Tetrahedron Letters 50 (2009) 4882–4884

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Novel synthetic route to the tricyclic core of (±)-galanthamine

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ARTICLE INFO

Article history:
Received 2 May 2009
Revised 8 June 2009
Accepted 10 June 2009
Available online 14 June 2009

ABSTRACT

In this Letter, we describe the novel synthetic approach to the tricyclic core of (±)-galanthamine from the easily available starting material isovanillin.

(−)-Galanthamine (**1a**), an alkaloid isolated from the bulbs of different Amaryllidaceae species and Caucasian snowdrop,[1] is a selective, reversible competitive acetyl cholinesterase (AChE) inhibitor that has been approved for the symptomatic treatment of Alzheimer's disease.[2] It has also been tested for use in anesthesiology,[3] from facial nerve paralysis to schizophrenia.[4] Galanthamine is a structural analog of lycoramine (**1c**), being devoid of the double bond, which inhibits the formation of the peptide bond in protein synthesis[5] and is related to the structure of morphine (**1d**) and other simplified analogs (e.g., morphinan, benzomorphan, and 4-phenylpiperidine derivatives) which are used for the treatment of pain.[6] Therefore, the compound containing simplified galanthamine-like skeleton may be of interest for the development of novel AChE inhibitors and the development of further analogs of morphine. Despite considerable effort to construct galanthamine analogs having enhanced efficacy,[7] there is no report which describes the synthesis of analog **1b** which is devoid of C ring (Fig. 1). Hence, this leaves the opportunity to explore this void and add to the structure–activity relationship of galanthamine. We have used diversity-oriented synthesis to construct the analog of the galanthamine, with the goal of discovering new molecules having biological effects beyond those previously associated with the natural product.

In the past decades, several elegant total syntheses of **1a** have been reported,[8] with the key transformations involved in the construction of the tricyclic benzofuran core with a sterically congested quaternary carbon, which was shared by galanthamine-type and morphine-type alkaloids (Fig. 1). In constructing the basic skeleton, many synthetic strategies, such as biomimetic phenolic oxidative coupling,[9] photochemical reaction,[10] semipinacol rearrangement,[11] radical cyclization,[12] intramolecular Heck reaction,[13] intermolecular alkylation,[14] and arylation[15] had been utilized. However, our novel synthetic approach to the galanthamine skeleton offers a range of functionalities for diversity-generating reactions and synthesis of different analogs.

The synthesis commenced with the commercially available 3-hydroxy-4-methoxy benzaldehyde (isovanillin) **2**. The phenolic hydroxyl group of **2** was protected as its allyl ether **3**. This was followed by a Claisen rearrangement of **3**, by heating to 200 °C for 4 h, in a solvent-free condition to obtain the rearranged product **4.** The phenol **4** was protected as its TBS-ether **5**, which was followed by reduction of the aldehyde functionality using sodium borohydride in methanol to obtain the alcohol **6**. The hydroxyl group of compound **6** was protected as its methoxymethylether to afford the compound **7**.

The osmium tetraoxide, sodium metaperiodate, 2,6-lutidine-promoted oxidative cleavage of the olefin **7** gave the aldehyde **8** which was transformed into its nitrile product **9** using hydroxylamine hydrochloride and pyridine followed by the addition of copper sulfate, triethylamine, and DCC with CH_2Cl_2 as solvent. The next objective was the sequential alkylation adjacent to the nitrile functionality. Accordingly, the homoallyl functionality was substi-

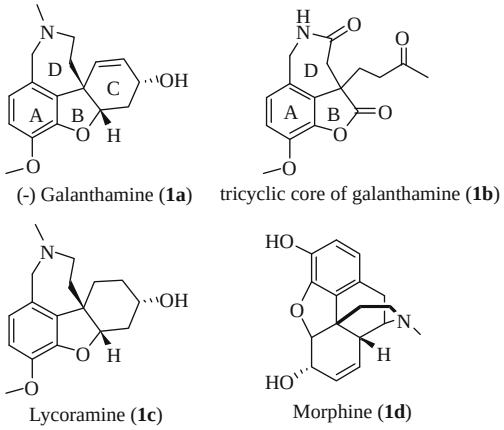

Figure 1.

