

## A New Commercially Viable Synthetic Route for Donepezil Hydrochloride: Anti-Alzheimer's Drug

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**An economical new process has been developed for the synthesis of donepezil hydrochloride (1) an anti-Alzheimer's drug. The process involves Darzen reaction of pyridine-4-carboxaldehyde and 2-bromo-5,6-dimethoxy indanone affording epoxide 5,6-dimethoxy-3-(pyridine-4-yl)spiro[indene-2,2'-oxiran]-1(3H)-one (4) as a key intermediate. The one-pot deoxygenation of 4 and hydrogenation of the aryl moiety in high yield improved the overall yield of the process.**

**Key words** donepezil hydrochloride; improved process; deoxygenation; epoxide; benzylation

Donepezil hydrochloride (E2020) alongside with galantamine and rivastigmine is a piperidine-based drug developed specifically for Alzheimer's disease (AD) by Eisai Pharmaceuticals (Aricept).<sup>1)</sup> It belongs to a class of acetylcholinesterase (AChE) inhibitors having *N*-benzylpiperidine and an indanone moiety which shows longer and more selective action.<sup>2–9)</sup> It is the second drug approved by US-FDA for the treatment of mild to moderate Alzheimer's disease.<sup>10)</sup> On a large-scale, donepezil hydrochloride **1** is being synthesized from alkylidene or arylidene-2-indanone formed by Aldol condensation chemistry as key intermediates (Sugimoto and co-workers)<sup>11,12)</sup> followed by catalytic reduction affording **1** with an overall yield of 27%. The process suffered from several disadvantages such as the use of unacceptable process solvent like hexamethyl phosphoric amide (HMPA), formation of side products during catalytic reduction and the need of column chromatography to remove the unwanted side products. Stephen Lensky<sup>13)</sup> designed an efficient and scalable three-step synthesis involving *N*-benzylation of arylidene intermediate to form a quaternary salt which was subsequently hydrogenated with PtO<sub>2</sub> to afford the target skeleton **1**. Though, Stephen Lensky process involves only three chemical transformations for the synthesis of **1**, it is not economical at commercial scale because of the use of highly expensive reagent like PtO<sub>2</sub>. Replacement of Adam's catalyst with Pd/C proceeded with debenzylated impurities which were very difficult to remove in final API. A strong demand of donepezil hydrochloride led to the development of several synthetic schemes which are either too long or led to formation of several process related impurities or use of an expensive catalyst such as PtO<sub>2</sub> and thus are not feasible for large scale preparation.<sup>14–18)</sup> The other drawback associated with most of the reported protocols is the limited solubility of the above mentioned intermediates consuming higher volumes of solvents for the reactions. We envisioned that an efficient route to **1** without involving hazardous reagents should make economic sense besides giving a new practical industrial method within the acceptable environmental and toxicological concerns. We further reasoned that the new method involving intermediates from cheap commercially available conventional starting material other than the usual alkylidene or arylidene indanone would be more appealing that display im-

proved solubility and hence employ lower volume of solvents for the synthesis of donepezil.

