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Protecting group-Free Concise Synthesis of (*RS*)/(*S*)-Lubeluzole

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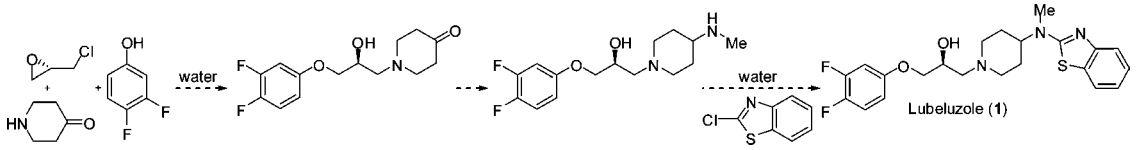
ABSTRACT

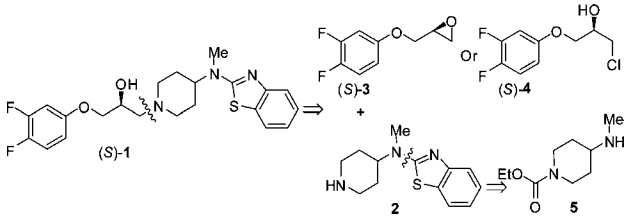


Three new, concise, and protecting group-free synthetic routes for (*RS*)- and (*S*)-lubeluzole are reported in higher (46−62%) overall yields compared to the reported procedures (6−35%). The key steps involve C−N bond formation via epoxide aminolysis and nucleophilic substitution of 2-chlorobenzothiazole with suitably designed precursor amines and are performed in aqueous medium. Water offers an advantage in promoting the reactions compared to organic solvents and its role is envisaged as hydrogen-bond mediated electrophile−nucleophile dual activation.

(*S*)-Lubeluzole (**1**) exhibits promising therapeutic effects for the treatment of acute ischemic stroke.[1] It is also associated with neuroprotective,[2] antinociceptive,[3] and antimyotonic[4] activities. The versatile therapeutic potential and multiple modes of action (e.g., NMDA antagonist, glutamate release and nitric oxide synthesis inhibitor, and calcium and sodium gated ion channel blocker) make it an attractive synthetic target.

However, there are only a few reports on the total synthesis of (*S*)-**1** based on a common synthetic strategy (Scheme 1)[5] that requires multistep (five to eight) operations involving the use of harmful/corrosive agents such as Br_2, HBr, DEAD, Et_3N (carcinogenic), organic solvents (diisopropyl ether, CCl_4, THF, DCM, DMF etc.), and costly [$Yb(OTf)_3$] and moisture-sensitive (NaH) catalyst/reagent at various stages of the synthesis that often require long reaction times (12−78 h) and afford poor to moderate overall yields (6−35%). We describe herein concise and sustainable processes for the synthesis of **1** in racemic (*RS*) and enantiopure (*S*) forms.

Scheme 1. Reported Synthetic Strategy for (*S*)-**1**



In devising alternative synthetic strategies, it was realized that the reported synthesis[5] involves undesirable[6] protection and deprotection steps to manipulate the reactivity of the two nitrogen centers of the 4-aminopiperidine component to incorporate it to the benzothiazole scaffold. Thus, it was planned to introduce the 4-aminopiperidine moiety using protecting group-free strategy through epoxide ring-opening by reaction of **6** with **3** in

(1) (a) Ashton, D.; Willems, R.; Wynants, J.; van Reempts, J.; Marrannes, R.; Clincke, G. *Brain Res.* **1997**, *745*, 210. (b) Grotta, J. *J. Neurol. Sci.* **1997**, *150*, S199. (c) De Ryck, M.; Keersmaekers, R.; Duytschaever, H.; Claes, C.; Clincke, G.; Janssen, M.; Van Reet, G. *J. Pharmacol Exp. Ther.* **1996**, *279*, 748.

(2) (a) Lesage, A. S.; Peeters, L.; Leysen, J. E. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 759. (b) Scheller, D.; Kolb, J.; Szathmary, S.; Zacharias, E.; De Ryck, M.; Van Reempts, J.; Clincke, G.; Tegtmeier, F. *J. Cereb. Blood Flow Metab* **1995**, *15*, S379.

(3) Blackburn-Munro, G.; Ibsen, N.; Erichsen, H. K. *Eur. J. Pharmacol.* **2002**, *445*, 231.