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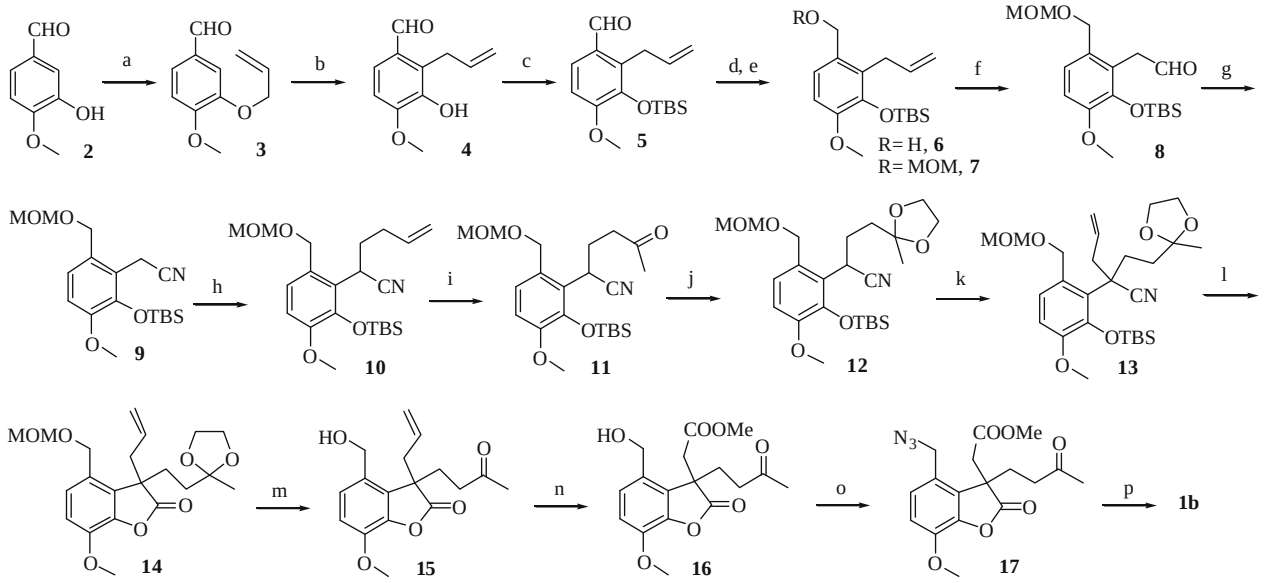
doi:10.1016/j.tetlet.2009.06.055



Scheme 1. Reagent and conditions: (a) Allyl bromide, K_2CO_3, acetone, 4 h, 96%; (b) 200 °C, 6 h, 85%; (c) TBSCl, imidazole, CH_2Cl_2, 4 h, 90%; (d) $NaBH_4$, MeOH, 85%; (e) MOMCl, DIPEA, CH_2Cl_2, 8 h, 85%; (f) OsO_4, 2,6-lutidine, $NaIO_4$, 1,4-dioxane/water, 28 h, 81%; (g) $NH_2OH{\cdot}HCl$, pyridine, then $CuSO_4$, Et_3N, DCC, CH_2Cl_2, 5 h, 87%; (h) homoallyl bromide, LDA, DMPU, THF, −78 °C, 2 h, 93%; (i) $PdCl_2$, CuCl, O_2, DMF/H_2O, 12 h, 92%; (j) ethyleneglycol, *p*TSA, benzene, 80 °C, 6 h, 88%; (k) allyl bromide, LDA, DMPU, THF, −78 °C, 2 h, 94%; (l) (i) 3 N KOH, C_2H_5OH, reflux, 0.5 h; (ii) aq solution of $NaHSO_4$ till pH 5, 86% for two steps; (m) 4 N HCl–THF, 2 h, 94%; (n) (i) O_3, CH_2Cl, −78 °C, 5 min, then $(CH_3)_2S$; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, acetonitrile–water, 56% for two steps; CH_2N_2, $(C_2H_5)_2O$, 5 min, quantative; (o) DPPA, DBU, toluene, 80 °C, 18 h, 92%; (p) Zn, NH_4Cl, EtOH, 80 °C, 5 min, 26%.

