hexane/ethyl acetate), compound **6** (641 mg, 73%) as a cream-coloured foam. ^1H NMR (400 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.73-7.63 (complex m, 3H), 7.26 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.8 Hz, 1H), 5.57 (m, 1H), 5.31 (m, 1H), 3.99-3.77 (complex m, 7H), 3.32 (m, 2H), 2.77 (s, 3H), 2.59 (m, 2H), 2.43 (m, 1H), 2.40 (s, 3H), 2.20 (m, 2H), 1.86 (ddd, J = 12.0, 5.9 and 2.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 157.1, 145.6, 143.0, 134.9(4), 134.8(9), 129.5, 129.2, 127.3, 126.7, 123.3, 111.8, 108.1, 101.5, 78.7, 64.3, 64.2, 56.1, 49.5, 37.8, 35.9, 34.9, 31.0, 21.4 ppm. IR: ν_{max} = 2978, 2937, 2880, 1682, 1573, 1476, 1336, 1273, 1246, 1159, 1019, 941, 729 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 650 (100) [$(M+Na)^+$]. HRMS (ESI, +ve): calcd for $C_{26}H_{30}INNaO_7S$ [$(M+Na)^+$] 650.0685; found 650.0685.

***rac*-*N*-(2-((4a*S*,9b*S*)-9-Formyl-6-methoxy-4,4a-dihydro-9b*H*spiro[dibenzo[*b*,*d*]furan-3,2'-[1,3]dioxolane]-9b-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide (7)**: A magnetically stirred and thoroughly degassed solution of compound **6** (240 mg, 0.382 mmol) in dry toluene (5 mL) maintained under a nitrogen atmosphere was treated, sequentially, with $Pd(OAc)_2$ (8.8 mg, 10 mol%), dppp (32.5 mg, 20 mol%) and Ag_2CO_3 (317 mg, 1.15 mmol). The resulting heterogeneous mixture was heated under reflux for 3 h then cooled, filtered through a pad of

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diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v DCM/diethyl ether elution) to afford, after concentration of the appropriate fractions (R_f = 0.8 in 8:2 v/v DCM/diethyl ether), compound **7** (184 mg, near quantitative yield) as a light-yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.4 Hz, 1H), 7.28 (m, 2H), 6.90 (d, J = 8.4 Hz, 1H), 6.42 (d, J = 10.3 Hz, 1H), 5.70 (d, J = 10.3 Hz, 1H), 4.95 (m, 1H), 4.03-3.90 (complex m, 7H), 3.05 (m, 1H), 2.83 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 2.37 (m, 1H), 2.23 (m, 2H), 2.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 150.2, 148.1, 143.1, 134.7, 131.6, 131.3, 130.1, 129.5, 128.0, 127.2, 126.5, 110.6, 103.2, 84.4, 64.8, 64.4, 56.0, 49.6, 46.4, 35.3, 34.7, 34.5, 21.3. IR: ν_{max} = 2959, 2932, 2885, 1686, 1607, 1571, 1506, 1436, 1337, 1284, 1159, 1015, 912, 729 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 522 (100) [$(M+Na)^+$]. HRMS (ESI, +ve): calcd for $C_{26}H_{29}NNaO_7S$ [$(M+Na)^+$] 522.1562; found 522.1561.

***rac*-(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 [(±)-narwedine, 2]**: A magnetically stirred solution of compound **7** (300 mg, 0.60 mmol) in dry THF (10 mL) was cooled to −78 °C then treated, dropwise, with sodium naphthalenide [prepared from napthalene (256 mg, 2.0 mmol) and sodium metal (48 mg, 2.0 mmol) in dry THF (10 mL)] until the dark-green colour of the reducing agent remained. The resulting solution was treated with acetic acid (2 mL) (CAUTION) then warmed to 0 °C and treated with sodium triacetoxyborohydride (200 mg, 0.90 mmol). The solution thus obtained was maintained at 22 °C for 4 h then treated with HCl (5 mL of a 1 M aqueous solution), maintained at 22 °C for 1 h then treated with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with $CHCl_3$ (3 x 20 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica gel; 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (R_f = 0.3), (±)-narwedine (**2**) **2**[13a, 23b] (50 mg, 29%) as an off-white powder, m.p. = 185–187 °C (lit.[23b] m.p. = 186-189 °C). ^{1}H NMR (800 MHz, $CDCl_3$): δ 6.95 (d, J = 10.4 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 6.04 (dd, J = 10.4 and 1.0 Hz, 1H), 4.73 (m, 1H), 4.11 (d, J = 15.5 Hz, 1H), 3.84 (s, 3H), 3.75 (d, J =15.5 Hz, 1H), 3.25 (t, J = 13.7 Hz, 1H), 3.16 (m, 2H), 2.75 (dd, J = 17.9 and 3.5 Hz, 1H), 2.44 (s, 3H), 2.28 (td, J = 13.7 and 3.5 Hz, 1H), 1.86 (d, J = 13.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 147.2, 144.5, 144.2, 130.7, 129.5, 127.3, 122.2, 112.1, 88.1, 60.8, 56.2, 54.3, 49.1, 42.5, 37.5, 33.4 ppm. IR: ν_{max} = 2926, 2848, 1683, 1622, 1507, 1437, 1280, 1223, 1166, 1145, 1050, 1031, 1008, 802, 771 cm^{-1}. MS (EI): *m/z* (%) = 285 (100) [$M^{+\cdot}$], 284 (98), 242 (47), 174 (42), 84 (68), 58 (82). HRMS (EI): calcd for $C_{17}H_{19}NO_3$ [$M^{+\cdot}$] 285.1365; found 285.1363.