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(5) (a) Stokbroekx, R. A.; Luyckx, M. G. M.; Janssens, F. E. US patent 4861785, 1989. (b) Stokbroekx, R. A.; Grauwels, G. A. J. European Patent, 0501552 A1, 1992. (c) Liu, H. −L.; Hoff, B. H.; Berg, T. C.; Anthonsen, T. *Chirality* **2001**, *13*, 135. (d) Bruno, C.; Carocci, A.; Catalano, A.; Cavalluzzi, M. M.; Corbo, F.; Franchini, C.; Lentini, G.; Tortorella, V. *Chirality* **2006**, *18*, 227.

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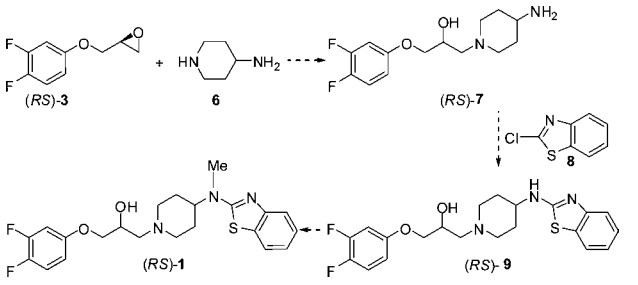
regioselective fashion with respect to the two nitrogen centers of **6** on the basis of the better reactivity of the secondary amine over the primary amine to obtain the required intermediate **7** which would be conveniently attached to the benzothiazole moiety to form **9**, the immediate precursor of **1** (Scheme 2).

Scheme 2. Design of Protecting Group-Free Synthetic Plan for **1**



In implementing the synthetic plan (Scheme 2), it was realized that although the aminolysis of epoxide is promoted by Lewis/Brönsted acid catalysts,[7] in view of the requirement of regioselectivity, a milder electrophilic activation of the epoxide ring is desirable and attention was focused toward the ability of water to accelerate the organic reaction through hydrogen-bond (HB) mediated electrophilic activation.[8]

Thus, the 1,2-epoxy-3-(3,4-difluorophenoxy)propane (**3**), prepared by a modified procedure,[7b] was treated with **6** in various reaction media (Table 1) in the absence of any Lewis/Brönsted acid catalyst to synthesize the 1-(4-aminopiperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (**7**). The best results were obtained in (demineralized) water at 10 °C (entry 4). The reaction at rt (~25−30 °C)[9] resulted in competitive formation of the side product **7a**[10] (entry 3) generated due to the reaction of **7** with **3**.

The poor results in organic solvents (entries 5−15) or under neat conditions (entries 1 and 2) highlighted the beneficial effects of water. The rate enhancement in water has been the subject of investigation and attributed to various factors such as enforced hydrophobic interactions,

Table 1. Influence of Solvent on Epoxide Ring-Opening of **3** with **6**[a]

entry	solvent	temp (°C)	yield[b] (%)
1	neat	rt	15[c]
2	neat	10	trace
3	water	rt	60[d]
4	water	10	90
5	DCM	10	trace
6	MeCN	10	trace
7	toluene	10	0
8	THF	10	0
9	1,4-dioxane	10	0
10	$MeNO_2$	10	0
11	MeOH	10	10
12	EtOH	10	11
13	^{i}PrOH	10	15
14	^{t}BuOH	10	18
15	TFE	10	40[e]

[a] Compound **3** (1 mmol) was treated with **6** (1 mmol, 1 equiv) in the indicated solvent (1 mL) (except for entries 1 and 2) for 2 h. [b] Isolated yield of **7**. [c] The side product **7a** was formed in 5% yield. [d] ESI-MS of the crude product revealed 17% conversion to **7a**.[10] [e] ESI-MS of the crude product revealed 20% conversion to **7a**.[10]

high cohesive energy density of water, and HB effect.[11] Although the HB effect appears to have gained popularity to account for "on water" catalysis,[8,12] the non-HB effect also has been invoked.[13] The excellent yields in water are attributed to its HB donor (HBD) ability in forming the supramolecular assembly (Figure 1). Hydrogen-bonded clusters involving the reactants and water molecule(s) have been postulated in various organic transformations,[8] water catalysis of radical-molecule gas-phase reactions,[14] and epoxide-opening cascades.[15] The poor results in alcohols could be due to their inferior HBD values.[16] However, the use of TFE[17] with a better HBD value compared to that of water led to competitive formation of the side product **7a** (entry 15, Table 1). The amount of water is also very important and 0.36 mL per mmol of **3** was found to be the optimal amount.[10] No improvement of the product yield was observed in using larger volume (1 mL) of water, but the yield decreased upon decreasing the amount of water.