tuted on treating **9** with lithiumdiisopropyl amide and homoallyl bromide in THF at −78 °C to obtain the homoallyl-substituted product **10**. The compound **10** was then subjected to Wacker oxidation to obtain the keto derivative **11** in high yield. The ketone functionality of **11** was protected as 1,3-dioxolane **12** using ethylene glycol and catalytic amount of *p*-TSA. Next, the allyl functionality was introduced by treating **12** with lithiumdiisopropyl amine and allyl bromide in THF–DMPU as solvent at −78 °C to obtain the key intermediate **13**. Having successfully synthesized the structural backbone, the next objective was to construct the B and C rings of galanthamine. Accordingly, the compound **13** was heated at reflux for 0.5 h in 3 N KOH–EtOH, and then on acidifying the reaction mixture to pH 5, the product lactone **14** was obtained in good yield. The methoxymethylether (MOM) group of the compound **14** was removed using 4 N HCl. Pleasingly, the reaction conditions also led to the desired 1,3-dioxolane deprotection of the ketone. Next, it was desired to functionalize the olefin moiety. Accordingly, the olefin **15** was subjected to ozonolysis and the crude aldehyde was then transformed to the corresponding acid using NaH_2PO_4, $NaClO_2$, and 2-methyl-2-butene in 56% yield in two steps. Next, the acid was esterified by diazomethane to its methylester **16** in quantitative yield. The azide functionality was introduced by substituting the primary alcohol of **17**, using diphenylphosphoryl azide (DPPA) and DBU in toluene. The seven-membered azapine ring was constructed by reducing the azide functionality, using zinc and ammonium chloride, to its amine which spontaneously cyclized to form the amide **1b** in moderate yield (Scheme 1).[16]

The acetyl cholinesterase (AChE) inhibitory activity of tricyclic core of galanthamine (**1b**) was measured in vitro by comparing with (−)-galanthamine (**1a**) using Ellman assay.[17] It was observed that, compound **1b** at 0.5 μM concentration inhibited AChE activity by 40% as compared to 55% inhibition by **1a**, a known AChE inhibitor at the same concentration. The values shown in Figure 2 are from three independent experiments.

In summary, a non-biomimetic synthetic route to the novel galanthamine analog, devoid of C ring, was established starting

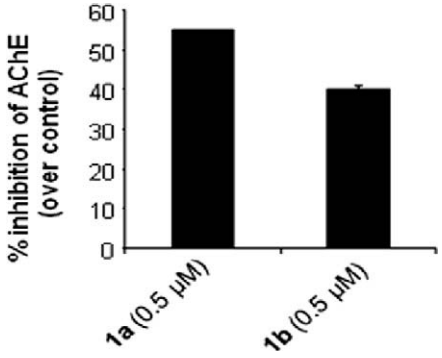


Figure 2.

with isovanillin. The final product, galanthamine devoid of C ring was shown to have AChE inhibitory activity by 40% as compared to galanthamine (55%) at the same concentration. The total synthesis of galanthamine and the synthesis of more galanthamine analogs are presently being actively pursued in our laboratory.

Acknowledgments

We thank CSIR New Delhi, for the research fellowship to Debjit Basu and DST, New Delhi, for financial assistance (GAP-0154). We also thank Dr. Rene Gree of University of Rennes for useful suggestions. This work has been the part of Indo-French Joint Laboratory for sustainable chemistry at interface.

