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Unexpected Formation of Naphtyl 1,3-Diaminopropan-2-ol Derivative through Azetidinium Ion Intermediate

Minsoo Han[†,‡] and Hoh-Gyu Hahn[†,*]

[†]*Organic Chemistry Laboratory, Korea Institute of Science and Technology, Seoul 136-791, Korea.* [*]*E-mail: hghahn@kist.re.kr*
[‡]*Department of Chemistry, Korea University, Seoul 136-701, Korea*
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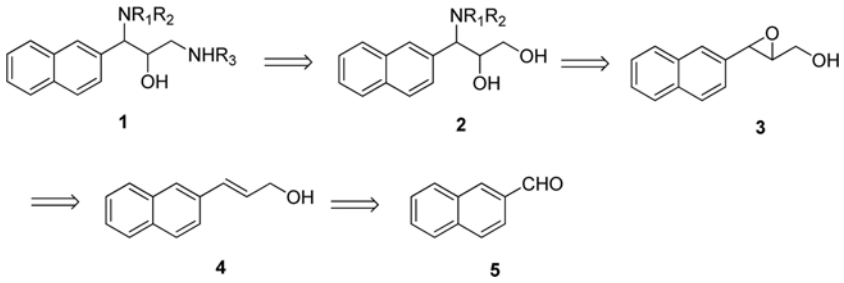
The cause of depression is commonly associated with a deficiency of monoamine neurotransmitters such as serotonin, norepinephrine and dopamine in the brain. Inhibition of monoamine reuptake has been an effective pharmacological treatment of various CNS disorders.[1] As a part of our continuing efforts to develop novel antidepressants for multiple therapeutic utilities, we designed diaminopropan-2-ol **1** through structure analysis and molecular modification and of currently marketed reuptake transporter based antidepressants.[2]

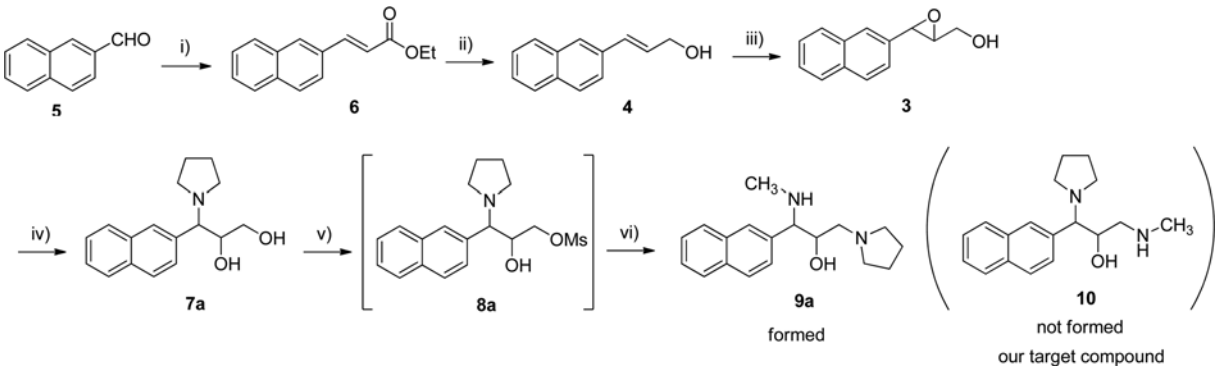
The retrosynthetic route of the designed diaminopropan-2-ol **1** is illustrated in Scheme 1. The diaminopropan-2-ol **1** would be synthesized from oxirane **3** *via* a diol intermediate **2** by nucleophilic attack of the amine (HNR_1R_2) to epoxide moiety. The oxirane **3** would be prepared from commercially available aldehyde **5** by the Wittig reaction, followed by epoxidation of the double bond of the resultant olefin **4**. The oxirane **3** is a key intermediate to accomplish the exploration of novel antidepressants. The epoxide is susceptible to the ring opening reaction with various nucleophiles, and the resulting hydroxy group would bear diverse substituents.