(7) Selective examples: (a) Pujala, B.; Rana, S.; Chakraborti, A. K. *J. Org. Chem.* **2011**, *76*, 8768. (b) Shivani, Pujala, B.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 3713. (c) Chakraborti, A. K.; Kondaskar, A.; Rudrawar, S. *Tetrahedron* **2004**, *60*, 9085. (d) Chakraborti, A. K.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* **2004**, 3597. (e) Chakraborti, A. K.; Rudrawar, S.; Kondaskar, A. *Org. Biomol. Chem.* **2004**, *2*, 1277. (f) Chakraborti, A. K.; Kondaskar, A. *Tetrahedron Lett.* **2003**, *44*, 8315.

(8) (a) Kommi, D. N.; Jadhavar, P. S.; Kumar, D.; Chakraborti, A. K. *Green Chem.* **2013**10.1039/C3GC37004F. (b) Kommi, D. N.; Kumar, D.; Chakraborti, A. K. *Green Chem.* **2013**10.1039/C3GC36997H. (c) Kommi, D. N.; Kumar, D.; Bansal, R.; Chebolu, R.; Chakraborti, A. K. *Green Chem.* **2012**, *14*, 3329. (d) A Chankeshwara, S. V.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 3259. (e) Khatik, G. L.; Kumar, R.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 2433. (f) Chakraborti, A. K.; Rudrawar, S.; Jadhav, K. B.; Kaur, G.; Chankeshwara, S. V. *Green Chem.* **2007**, *9*, 1335.

(9) (a) Azizi, N.; Saidi, M. R. *Org. Lett.* **2005**, *7*, 3649. (b) Bonollo, S.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2006**, *8*, 960.

(10) For details (structure, IUPAC name, and mass spectrometry based identification and estimation of this side product), see the Supporting Information.

(11) Mellouli, S.; Bousekkine, L.; Theberge, A. B.; Huck, W. T. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7981.

(12) Zheng, Y.; Zhang, J. *ChemPhysChem* **2010**, *11*, 65.

(13) (a) Norcott, P.; Spielman, C.; Mcerlean, C. S. P. *Green Chem.* **2012**, *14*, 605. (b) Beattie, J. K.; Mcerlean, C. S. P.; Phippen, C. B. W. *Chem.—Eur. J.* **2010**, *16*, 8972. (c) Phippen, C. B. W.; Beattie, J. K.; Mcerlean, C. S. P. *Chem. Commun.* **2010**, *46*, 8234.

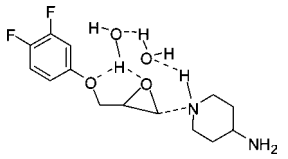
(14) Vohringer-Martinez, E.; Hansmann, B.; Hernandez, Francisco, J. S.; Troe, J.; Abel, B. *Science* **2007**, *315*, 497.

(15) Viotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189.

(16) The HBD values (α) of water, MeOH, EtOH, ^{i}PrOH, ^{t}BuOH, and TFE are 1.17, 0.93, 0.83, 0.76, 0.68, and 1.51, respectively. Kamlet, M. J.; Abboud, J.-M.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877.

(17) (a) Chebolu, R.; Kommi, D. N.; Kumar, D.; Bollineni, N.; Chakraborti, A. K. *J. Org. Chem.* **2012**, *77*, 10158. (b) Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2000**, *65*, 369.

Figure 1. Role of water for epoxide aminolysis of **3** with **6**.



The preparation of 1-(4-(benzothiazol-2-ylamino)piperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (**9**) would involve *N*-arylation of **7** with **8**. The reported procedures for *N*-arylation of amine with haloheterocycles[18] require costly catalysts/reagents, excess of amine, and volatile organic solvents. A base/metal-free protocol was planned taking advantage of the HB-driven "electrophile-nucleophile" dual activation ability of water.[8] However, the treatment of **7** with **8** in water at rt for 24 h did not produce any significant amount of **9** (Table 2, entry 1) but increase of the reaction temperature to 80 °C afforded **9** in 30% yield after 10 h (Table 2, entry 2) and in 91% yield at 110 °C after 10 h (Table 2, entry 3). Apart from the reaction temperature, the quantity of water used was also found to be a critical factor, and 0.5 mL per mmol of **3** is the optimal amount.[10] The yield did not increase in using larger volume (1 mL) of water but was reduced in decreasing the amount of water.[10]