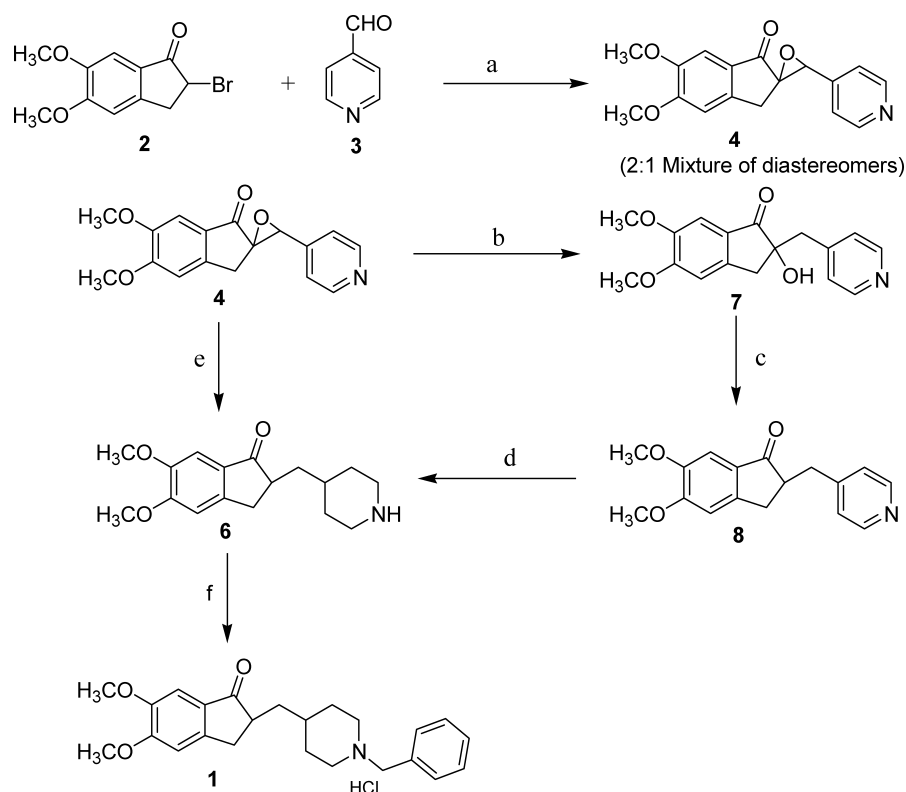
In this contribution, we report a convenient and reliable process, which is novel, economical, high yielding and is industrially applicable for the synthesis of donepezil hydrochloride.

The first step of our synthetic strategy commences from commercially available 2-bromo-5,6-dimethoxy indanone **2** which undergoes Darzens condensation<sup>19–21)</sup> with pyridine-4-carboxaldehyde **3** in the presence of a suitable base affording the epoxy intermediate **4** as diastereomers (Chart 1) along with dehydrated side product **5**, formed as a result of competitive side reaction. An optimization of the reaction process to minimize the formation of **5** was performed by screening nature of base, reaction temperature and reaction solvents (Table 1). It is quite evident from the table that condensation requires strong nucleophilic organic base and lower temperature. Among various bases examined for the reaction, <sup>t</sup>BuLi and KO<sup>t</sup>Bu showed significant formation of **4** in tetrahydrofuran (THF). Dehydration product **5** was the only product for reactions employing NaH (Table 1, entries 1–4). Other solvents at various temperatures failed to eliminate the formation of impurity **5** in the case of KO<sup>t</sup>Bu (Table 1, entries 5–9). Surprisingly, reaction performed using <sup>t</sup>BuLi at –78 °C in THF reduced the impurity as low as 6%

Table 1. Optimization of Reaction Parameters for the Darzen Condensation of 2-Bromo-5,6-dimethoxy Indanone **2** with Pyridine-4-carboxaldehyde **3**

Entry	Base	Solvent	Temp. (°C)	Conversion (%) <sup>a)</sup>
1	NaH (60%)	Toluene	20–25	— (—)
2	NaH (60%)	DMF	20–25	— (100)
3	NaH (60%)	THF	20–25	— (100)
4	NaH (60%)	THF	0–5	— (—)
5	KO <sup>t</sup> Bu	THF	20–25	20 (80)
6	KO <sup>t</sup> Bu	THF	0–5	30 (70)
7	KO <sup>t</sup> Bu	THF	–10––15	50 (50)
8	KO <sup>t</sup> Bu	DMSO	15–20	— (100)
9	KO <sup>t</sup> Bu	DMF	0–5	— (100)
10	<sup>t</sup> BuLi	THF	–20	60 (40)
11	<sup>t</sup> BuLi	THF	–78	94 (6)

<sup>a)</sup> Yields in the paranthesis refer to percentage of impurity **5** formed during the reaction.