(±)3-((8-(2,2-Dimethoxyethyl)-1,4-dioxaspiro[4.5]dec-8-en-7-yl)oxy)-2-iodo-4-methoxy-benzaldehyde (9): A magnetically stirred solution of compound **8**[17] (530 mg, 2.16 mmol), compound **5** (840 mg, 3.05 mmol) and tri-*n*-butylphosphine (0.88 mL, 3.05 mmol) in dry THF (40 mL) was cooled to 0 °C then treated with DEAD (0.48 mL, 3.05 mmol). The resulting yellow solution was maintained at 0 °C for 0.25 h then warmed and maintained at room temperature for 4 h before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v hexane/ethyl acetate elution) and after concentration of the appropriate fractions (R_f = 0.3 in 1:1 v/v hexane/ethyl acetate) compound **9** (830 mg, 76%) was obtained as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 5.64 (m, 1H), 5.33 (m, 1H), 4.78 (t, J = 5.8 Hz, 1H), 4.05–3.76 (complex m, 4H), 3.94 (s,

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3H), 3.38 (s, 3H), 3.35 (s, 3H), 2.69 (m, 2H), 2.48 (m, 1H), 2.26 (m, 2H), 1.89 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 157.1, 146.0, 133.5, 129.3, 126.6, 123.8, 111.8, 108.3, 103.6, 101.8, 79.2, 64.4, 64.2, 56.1, 53.5, 52.8, 38.0, 36.0(4), 36.0(1) ppm. IR: ν_{max} = 2937, 2887, 2829, 1682, 1573, 1475, 1439, 1272, 1245, 1017, 811, 729 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 527 (100) [(M+Na)$^+$]. HRMS (ESI, +ve): calcd for $C_{20}H_{25}INaO_7$ [(M+Na)$^+$] 527.0543; found 527.0554.

***rac*-(4a*S*,9b*S*)-9b-(2,2-Dimethoxyethyl)-6-methoxy-4a,9b-dihydro-4*H*-spiro[dibenzo[*b*,*d*]-furan-3,2'-[1,3]dioxolane]-9-carbaldehyde (10)**: A magnetically stirred and thoroughly degassed solution of compound **9** (1.50 g, 2.97 mmol) in dry toluene (60 mL) maintained under a nitrogen atmosphere was treated, sequentially, with $Pd(OAc)_2$ (68 mg, 10 mol%), dppp (251 mg, 20 mol%) and Ag_2CO_3 (2.40 g, 8.9 mmol). The resulting heterogeneous mixture was heated at reflux for 4 h then cooled, filtered through a pad of diatomaceous earth and the filtrate evaporated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v DCM/diethyl ether elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 9:1 v/v DCM/diethyl ether), compound **10** (1.00 g, 90%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.52 (d, *J* = 10.3 Hz, 1H), 5.72 (d, *J* = 10.3 Hz, 1H), 5.23 (m, 1H), 4.32 (t, *J* = 5.2 Hz, 1H), 3.95 (m, 7H), 3.23 (s, 3H), 3.22 (s, 3H), 2.37–2.16 (complex m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 150.2, 148.3, 132.1, 131.5, 130.6, 127.7, 126.7, 110.4, 103.4, 102.7, 85.0, 64.9, 64.4, 56.0, 53.1, 53.0, 48.9, 39.8, 35.0 ppm. IR: ν_{max} = 2934, 2888, 2836, 2730, 1686, 1607, 1570, 1283, 1117, 1045, 1013 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 399 (100) [(M+Na)$^+$]. HRMS (ESI, +ve): calcd for $C_{20}H_{24}NaO_7$ [(M+Na)$^+$] 399.1420; found 399.1422.

