Carbocyclic galanthamine analogues: construction of the novel 6*H*-benzo[*a*]cyclohepta[*hi*]benzofuran ring system

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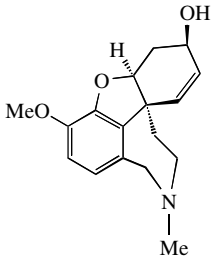
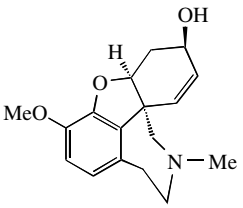
Unnatural analogues of the anti-Alzheimer drug (–)-galanthamine have been synthesised using $K_3[Fe(CN)]_6$ at the key step to construct the novel (±)-6*H*-benzo[*a*]cyclohepta[*hi*]benzofuran ring system *via* oxidative tandem cyclization.

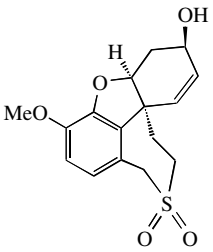
Galanthamine (or galantamine, Reminyl®) is a tertiary alkaloid acetylcholinesterase inhibitor (AChEI), which has been approved in several countries for treating the symptoms of Alzheimer's type senile dementia.[1] The key step comprises the $K_3[Fe(CN)]_6$ induced oxidative tandem cyclization of suitable norbelladine analogues, whereby the tetracyclic ring system is established in a cascade of radical reactions and Michael addition. We are currently studying this phenol oxidation, which was developed for the synthesis of the galanthamine ring system[2,3] and is now performed on an industrial scale.[4] We have extended this reaction for the preparation of 6*H*-benzofuro[3a,3,2-*ef*][3]benzazepine[5] and 12*H*-[2]benzothiepino[6,5a,5-*bc*]benzofuran[6] ring systems (Figure 1).



(–)-Galanthamine



(4aα,6β,8a*R**)-4a,5,9,10,11,12-Hexahydro-3-methoxy-10-methyl-6*H*-benzofuro[3a,3,2-*ef*]-[3]-benzazepin-6-ol (see ref. 5)



(4aα,6β,8a*R**)-4a,5,9,10-Tetrahydro-3-methoxy-11,11-dioxo-12*H*-[2]benzothiepino[6,5a,5-*bc*]-benzofuran-6-ol (see ref. 6)

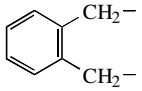
Figure 1

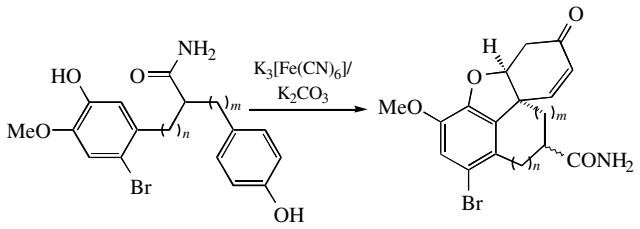
Here, we report the successful use of this reaction for the synthesis of the novel 6*H*-benzo[*a*]cyclohepta[*hi*]benzofuran ring system starting from diphenol compounds **1a–d**. Generally, this type of reaction is successful for the creation of 5-6-6-7 ring systems† under conditions found to be optimal in the synthesis of galanthamine[4] (Scheme 1 and Table 1). For all reactions, the quantitative conversion of diphenol was observed by TLC.

Table 1 Tandem cyclization of **1a–d**.

Compound	*m*	*n*	yield of **2** (%)
1a	1	1	0
1b	0	3	8
1c	1	2	19
1d	2	1	6

Table 2 Unsuccessful cyclization attempts.