(a)  $^n\text{BuLi}$ ,  $-78^\circ\text{C}$ , THF, 6 h, 82%; (b) 5% Pd/C,  $\text{H}_2$  (0.5  $\text{kg}/\text{cm}^2$ ), 1:1 MeOH- $\text{CH}_2\text{Cl}_2$ , RT, 2 h, 85%; (c) Zn-AcOH,  $55^\circ\text{C}$ , 3 h, 81%; (d) 5% Pd/C,  $\text{H}_2$  (6.5–7.0  $\text{kg}/\text{cm}^2$ ),  $\text{CH}_3\text{COOH}$ ,  $\text{CH}_3\text{COONa}$ , 1:1 MeOH- $\text{CH}_2\text{Cl}_2$ ,  $75^\circ\text{C}$ , 10 h, 70%; (e) 5% Pd/C,  $\text{H}_2$  (6.5–7.0  $\text{kg}/\text{cm}^2$ ), perchloric acid (cat.), 1:1 MeOH- $\text{CH}_2\text{Cl}_2$ ,  $75^\circ\text{C}$ , 10 h, 90%; (f) (i)  $\text{BnCl}$ , 9:1 EtOAc- $\text{H}_2\text{O}$ ,  $\text{K}_2\text{CO}_3$ , PEG-200 (cat.),  $55^\circ\text{C}$ , 14 h; (ii) Con. HCl, 80%.

Chart 1. Process for the Synthesis of Donepezil Hydrochloride 1

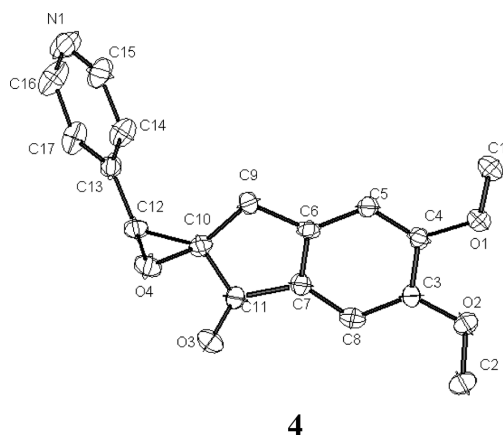


Fig. 1. ORTEP Representation (30% Probability) of Single-Crystal X-Ray Structure of Epoxide 4 (Hydrogen Atoms Are Omitted for Clarity)

affording the best condition for the transformation (Table 1, entry 11). The structure of epoxy intermediate 4 was confirmed by spectral data and single crystal X-ray diffraction structure (Fig. 1).<sup>22)</sup> One of the most important features of this reaction is that the product is obtained in high yield (85–90%) without any chromatographic purification as compared to the known literature process.

The conversion of epoxide 4 to 6 was troublesome and required optimization. Two different approaches were adopted for the above transformation (Chart 1).<sup>23–25)</sup> The first route is a three step transformation that involves epoxide-ring opening of 4 under catalytic hydrogenation in aque-

ous methanol in the presence of Pd/C at 20–25 °C and 0.5  $\text{kg}/\text{cm}^2$  hydrogen pressure forming 7 in 85% yield.<sup>25)</sup> Deoxygenation of the resulting secondary alcohol was achieved with zinc-acetic acid at 50–55 °C affording 8 in 81% yield.<sup>26)</sup> The final hydrogenation of 8 to compound 6 was studied with different metal catalysts (platinum, rhodium, palladium *etc.*) but due to economical barrier, Pd/C remained the best choice of reagent for this particular transformation. The optimized procedure for the aromatic hydrogenation employs 5% Pd/C, an organic acid and its salts (acetic acid and sodium acetate) in the presence of an alcoholic or non alcoholic solvents (methanol, ethanol or chloroform, dichloromethane) or in the mixture of dichloromethane and methanol at 70–75 °C and at about 6.0–7.0  $\text{kg}/\text{cm}^2$  of hydrogen pressure.<sup>17)</sup> The mixture of solvents was however preferred because of the enhanced solubility of intermediate 8 (1.5 times reduction of solvent volume was achieved with the binary solvent system).