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16. Spectral data of selected new compounds: *3-(allyloxy)-4-methoxybenzaldehyde* (**3**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.48–7.40 (m, 2H), 7.00 (d, J = 8.3 Hz, 1H), 6.16–6.03 (m, 1H), 5.48–5.29 (m, 2H), 4.68 (d, J = 5.2 Hz, 2H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.6, 154.6, 148.3, 132.3, 129.7, 126.6, 118.3, 110.6, 110.4, 69.5, 55.9; HRMS (ESI): Calcd for $C_{11}H_{13}O_3$: 193.0864 $[M+H]^+$, Found: 193.0861 $[M+H]^+$; IR (KBr): ν_{max} 1685, 1589, 1267 cm^{-1}.
2-Allyl-3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-4-methoxybenzaldehyde (**5**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.01 (s, 1H), 7.47 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.01–5.88 (m, 1H), 5.00–4.81 (m, 2H), 3.87 (s, 3H), 3.86 (d, J = 7.5 Hz, 2H), 0.99 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.0, 154.3, 142.9, 136.7, 132.8, 128.1, 125.9, 115.1, 108.8, 54.6, 28.5, 25.9, 18.76, −3.9; HRMS (ESI): Calcd for $C_{17}H_{27}O_3Si$: 307.1729 $[M+H]^+$, Found: 307.1732 $[M+H]^+$; IR (KBr): ν_{max} 2929, 1680, 1584, 1292, 833 cm^{-1}.
2-Allyl-6-methoxy-3-[(methoxymethoxy)methyl] phenoxy(tert-butyl)dimethylsilane (**7**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (d, J = 8.3 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 5.93–5.82 (m, 1H), 4.95–4.80 (m, 2H), 4.60 (s, 2H), 4.46 (s, 2H), 3.78 (s, 3H), 3.52–3.47 (m, 2H), 3.37 (s, 3H), 1.01 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6, 143.0, 136.6, 129.7, 129.0, 122.1, 114.5, 108.7, 95.4, 67.1, 55.3, 54.6, 30.3, 26.2, 18.9, −3.7; HRMS (ESI): Calcd for $C_{19}H_{32}O_4NaSi$: 375.1967 $[M+Na]^+$, Found: 375.1959 $[M+Na]^+$; IR (KBr): ν_{max} 2932, 2857, 1492, 1442, 1285 cm^{-1}.
2-[1-(tert-Butyl)-1,1-dimethylsilyl]oxy-3-methoxy-6-[(methoxymethoxy)methyl]-benzylcyanide (**9**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88 (d, J = 8.3 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 4.60 (s, 2H), 4.58 (s, 2H), 3.80 (s, 5H), 3.38 (s, 2H), 1.03 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 143.5, 128.5, 122.8, 121.2, 117.8, 110.4, 95.1, 67.3, 55.5, 54.7, 29.6, 26.0, 14.7, −3.75; HRMS (ESI): Calcd for $C_{18}H_{29}NO_4NaSi$: 374.1763 $[M+Na]^+$, Found: 374.1758 $[M+Na]^+$; IR (KBr): ν_{max} 2932, 2248, 1497, 1030, 833 cm^{-1}.
1-2-[1-(tert-Butyl)-1,1-dimethylsilyl]oxy-3-methoxy-6-[(methoxymethoxy)methyl]phenyl-4-pentenyl cyanide (**10**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (d, J = 8.3 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 5.80–5.69 (m, 1H), 5.13–5.00 (m, 2H), 4.75–4.56 (m, 5H), 3.79 (s, 3H), 3.39 (s, 3H), 2.38–1.73 (m, 4H), 0.99 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 142.7, 136.4, 128.4, 125.5, 123.4, 120.5, 116.1, 110.4, 95.5, 66.8, 55.5, 54.6, 31.8, 31.6, 28.0, 26.2, 19.1, −3.0; HRMS (ESI): Calcd for $C_{22}H_{35}NO_4NaSi$: 428.2233 $[M+Na]^+$, Found: 428.2241 $[M+Na]^+$; IR (KBr): ν_{max} 3432, 2931, 2238, 1743, 1494, 758 cm^{-1}.
1-2-[1-(tert-Butyl)-1,1-dimethylsilyl]oxy-3-methoxy-6-[(methoxymethoxy)methyl]phenyl-4-oxopentyl cyanide (**11**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (d, J = 8.3 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 4.74–4.51 (m, 5H), 3.80 (s, 3H), 3.39 (s, 3H), 2.66–2.15 (m, 4H), 2.13 (s, 3H), 0.99 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4, 149.3, 124.8, 123.4, 120.3, 110.5, 115.1, 95.4, 95.3, 66.7, 55.5, 54.5, 42.9, 40.5, 29.9, 27.6, 27.2, 26.3, −3.0; HRMS (ESI): Calcd for $C_{22}H_{35}NO_5NaSi$: 444.2182 $[M+Na]^+$, Found: 444.2176 $[M+Na]^+$; IR (KBr): ν_{max} 2933, 2238, 1718, 1495, 840 cm^{-1}.