The overall synthetic route is summarized in Scheme 2. The Wittig reaction of aldehyde **5** with ethyl 2-(triphenylphosphoranylidene)acetate in methylene chloride at room temperature afford the ester **6** in quantitative yield. The reduction of the ester **6** by the treatment with diisobutylaluminium hydride (DABAL-H) in methylene chloride under a nitrogen atmosphere at –78 ºC provided the corresponding alcohol **4**. Epoxidation of the double bond in **4** by reaction with *m*-chloroperbenzoic acid (*m*-CPBA) in methylene chloride at room temperature proceeded smoothly, resulting in oxirane **3**.[3]

The initial attempt for the synthesis of our target compound



Scheme 1. Retrosynthetic analysis of the diaminopropan-2-ol **1**.



Scheme 2. Reagents and conditions: i) Ph_3PCHCO_2Et, CH_2Cl_2, rt, 93%. ii) DIBAL-H, CH_2Cl_2, –78 ºC, 78%. iii) *m*-CPBA, CH_2Cl_2, rt, 89%. iv) pyrrolidine, 110 ºC, 89%. v) MsCl, TEA, CH_2Cl_2, 0 ºC. vi) CH_3NH_2, CH_2Cl_2, rt, 53%.

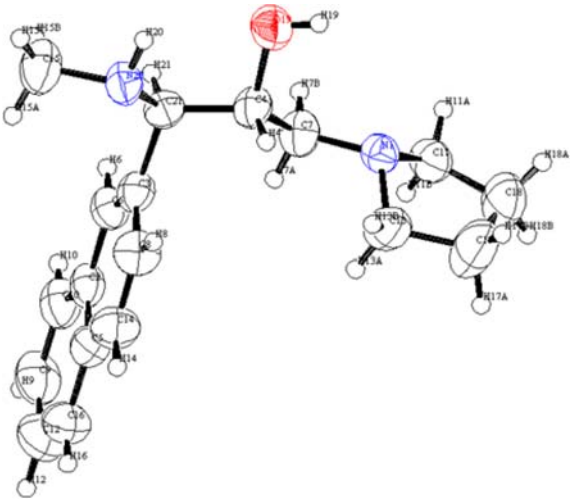


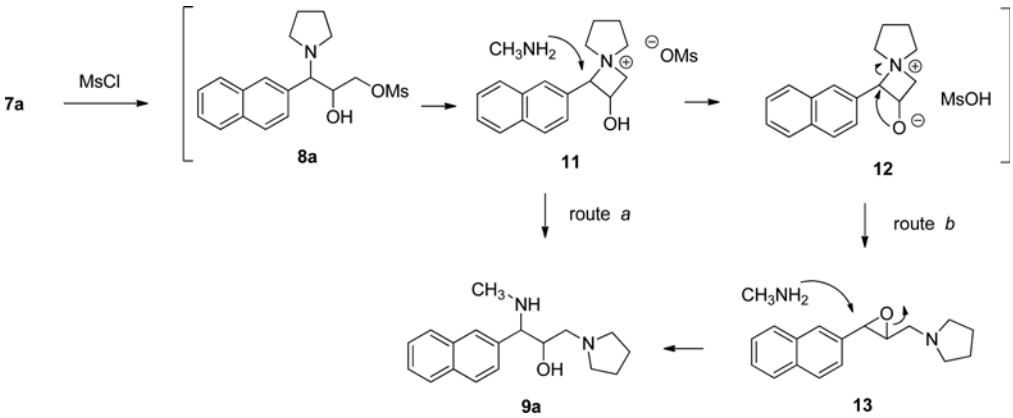
Figure 1. ORTEP plots of the prepared naphtyl 1,3-diamino-propan-2-ol **9a**.

involved the reaction of oxirane **3** with pyrrolidine. Regio-specific nucleophilic attack[2,4] of nitrogen on pyrrolidine of **3** afforded a diol **7a** yield of 89% (see supporting information of X-ray crystallographic analysis). The diol **7a** was treated with methanesulfonyl chloride (MsCl) in the presence of triethylamine in methylene chloride at 0 ºC, and was then reacted with excess methylamine dissolved in ethanol solution at room temperature. We expected that the nucleophilic conversion of nitrogen of the methylamine, to methylene carbon, neighboring the mesyl moiety would result in our target compound **10** through an intermediate **8a**. Unexpectedly, the resulting product **9a** was obtained with a 53% yield as a solid. From the ^{1}H and ^{13}C NMR spectroscopic analysis of the end product, it was not possible to structurally distinguish between **9a** and **10**. Hence, we elucidated the structure using X-ray crystallographic analysis (Figure 1), and surprisingly, it was clearly identified as **9a**.