The other route is a one shot conversion of 4 to 6 that involves deoxygenation and ring hydrogenation in one step. The process was complicated by formation of a major impurity 9 (Fig. 2) by competitive side reaction of carbonyl moiety. Hence, to minimize side products formation, optimization studies were carried out on the basis of previous results adopted for the stepwise transformation of 4 to 6 (temperature, reaction time, hydrogen pressure and choice of solvents *etc.*). A catalytic amount of perchloric acid (1% by weight) proved essential for the reaction and the best hydrogenation procedure was optimized by hydrogenating 4 with 5% Pd/C in a 1:1 mixture of methanol-dichloromethane in the pres-

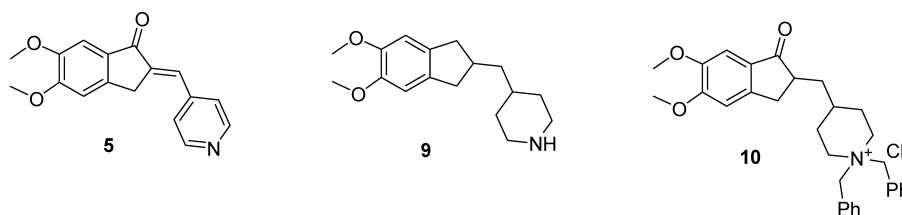


Fig. 2. Structures of Process Related Impurities

Table 2. Optimization of High Pressure Hydrogenation Reactions with Metal Catalysts

Entry	Substrate	Catalyst <sup>a)</sup>	Solvent <sup>b)</sup>	Time (h)	Conversion (%) <sup>c)</sup>	Yield of <b>6</b> (%) <sup>d)</sup>
1	<b>8</b>	5% Rh/C	MeOH	4	86 (14)	72
2	<b>8</b>	5% Pt/C	MeOH	9	98 (2)	90
3	<b>8</b>	5% Pt/C	MeOH	12	92 (8)	75
4	<b>8</b>	10% Pd/C	MeOH–DCM	8	97.5 (2.5)	86
5	<b>8</b>	5% Pd/C	MeOH–DCM	10	98.5 (1.5)	91
6	<b>4</b>	5% Pd/C+Cat. HClO <sub>4</sub>	MeOH	12	80 (18)	70
7	<b>4</b>	10% Pd/C+Cat. HClO <sub>4</sub>	MeOH	7	75 (22)	63
8	<b>4</b>	5% Pd/C+Cat. HClO <sub>4</sub>	MeOH–DCM	10	94 (5)	90
9	<b>4</b>	5% Pd/C+Cat. HCl	MeOH–DCM	10	87 (13)	81
10	<b>4</b>	5% Pd/C+Cat. AcOH	MeOH–DCM	24	73 (10)	68
11	<b>4</b>	10% Pd/C+Cat. HClO <sub>4</sub>	MeOH–DCM	5	82 (15)	73

a) All the reactions were performed at 70–75 °C and at 6.0–7.0 kg/cm<sup>2</sup> pressure. b) MeOH (15 volumes); 1 : 1 MeOH–DCM (10 volume). c) Yields in the parenthesis refer to impurity **9**. d) Isolated yields.

Table 3. Effect of Phase Transfer Catalyst (PTC) on *N*-Benzylation<sup>a)</sup> of **6**

Entry	PTC <sup>b)</sup>	Time (h)	Conversion (%)	Dibenzylated impurity <b>10</b> (%)	Yield (%) <sup>c)</sup>
1	TBAI	10	90	10	65
2	PEG-200	12	90	3	80
3	18-crown-6	14	75	15	60

a) 1.1 eq K<sub>2</sub>CO<sub>3</sub>, 9:1 EtOAc–H<sub>2</sub>O, 55 °C. b) 2% by weight. c) Isolated yields.

ence of perchloric acid at 70–75 °C and 6.0–7.0 kg/cm<sup>2</sup> hydrogen pressure for 8–10 h to accomplish **6** with 90% yield and more than 98.5% purity (HPLC purity). Other acids like HCl and AcOH used in the place of perchloric acid afforded lower yield of products as a result of impurity formation in the former case and a longer reaction time in the later.