Compound	G	Ring system expected
3a	–N(CHO)–	5-6-6-6
3b	–N(CHO)–$(CH_2)_2$–	5-6-6-8
3c	–$(CH_2)_2$–	5-6-6-7
3d		5-6-6-6-7



1a–d **2a–d**

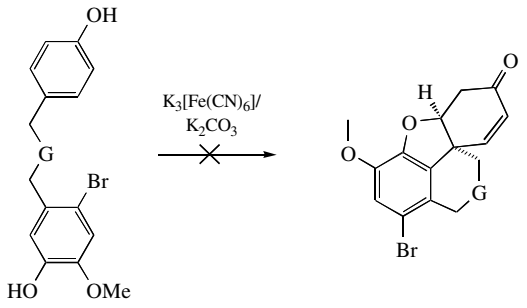
Scheme 1

These results were rationalised by molecular models generated using the CORINA software[7] as described below. A low-energy conformation characterised by the interaction of the bromine atom and the carboxamide moiety show favourable distances between the carbon atoms to be engaged in the radical cyclization. Further attempts to cyclise compounds **3a–d**, which were expected to give 5-6-6-6, 5-6-6-8 and unfunctionalised 5-6-6-7 ring systems, were unsuccessful (Scheme 2). These observations were rationalised by the ring tension of 5-6-6-6 ring systems in the case of **3a**, as well as **1a**, the lack of supportive conformative restriction and the comparatively high flexibility of **3b** and **3c**, and the formation of coloured decomposition products in the case of **3d** (Scheme 2 and Table 2).

† *Representative example of tandem cyclization: (4aβ,8aβ,12*R**)-1-bromo-4a,5,9,10,11,12-hexahydro-3-methoxy-6-oxa-6*H*-benzo[*a*]cyclohepta[*hi*]-benzofuran-12-carboxamide* **2b**. $K_3[Fe(CN)_6]$ (13.2 g, 40.0 mmol) and K_2CO_3 (7.50 g, 53.1 mmol) in water (75 ml) were added to a suspension of **1b** (3.00 g, 7.61 mmol) in $CHCl_3$ (300 ml), and the mixture was stirred vigorously for 45 min at room temperature. The mixture was filtered using diatomaceous earth, and the filtrate was washed with water (3×200 ml) and brine (200 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was obtained as a mixture of diastereomers and purified by flash chromatography (SiO_2; $CHCl_3$–MeOH, 96:4). A diastereomer with the higher R_f was formed as colourless crystals (0.24 g, 8%), mp 257–258 °C (decomp.), R_f 0.6 (EtOAc). ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.57 (s, 1H), 7.48 (d, 1H, *J* 14.5 Hz), 7.14 (s, 2H), 5.89 (d, 1H, *J* 14.5 Hz), 4.66 (s, 1H), 4.32 (s, 1H), 4.01 (q, 1H, *J* 7.7 Hz), 3.78 (s, 3H), 3.02 (d, *J* 19.6 Hz, 1H), 2.79 (d, 1H, *J* 19.6 Hz), 2.52 (d, 1H, *J* 16.5 Hz), 2.16 (d, *J* 16.5 Hz, 1H), 1.96–1.67 (m, 2H), 1.14 (t, 1H, *J* 7.7 Hz). ^{13}C NMR ([$^2H_6$]DMSO) δ: 195.6 (s), 174.6 (s), 149.5 (d), 147.9 (s), 144.4 (s), 133.6 (s), 130.6 (s), 126.5 (d), 117.5 (s), 117.1 (d), 88.4 (d), 56.8 (q), 52.1 (s), 51.6 (d), 37.9 (t), 36.6 (t), 33.3 (t), 21.5 (t). Found (%): C, 55.15; H, 4.71; N, 3.38. Calc. for $C_{18}H_{18}BrNO_4$ (%): C, 55.12; H, 4.63; N, 3.57.

The diastereomer with the lower R_f which was formed as a minor by-product was detected using TLC and NMR spectroscopy, it was isomerised to the main isomer. R_f 0.45 (EtOAc). Found (%): C, 55.10; H, 4.59; N, 3.46. Calc. for $C_{18}H_{18}BrNO_4$ (%): C, 55.12; H, 4.63; N, 3.57.

In all cases, the starting material was quantitatively consumed under the reaction conditions as observed by TLC.



3a–d

Scheme 2

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