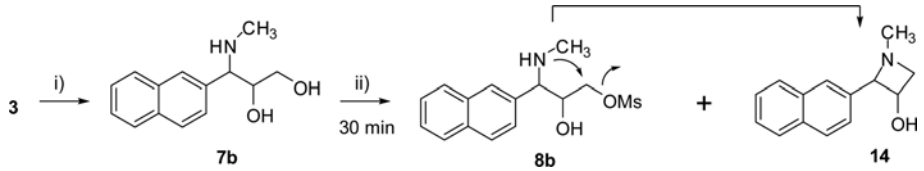
The proposed reaction mechanism for the formation of **9a** is illustrated in Scheme 3.

It is most likely that the intermediate **8a** was initially formed from the reaction of the diol **7a** with MsCl. Internal nucleophilic attack of nitrogen to methylene carbon neighboring the mesyl moiety would result in azetidium as an intermediate **11**.[5] The next reaction would then proceed through two possible routes, route *a* and route *b*, as depicted in Scheme 3. Nucleophilic attack of nitrogen of methylamine, to the carbon α, attached to nitrogen of the azetidine skeleton would result in **9a** (route *a*). In this case, the regioselectivity of the nucleophilic opening of azetidinium ions, in the presence of a naphtyl group substituted in carbon α, attached to nitrogen of the azetidine skeleton, would dictate the nucleophilic attack to occur at the carbon bearing the substituent.[6] Another possible process for the formation of **9a** was the route through the azetidinium ylide **12**, and following epoxide **13** (route *b*). The opening of the strained four-membered ring, by the internal addition of oxygen of the alkoxide to the neighboring carbon of the naphtyl group, would result in **13**. Apparently, a positively charged nitrogen atom drove the internal nucleophilic attack of oxygen, of the alkoxide in the azetidinium ylide intermediate **12**, of which the molecular entity is discussed below. Interestingly, the epoxide **13** was a transient intermediate in the reaction and hence, could not be isolated. However, we did successfully isolate **13**, with a 47% yield, as a solid, from the independent reaction of the addition of triethylamine instead of methylamine under the similar reaction conditions. Therefore, it was conceivable that route *b* is a more feasible pathway of the reaction. In the presence of an excess amount of methylamine, the epoxide **13** was converted to **9a** through the nucleophilic attack of nitrogen of methylamine, to carbon α of epoxide **13**.

Further proof that the proposed mechanism involving the azetidinium ion intermediate was correct, was provided by an isolation of an azetidine derivative **14** from the reaction of a methylamino diol **7b** with MsCl in the presence of an excess amount (2 molar equivalent) of triethylamine at room temperature (Scheme 4). The reaction was quenched at 30 min (approximately halfway) to give a 79:21 mixture of **8b** and **14**. The mesylate **8b** was a transient intermediate in the reaction, and transformed slowly to form **14**, which was identified using TLC. Careful isolation of the mixture through flash chromatography on silica gel provided mesylate **8b** as a fomy solid, and azetidine derivative **14** as a white solid. Their structures were confirmed by respective ^{1}H NMR spectra.

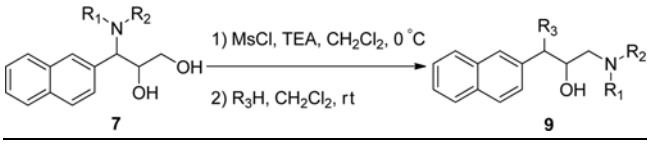


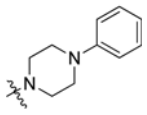
Scheme 3. Proposed reaction mechanism for the formation of **9a**.



Scheme 4. Reagents and conditions: i) CH_3NH_2, EtOH, 50 ºC; ii) MsCl, TEA, CH_2Cl_2, rt.

Table 1. Physical properties and isolated yields of the prepared naphtyl 1,3-diaminopropan-2-ol derivatives **9a-g**



No	Compound	NR_1R_2	R_3	mp (ºC)	Yields[a] (%)
1	**9a**		NH-CH_3	100	53
2	**9b**		NH-CH_3	109	44
3	**9c**		NH-CH_3	110	71
4	**9d**		NH-CH_3	105	55
5	**9e**		NH-CH_3	141	48
6	**9f**		S-C_6H_4(4-Cl)	133	42
7	**9g**		S-C_6H_4(4-Cl)	125	53

[a]Yields: isolated yields

Similar reactions, using 4-chlorobenzenethiol instead of methylamine, resulted in the corresponding thio analogues (see entries 6 and 7 in Table 1). We prepared several naphtyl 1,3-diaminopropan-2-ol analogues **9** through a similar manner, achieving moderate yields (42-71%) (Table 1).