The final *N*-benzylation of **6** was achieved using benzyl chloride (Chart 1). Though this chemical transformation appears simple and straight, it afforded very unpredictable results at the initial feasibility studies. The reported procedures for benzylation (benzyl chloride, 60–65 °C, triethylamine)<sup>14</sup> resulted in a very poor yield (19.5%) with formation of dibenzylated quaternary salt **10** (Fig. 2) (around 15%) as impurity. The reaction conditions were therefore modified suitably that precludes the contamination of the final product by **10**. Preliminary experiments on the *N*-alkylation disclosed that the nature of solvent and quantity of benzyl chloride plays critical role in controlling competitive dibenzyl product **10**. Various single organic solvents (acetone, dichloromethane, acetonitrile, isopropyl ether *etc.*) employed for the reaction resulted in poor yields of **1**. Therefore *N*-benzylation was examined in biphasic medium (toluene–Water, ethyl acetate–water *etc.*) in the presence of phase transfer catalyst (PTC) and inorganic base (K<sub>2</sub>CO<sub>3</sub>, KHCO<sub>3</sub>, NaHCO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, *etc.*). Considerable improvement in the yield of **1** was observed with biphasic solvent medium though the formation of

dibenzylated product could not be eliminated. Careful screening of various PTC revealed that 2% by weight of PEG-200 added to the reaction mixture restricted **10** to 2–4% (Table 3, entry 2). A 9 : 1 ethyl acetate–water system with benzyl chloride, potassium carbonate in the presence of PEG-200 gave the best acceptable result with satisfactory yield (90%) of **1**, as well as facilitated the precipitation of the unwanted dibenzyl impurity **10** as a filterable solid from the reaction mass. Purification of the crude **1** with methanol–diisopropylether afforded highly pure donepezil hydrochloride in 60% overall yield.

In summary, we have developed a novel and efficient route for the synthesis of donepezil hydrochloride (E2020) with the potential for the production at commercial scale. The improved process for the preparation of donepezil hydrochloride **1** has an overall yield around 60% and involves only three isolation and drying steps. The enhanced solubility of the newly developed key intermediate 5,6-dimethoxy-3-pyridine-4-ylspiro(indene-2,2'-oxiran)-1(3*H*)-one **4** is the significant feature of the method. The process offers distinctive advantages over earlier reported procedures in terms of minimal effluent generation, avoiding the use of hazardous reagents as well as significant cost reduction on commercial scale.

### Experimental

All reactions were carried out in anhydrous solvents. THF was distilled from sodium-benzophenone under argon and CH<sub>2</sub>Cl<sub>2</sub> was distilled from CaH<sub>2</sub>. <sup>1</sup>H-NMR spectra were obtained at 400 MHz, and <sup>13</sup>C-NMR spectra were obtained at 100.6 MHz using a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to CDCl<sub>3</sub> (7.26, 77.0 ppm). Infrared spectra were recorded using a JASCO FT/IR 410 spectrometer.

**5,6-Dimethoxy-3-(pyridine-4-yl)spiro[indene-2,2'-oxiran]-1(3*H*)-one (**4**)** THF (250 ml) was taken in a 500 ml three-neck flask equipped with a stirrer, nitrogen inlet, gas bubbler and thermometer and cooled to –78 °C. To this cold solution was added *n*-butyllithium (11.77 g, 1.6 M in hexane, 0.184 mol) followed by the addition of 2-bromo-5,6-dimethoxyindanone **2** (50 g, 0.184 mol). After 10 min, pyridine-4-carboxaldehyde **3** (19.74 g,

0.184 mol) was added to the reaction mass at  $-78^{\circ}\text{C}$  and stirred at the same temperature till the completion of the reaction. After completion of reaction (5 h) water (750 ml) was added to the reaction mass to precipitate the product. The solid was filtered, washed with methanol and dried under vacuum to yield the product **4** as a 2 : 1 mixture of diastereomers. Yield: 45 g (82%); Yellow solid; HPLC 98.5%; FT-IR (KBr,  $\text{cm}^{-1}$ ): 3545, 3419, 2959, 1688, 1634, 1595, 1545, 1500, 1306, 1258, 1125; Major diastereomer:  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.55 (d,  $J=5.2$  Hz, 2H), 7.45 (d,  $J=6.0$  Hz, 2H), 7.01 (s, 1H), 6.89 (s, 1H), 4.41 (s, 1H), 3.96 (s, 3H), 3.81 (s, 3H), 3.38 (dd,  $J=17.2, 34.4$  Hz, 2H);  $^{13}\text{C-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 195.2, 156.2, 149.8, 148.9, 144.8, 141.8, 129.2, 122.1, 107.4, 104.3, 66.8, 63.9, 56.3, 55.9, 32.8; Minor diastereomer:  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.61 (dd,  $J=1.6, 4.4$  Hz, 2H), 7.22–7.25 (m, 2H), 6.81 (s, 1H), 4.42 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.13 (d,  $J=18$  Hz, 1H), 2.76 (d,  $J=18$  Hz, 1H);  $^{13}\text{C-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 196.4, 159.4, 149.8, 146.4, 144.0, 128.3, 121.1, 107.5, 104.4, 67.3, 60.7, 56.2, 56.1, 28.6; MS electrospray ionization (ESI)  $m/z$  298.6 [ $\text{M}^+ + 1$ ].