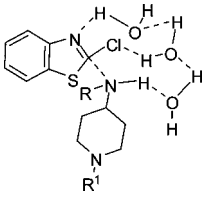
Table 2. Base/Metal-Free *N*-Arylation of **7** with **8**[a]

entry	solvent	temp[b] (°C)	time (h)	yield[c] (%)
1	water	rt	24	0
2	water	80	10	30
3	water	110	10	91
4	DCM	reflux	10	0
5	CH_3CN	reflux	10	trace
6	toluene	reflux	10	15
7	THF	reflux	10	trace
8	$MeNO_2$	reflux	10	12
9	DMF	110	10	17
10	1,4-dioxane	reflux	10	15
11	MeOH	reflux	10	14
12	EtOH	reflux	10	20
13	^{i}PrOH	reflux	10	18
14	^{t}BuOH	reflux	10	35
15	TFE	reflux	10	38
16	water	110/μw	0.5	88[d]
17	neat	110	10	20
18	neat	110/μw	0.5	52[d]

[a] Compound **7** (1 mmol) was treated with **8** (1 mmol, 1 equiv) in the solvent (2 mL) at different temperatures. [b] Oil bath. [c] Isolated yield of **9**. [d] The reaction was performed under microwave irradiation.

The advantage of using water is adequately reflected by the poor results in organic solvents (Table 2, entries 4–15) and may be rationalized due to its dual activation role wherein the HBD and HB acceptor (HBA) properties are of paramount importance and may be accounted for through the involvement of hydrogen-bonded reacting species (Figure 2) generated at the oil–water interface.[19] Thus, although TFE has better HBD value than that of water, the poor HBA[16] property of TFE makes it less effective in promoting the reaction.

Figure 2. Role of water in promoting *N*-arylation of **7** with **8**.

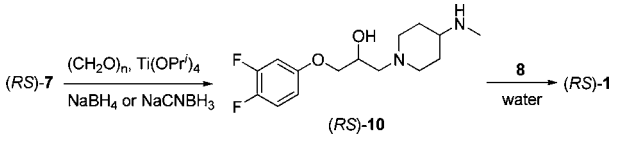


Further efforts were made to standardize the optimal reaction conditions for a shorter time (less than 10 h). As surfactants often enhance the organic reactions in aqueous medium,[20] the reaction of **7** with **8** was performed in the presence of 10 mol % of SDOSS/SDS. However, no improvement of the reaction time was observed.[17] In order to take advantage of the microwave irradiation to accelerate the reaction,[21] the reaction was performed under microwave irradiation for 30 min to obtain comparable yields (Table 2, entry 16).

In the final step, *N*-methylation of **9** was attempted using the different methylating agents under varied experimental conditions.[10] Competitive *O*-methylation took place, and the best result was obtained with MeI in the presence of NaH (1.3 equiv) in THF affording 70% yield of (*RS*)-**1** after 5 h at rt (overall yield 46.4%).

Alternatively, we planned to synthesize the *N*-methylated intermediate **10** that would undergo water-assisted *N*-arylation with **8** to form **1** (Scheme 3).

Scheme 3. New Protecting Group-Free Synthetic Strategy for **1**



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(19) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492.

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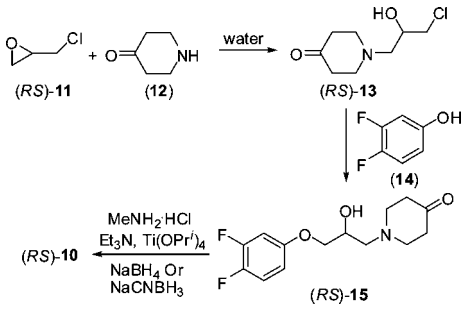
(21) Representative examples of microwave-assisted reactions: (a) Motiwala, H. F; Kumar, R.; Chakraborti, A. K. *Aust. J. Chem.* **2007**, *60*, 369. (b) Kumar, R.; Selvam, C.; Kaur, G.; Chakraborti, A K. *Synlett* **2005**, 1401. (c) Chakraborti, A. K.; Selvam, C.; Kaur, G.; Bhagat, S. *Synlett* **2004**, 851. (d) Chakraborti, A. K.; Kaur, G. *Tetrahedron* **1999**, *55*, 13265.

Various attempts of *N*-methylation of **7** using MeI, Me_2SO_4, DMC, and DMDC resulted in the formation of the *N*,*N*-dimethylated product **10a** or a mixture of **10** and **10a** in poor yields.[10] Finally, the reductive methylation[22] with paraformaldehyde and $NaBH_4$ or $NaCNBH_3$ in the presence of $Ti(OPr^i)_4$ afforded **10** in 75% yield. In the final step, water-assisted *N*-arylation of **10** with **8** was achieved to afford **1** in 65% yield under reflux in water for 12 h. The yield was improved to 84% under microwave irradiation in water at 120 °C for 30 min (overall yield 46%). The replacement of water by organic solvents did not afford any significant yield of **1**[10] and further demonstrated the beneficial effect of water for the *N*-arylation.