***rac*-1-((4a*S*,9b*S*)-9b-(2,2-Dimethoxyethyl)-6-methoxy-4a,9b-dihydro-4*H*spiro[dibenzo-[*b*,*d*]furan-3,2'-[1,3]dioxolan]-9-yl)-*N*-methylmethanamine (11)**: A magnetically stirred solution of compound **10** (100 mg, 0.265 mmol), methylamine (0.2 mL of a 2 M solution in THF, 0.4 mmol) and AcOH (0.1 mL) in dry DCM (2 mL) was treated with sodium triacetoxyborohydride (85 mg, 0.4 mmol). The resulting mixture was maintained at room temperature for 16 h then treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with DCM (3 x 5 mL). The combined organic phases were washed with brine (1 x 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica gel; 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (R_f = 0.2), compound **11** (60 mg, 57%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.19 (d, *J* = 10.2 Hz, 1H), 5.75 (d, *J* = 10.2 Hz, 1H), 5.07 (m, 1H), 4.37 (t, *J* = 5.0 Hz, 1H), 4.31 (broad s, 1H), 3.96 (m, 4H), 3.84 (s, 3H), 3.77 (s, 2H), 3.24 (s, 3H), 3.21 (s, 3H), 2.46 (s, 3H), 2.24–2.03 (complex m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 144.7, 132.2, 130.3, 128.2, 126.8, 122.5, 111.5, 104.1, 102.0, 83.8, 64.7, 64.5, 55.8, 52.7, 52.6, 51.6, 49.3, 41.3, 35.3, 35.1 ppm. IR: ν_{max} = 2954, 2934, 2891, 2835, 2789, 1621, 1581, 1506, 1428, 1277, 1203, 1116, 1046, 1014, 966, 948 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 392 (100) [(M+H)$^+$]. HRMS (ESI, +ve): calcd for $C_{21}H_{30}NO_6$ [(M+H)$^+$] 392.2073; found 392.2075.

Compound 12: A magnetically stirred solution of compound **10** (360 mg, 0.96 mmol) in THF (20 mL) was treated with HCl (5 mL of a 1 M aqueous solution) then heated at reflux for 2 h. The resulting mixture was cooled to room temperature then treated with $NaHCO_3$ (20 mL of a saturated aqueous solution) and extracted with EtOAc (4 x 15 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na_2SO_4), filtered,

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and concentrated under reduced pressure. The ensuing off-white powder was subjected to flash chromatography (silica gel; 2:1 v/v hexane/EtOAc) to give, after concentration of the appropriate fractions (R_f = 0.3), compound **12**[10] (250 mg, 86%) as a >10:1 mixture of anomers and a white powder, m.p. = 188−192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (major anomer) 9.81 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.17 (d, J = 11.4 Hz, 1H), 5.64 (m, 1H), 4.79 (t, J = 3.1 Hz, 1H), 4.57 (t, J = 2.9 Hz, 1H), 3.99 (s, 3H), 3.08–2.98 (complex m, 2H), 2.84 (dd, J = 18.2 and 2.9 Hz, 1H), 2.75 (dd, J = 18.2 and 3.5 Hz, 1H), 2.34–2.20 (complex m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major anomer) 204.6, 192.4, 150.5, 149.6, 133.5, 129.7, 125.9, 111.3, 98.3, 90.1, 77.5, 56.3, 53.9, 46.9, 39.1, 38.2 ppm. IR: ν_{max} = 3444, 2945, 2916, 2846, 1720, 1681, 1608, 1572, 1437, 1292, 1240, 1203, 1049 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 327 (100) [$(M+Na)^+$]. HRMS (ESI, +ve): calcd for $C_{16}H_{16}NaO_6$ [$(M+Na)^+$] 327.0845; found 327.0844.

***rac*-(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 [(±)-narwedine, (±)-2]**: A magnetically stirred solution of compound **12** (110 mg, 0.36 mmol) and freshly recrystallised methylamine hydrochloride (35 mg, 0.51 mmol) in dry 1,4-dioxane (6 mL) was treated with and triethylamine (0.1 mL, 0.7 mmol) then the vessel was sealed and maintained at room temperature for 30 h. The resulting suspension was then treated with acetic acid (0.5 mL, 8.7 mmol) and sodium cyanoborohydride (42 mg, 0.67 mmol) and maintained at room temperature for a further 24 h. The resulting suspension was then treated with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with $CHCl_3$ (4 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing residue was immediately suspended in 1,4-dioxane (5 mL) then treated with $MeSO_3H$ (0.5 mL of a 20% aqueous solution) and the resulting mixture heated at reflux for 4 h then cooled to room temperature and treated with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with $CHCl_3$ (4 x 15 mL). The combined organic phases were washed with brine (1 x 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica gel; 9:1 v/v DCM:MeOH) to give, after concentration of the appropriate fractions (R_f = 0.3), compound (±)-**2**[13a, 23b] (49 mg, 48%) as an off-white powder. This material was identical, in all respects, with that obtained by the route detailed above.