**2-[(4-Piperidinyl)methyl]-5,6-dimethoxyindanone (6)** To a stirred solution of 5,6-dimethoxy-3-pyridine-4-yl-spiro(indene-2,2-oxiran)-1(3H)-one **4** (50 g, 0.168 mol) in 1 : 1 MeOH– $\text{CH}_2\text{Cl}_2$  (500 ml) was added 5% Pd/C (5 g, 10% by wt) and a catalytic amount of perchloric acid (0.5 g, 1% by weight). The solution was hydrogenated at 6.5 kg/cm<sup>2</sup> hydrogen pressure at 60–65  $^{\circ}\text{C}$ , till the reaction was completed by TLC (10 h). After the completion of the reaction, the catalyst was filtered through a pad of celite and washed with 1 : 1 MeOH– $\text{CH}_2\text{Cl}_2$  (10 ml). The combined filtrate was evaporated under vacuum and the residue was taken in ethyl acetate (500 ml) and washed with water (50 ml). The EtOAc layer was separated, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to yield the product **6**. Yield 43.7 g (90%); HPLC 98.5%; IR (KBr,  $\text{cm}^{-1}$ ) 2938, 2797, 2717, 2630, 2511, 2460, 1678, 1589, 1500, 1473, 1365, 1315, 1265, 1118, 1039;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.65 (s, 1H), 9.39 (s, 1H), 7.15 (s, 1H), 6.87 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.51 (t,  $J=12$  Hz, 2H), 3.29 (dd,  $J=8, 17.6$  Hz, 1H), 2.86–2.93 (m, 2H), 2.66–2.71 (m, 2H), 1.93–2.05 (m, 4H), 1.72–1.84 (m, 2H), 1.41–1.52 (m, 1H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 206.7, 155.7, 149.6, 148.5, 129.0, 107.4, 104.4, 56.3, 56.1, 44.5, 44.0, 38.1, 33.6, 32.5, 29.7, 28.9, 28.7. MS (ESI)  $m/z$  290 [ $\text{M}^+ + 1$ ].

**2-Hydroxy-5,6-dimethoxy-2-(pyridine-4-yl-methyl)indan-1-one (7)** To a stirred solution of 5,6-dimethoxy-3-pyridine-4-yl-spiro(indene-2,2-oxiran)-1(3H)-one **4** (50 g, 0.168 mol) in 1 : 1 MeOH– $\text{CH}_2\text{Cl}_2$  (500 ml) was added 5% Pd/C (5.0 g, 10% by weight). The solution was hydrogenated at 0.5 kg/cm<sup>2</sup> hydrogen pressure at room temperature till the reaction was completed. The reaction mixture was worked-up as described above to afford **7** which was taken for next step without any further purification. Yield: 42.6 g (85%); HPLC 98.2%;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.41 (dd,  $J=1.36, 4.6$  Hz, 2H), 7.09–7.11 (m, 3H), 6.72 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.13 (d,  $J=17$  Hz, 1H), 2.94 (dd,  $J=13.6, 17$  Hz, 2H), 2.82 (d,  $J=13.6$  Hz, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 204.8, 156.8, 150.0, 149.3, 146.9, 145.3, 126.1, 125.6, 107.4, 104.9, 79.5, 56.3, 56.2, 43.5, 39.3; MS (ESI)  $m/z$  300 [ $\text{M}^+ + 1$ ].