A more concise synthetic plan for **1** was made (Scheme 4) involving chemoselective epoxide aminolysis of epichlorohydrine (**11**) with 4-piperidone (**12**) to form the halohydrine **13** followed by alkylation with 3,4-difluorophenol (**14**) to (*RS*)-1-[3-(3,4-difluorophenoxy)-2-hydroxypropyl]piperidin-4-one (**15**) and subsequent $Ti(OPr^i)_4$-promoted reductive amination with methylammonium hydrochloride to afford **10**.

Scheme 4. More Concise Synthetic Strategy for **1**



To implement this synthetic plan, the reaction of **11** with **12** was performed in various solvents under catalyst-free conditions to form **13** and the best result was obtained in water (96% yield) at rt for 1 h.[10] The organic solvents gave **13** in poor yields or showed lack of chemoselectivity due to competitive formation of the *N*-alkylation side product through substitution of the chlorine and demonstrated the beneficial effect of water. The *O*-alkylation of **13** with **14** was tried under various conditions[10] and **15** was obtained in 95% in the presence of K_2CO_3 or Cs_2CO_3 (1.3 equiv) in water under heating at 80 °C for 5 h.

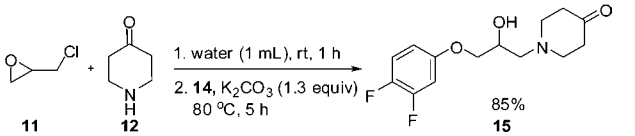
The intermediate **15** was obtained in 85% overall yield in a one-pot process following the tandem water-assisted epoxide aminolysis and *O*-alkylation (Scheme 5).

The $Ti(OPr^i)_4$-promoted reductive amination of **15** with methylammonium hydrochloride afforded **10** in 87% yield (Scheme 6).

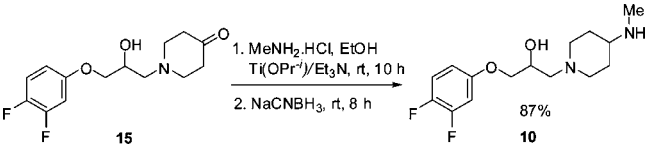
A more concise synthesis of (*S*)-**1** was achieved through the following sequence of reactions: (i) one-pot tandem water-assisted epoxide ring-opening of (*S*)-**11** with **12** and

(22) Neidigh, K. A.; Avery, M. A.; Williamson, J. S.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2527.

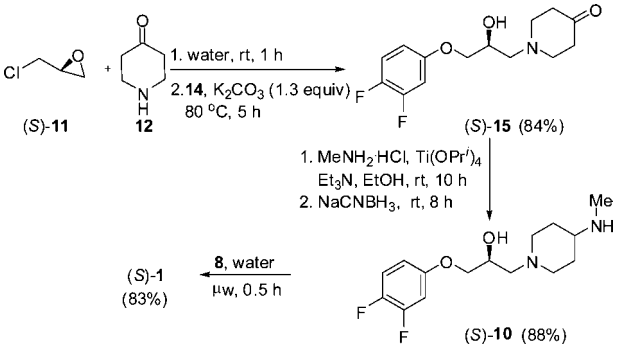
Scheme 5. One-Pot Synthesis of (*RS*)-**15** via Tandem Epoxide Aminolysis of **11** with **12** and *O*-Alkylation of **13** with **14**



Scheme 6. Synthesis of (*RS*)-**10** from (*RS*)-**15**



Scheme 7. More Concise Route to (*S*)-**1**



O-alkylation of the in situ formed (*S*)-**13** with **14** to form (*S*)-**15**, (ii) $Ti(OPr^i)_4$ promoted reductive amination of (*S*)-**15** to (*S*)-**10**, and (iii) water-assisted *N*-arylation of (*S*)-**10** with **8** under microwave irradiation to afford (*S*)-**1** in 62% overall yield (Scheme 7).

Three new and protecting group-free synthetic processes have been achieved for concise total synthesis of (*RS*)- and (*S*)-lubeluzole with higher (46−62%) overall yields. In the crucial stages of the synthesis, water provides beneficial effect in promoting the reactions through hydrogen-bond mediated electrophile-nucleophile dual activation in maintaining chemo- and regio-selectivities not achievable with organic solvents.

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Supporting Information Available. Experimental details, spectral data, and scanned spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.