1-2-[1-(tert-Butyl)-1,1-dimethylsilyl]oxy-3-methoxy-6-[(methoxymethoxy)methyl]phenyl-1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3-butenyl cyanide (**13**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 5.83–5.69 (m, 1H), 5.19–5.07 (m, 2H), 4.90–4.78 (q, J = 12.0, 13.5 Hz, 2H) 4.65 (s, 2H), 3.89–3.80 (s, 4H), 3.77 (s, 3H), 3.38 (s, 3H), 2.75–2.63 (m, 2H), 2.05–1.45 (m, 4H), 1.27 (s, 3H), 0.95 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0, 143.2, 133.0, 129.1, 124.4, 124.0, 119.0, 109.4, 95.3, 68.4, 64.4, 55.5, 54.2, 46.4, 42.1, 36.8, 34.8, 32.8, 27.1, 26.3, 23.8, 19.9, −1.4; HRMS (ESI): Calcd for $C_{27}H_{43}NO_6NaSi$: 528.2757 $[M+Na]^+$, Found: 528.2770 $[M+Na]^+$; IR (KBr): ν_{max} 2933, 2887, 2237, 1477 cm^{-1}.
3-Allyl-7-methoxy-4-[(methoxymethoxy)methyl]-3-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]2,3-dihydrobenzo[b] furan-2-one (**14**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (d, J = 8.3 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 5.38–5.24 (m, 1H), 5.05–4.88 (m, 2H), 4.68 (s, 2H) 4.62–4.52 (q, J = 7.3, 11.8 Hz, 2H), 3.91 (s, 3H), 3.88–3.76 (m, 4H), 2.88–2.66 (m, 2H), 2.21–2.10 (m, 2H), 1.43–1.12 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 143.8, 141.5, 131.4, 127.9, 126.0, 125.9, 119.4, 112.1, 109.0, 95.4, 65.2, 64.4, 56.1, 55.5, 54.2, 42.1, 34.0, 31.6, 29.6, 23.5; ESI (MS): m/z 415 $[M+Na]^+$; IR (KBr): ν_{max} 2930, 1750, 1223 cm^{-1}.
Methyl2-[4-(hydroxymethyl)-7-methoxy-2-oxo-3-(3-oxobutyl)-2,3-dihydrobenzo-[b]furan-3-yl]acetate (**16**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (d, J = 8.3 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 4.64 (s, 2H), 3.96 (s, 3H), 3.50 (s, 3H), 3.43–3.13 (m, 2H), 2.65–1.99 (m, 4H,),1.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.2, 177.9, 170.1, 143.0, 140.6, 130.8, 126.1, 124.9, 119.1, 112.0, 60.6, 55.6, 53.3, 41.0, 38.1, 30.4, 29.5; ESI (MS): m/z 336 $[M+H]^+$; IR (KBr): ν_{max} 3449, 2925, 1801, 1736, 1287 cm^{-1}.
1-[7-Methoxy-3-(2-methoxy-2-oxoethyl)-2-oxo-3-(3-oxobutyl)-2,3-dihydrobenzo-[b]furan-4-yl]methyl-1,2-triazadien-2-ium (**17**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.32–4.19 (q, J = 13.7, 10.7 Hz, 2H), 3.96 (s, 3H), 3.50 (s, 3H), 3.20 (d, J = 3.0 Hz, 2H), 2.43–1.96 (m, 4H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.9, 177.8, 169.4, 144.4, 142.5, 127.1, 126.6, 123.2, 112.8, 56.2, 52.0, 50.8, 49.5, 41.5, 37.5, 31.0, 29.8; HRMS (ESI): Calcd for $C_{17}H_{19}N_3O_6$: 379.1621 $[M+NH_4]^+$, Found: 379.1616 $[M+NH_4]^+$; IR (KBr): ν_{max} 3430, 2923, 2106, 1803, 1734, 1193 cm^{-1}.
3-Methoxy-9a-(3-oxobutyl)-1,6,7,8,9,9a-hexahydro-2-oxa-7-azabenzo[cd]azulene-1,8-dione (**1b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.14 (br s, 1H), 4.71–4.68 (m, 2H), 3.89 (s, 3H), 2.30–2.34 (m, 2H), 2.19–1.96 (m, 4H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0, 177.8, 172.8, 147.5, 144.8, 126.7, 123.2, 113.0, 111.2, 56.2, 52.1, 50.9, 49.3, 37.54, 29.6, 26.1; HRMS (ESI): Calcd for $C_{16}H_{17}NO_5$: 326.1004 $[M+Na]^+$, Found: 326.0999 $[M+Na]^+$; IR (KBr): ν_{max} 3432, 2923, 1803, 1735, 1632 cm^{-1}.
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