**2-[(4-Pyridyl)methyl]-5,6-dimethoxyindanone (8)** Zinc powder (10 g, 0.153 mol) was added to a stirred solution of 2-hydroxy-5,6-dimethoxy-2-(pyridine-4-yl-methyl)indan-1-one **7** (50 g, 0.167 mol) in acetic acid (200 ml) at ambient temperature. The reaction mixture was heated to 50–55  $^{\circ}\text{C}$  and stirred for 2 h at the same temperature. After completion of the reaction (3 h, TLC), the reaction was cooled to room temperature, filtered and the filtrate was concentrated under reduced pressure to yield a residue. The residue was taken in ethyl acetate (100 ml) and water (100 ml) and the solution was basified (pH 7–7.5) with 50% NaOH solution. The organic layer was separated, washed with water and the solvent was evaporated under vacuum to yield **8**. Yield: 38.3 g (81%).

**2-[(4-Piperidinyl)methyl]-5,6-dimethoxyindanone (6)** To a solution of 2-[(4-pyridyl)methyl]-5,6-dimethoxyindan-1-one **8** (10 g, 35.30 mmol) in 1 : 1 methanol– $\text{CH}_2\text{Cl}_2$  (200 ml) was added sodium acetate (2.83 g, 34.51 mmol) and acetic acid (2.04 ml, 35.66 mmol). 5% Pd/C (1.0 g, 10% by weight) was then added and the reaction mixture was hydrogenated at 70–75  $^{\circ}\text{C}$  and 6–7 kg/cm<sup>2</sup> hydrogen pressure for 10 h. After completion of the reaction, the reaction mixture was filtered through a pad of celite, washed with 1 : 1 MeOH– $\text{CH}_2\text{Cl}_2$  (20 ml) and evaporated under reduced pressure. The residue was taken in ethyl acetate (30 ml) and water (25 ml) and the solution was basified (pH 9–9.5) with 50% NaOH solution. The organic layer was separated, washed with water, brine and dried over anhydrous sodium sulfate. The solution was filtered and evaporated under vacuum to yield **6**. Yield 7.14 g (70%). HPLC: 99.03%.

**2-[(4-(N-Benzylpiperidinyl)methyl]-5,6-dimethoxyindanone hydrochloride (1)** Benzyl chloride (1.92 g, 0.0156 mol), potassium carbonate (2.28 g, 0.0165 mol) and PEG-200 (80 mg, 2% by weight) were added to a clear biphasic solution of 2-[(4-piperidinyl)methyl]-5,6-dimethoxyindan-1-one **6** (4 g, 0.0138 mol) in 9 : 1 EtOAc– $\text{H}_2\text{O}$  (40 ml). The reaction mixture was heated to 50–55  $^{\circ}\text{C}$  and monitored on TLC. After completion of reaction (14 h), the solid was filtered and the filtrate was washed with water (4 ml). The EtOAc layer was separated, added water (8 ml) and acidified with conc. HCl till a pH 2. EtOAc layer was discarded and the acidic aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  16 ml). The  $\text{CH}_2\text{Cl}_2$  layer was separated, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and evaporated under vacuum to yield the crude salt as a residue. The residue was dissolved in methanol (20 ml) followed by the addition of isopropyl ether (40 ml) and stirred for a further 1 h. The precipitated solid was filtered and dried under vacuum to yield pure donepezil hydrochloride **1**. Yield 5.14 g (89%); HPLC: 99.963%; IR (KBr,  $\text{cm}^{-1}$ ) 3588, 3372, 2923, 2535, 1683, 1591, 1501, 1455, 1315, 1266, 1217, 1119, 1038, 700;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.44–7.63 (m, 3H), 7.12 (s, 1H), 6.85 (s, 1H), 4.12–4.19 (m, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.38–3.45 (m, 2H), 3.28 (dd,  $J=8, 17.6$  Hz, 1H), 2.63–2.67 (m, 4H), 1.82–2.08 (m, 6H), 1.49–1.51 (m, 1H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 206.9, 155.7, 149.5, 148.7, 131.5, 130.1, 129.2, 128.8, 128.1, 107.3, 104.3, 60.9, 56.2, 56.0, 52.4, 52.3, 44.1, 38.1, 34.0, 32.1, 29.4, 28.4; MS (ESI)  $m/z$  380 [ $\text{M}^+ + 1$ ].

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