***rac*-(4a*S*,6*R*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzo-furo[4,3-*cd*]azepin-6-ol [(±)-galanthamine, (±)-1]**:A magnetically stirred solution of (±)-narwedine [(±)-**2**] (12.0 mg, 0.042 mmol) in anhydrous THF (2 mL) was cooled to –78 °C and then treated with L-selectride (0.13 mL of a 1 M solution in THF, 0.13 mmol). The resulting mixture was maintained at –78 °C for 3 h and then treated with water (1 mL) and NaOH (1 mL of a 3 M aqueous solution) before being extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil subjected to flash chromatography (silica gel, 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (R_f = 0.3), (±)-galanthamine [(±)-**1**][15] (10 mg, 83%) as a light-brown, waxy solid. ^{1}H NMR (800 MHz, $CDCl_3$): δ 6.66 (d, J = 8.1 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.06 (ddd, J = 10.3, 1.4 and 0.7 Hz, 1H), 6.01 (ddd, J = 10.3, 5.1 and 1.4 Hz, 1H), 4.61 (m, 1H), 4.14 (m, 1H), 4.10 (d, J = 15.4 Hz, 1H), 3.83 (s, 3H), 3.70 (dd, J = 15.4 and 0.7 Hz, 1H), 3.28 (t, J = 13.5 Hz, 1H), 3.06 (d, J = 14.3 Hz, 1H), 2.69 (ddt, J = 15.7, 3.3 and 1.4 Hz, 1H), 2.41 (s, 3H), 2.09 (td, J = 13.5 and 3.3 Hz, 1H), 2.01 (ddd, J = 15.7, 5.1 and 2.5 Hz, 1H), 1.59 (dd, J = 13.5 and 2.1 Hz, 1H) (signal due to hydroxyl group proton not observed) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 144.3, 133.2, 129.2, 127.8, 126.9, 122.3, 111.4, 88.9, 62.2, 60.7,

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56.1, 54.0, 48.4, 42.2, 33.9, 30.1 ppm. IR: ν_{max} = 3339, 2917, 2835, 1958, 1623, 1590, 1506, 1438, 1281, 1230, 1202, 1166, 1046 cm^{-1}. MS (EI): *m/z* (%) = 287 (90) [$M^{+\cdot}$], 286 (100), 270 (22), 244 (41), 216 (50), 174 (47). HRMS (EI): calcd for $C_{17}H_{21}NO_3$ [$M^{+\cdot}$] 287.1521; found 287.1521.

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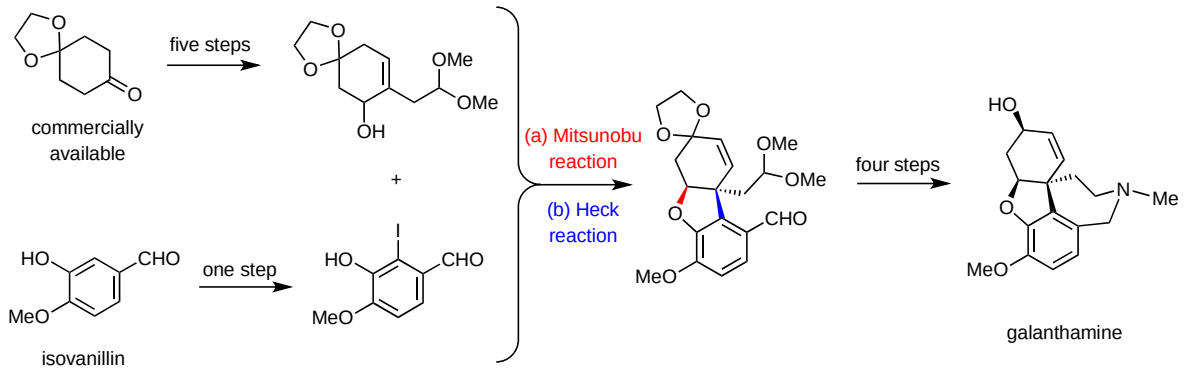
Alkaloid Synthesis



The alkaloid galanthamine, which is used for the clinical treatment of Alzheimer's disease, has been prepared over eleven steps (longest linear sequence) from commercially available materials. The two key steps are an intermolecular Mitsunobu reaction and a Heck cyclisation that ultimately provides racemic narwedine, an established precursor to either enantiomeric form of galanthamine.

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