In summary, 3-amino-1,2-diol derivatives **7** were converted to the corresponding diaminopropan-2-ol derivatives **9** by the reaction with MsCl in the presence of triethylamine followed by the treatment of either amine or thiol. We proposed azetdinium ion **11** or azetidinium ylide **12** as an intermediate in the reaction, and prepared **7** analogues by similar manner

Experimental Section

Synthesis of (*E*)-ethyl 3-(naphthalen-2-yl)acrylate (6). To a solution of 2-naphthaldehyde **5** (9.7 g, 6.2 mmol) in methylene chloride (120 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (25 g, 7.2 mmol), and the reaction mixture was stirred for 20 h at room temperature. The solvent was removed by evaporation and the resulting crude product was purified by flash chromatography (*n*-hexane: ethyl acetate = 2:1) on silica gel to obtain **6**.

Yield 93%, mp 69 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3H, J = 6.9 Hz, $CO_2CH_2\underline{CH_3}$), 4.28 (q, 2H, J = 6.9 Hz, $CO_2\underline{CH_2}CH_3$), 6.52 (d, 1H, J = 1.5 Hz, vinyl-H), 6.58 (d, 1H, J = 1.5 Hz, vinyl-H), 7.48-7.92 (m, 7H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.37, 60.53, 118.46, 123.52, 126.70, 127.20, 127.78, 128.56, 128.68, 129.87, 131.99, 133.31, 134.22, 144.63, 167.06.

Synthesis of (*E*)-3-(naphthalen-2-yl)prop-2-en-1-ol (4). To a solution of **6** (6.0 g, 26 mmol) in methylene chloride (170 mL) at –78 ºC cooled under dry ice/acetone cooling bath was added dropwise diisopropylaluminum hydride (1.0 M solution in methylene chloride, 94 mL, 93 mmol) under N_2 atmosphere. The reaction mixture was stirred at the same temperature for 3 h. $Na_2SO_4{\cdot}10H_2O$ (15 g, 47 mol) was added to destroy excess diisopropylaluminum hydride while stirring over 1 h at room temperature. The precipitates were removed by filtration through celite. The solvent was removed by evaporation to afford **4**.

Yield 78%, mp 94 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 1H, OH), 4.36 (dd, 2H, J = 5.7 Hz, CH_2), 6.48 (dt, 1H, J = 15.9 Hz, J = 5.7 Hz, vinyl-H) 6.76 (d, 1H, J = 15.9 Hz, vinyl-H) 7.42-7.80 (m, 7H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 63.81, 123.58, 125.94, 126.30, 126.48, 127.69, 128.01, 128.26, 128.88, 131326, 133.06, 133.60, 134.15.

Synthesis of (*E*)-(3-(naphthalen-2-yl)oxiran-2-yl)methanol (3). To a solution of **4** (1.0 g, 5.4 mmol) in methylene chloride (25 mL) at 0 ºC under N_2 atmosphere was added a solution of *m*-chloroperbenzoic acid (1.4 g, 6.2 mmol) dissolved in methylene chloride (20 mL). The reaction mixture was stirred at the same temperature for 3 h. To the resulting reaction mixture was added saturated aqueous $NaHCO_3$ solution while stirring. This mixture was stirred at room temperature for 1 h and then extracted with methylene chloride. The organic extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation to afford **3**.

Yield 89%, mp 107 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (br.s, 1H, OH), 3.38 (dt, 1H, J = 3.6 Hz, J = 2.1Hz, CH), 3.92 (dd, 1H, J = 12.9 Hz, J = 3.6 Hz, CH), 4.13 (dd, 1H, J = 12.6 Hz, J = 2.1 Hz, CH), 4.16 (d, 1H, J = 2.1 Hz, CH) 7.31-7.90 (m, 7H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 55.86, 61.29, 62.53, 122.89, 125.44, 126.20, 126.44, 127.79, 127.81, 128.45, 133.15, 133.36, 134.11.

Synthesis of the Naphtyl 3-aminopropane-1,2-diol (7) (General Procedure). A mixture of **3** (0.50 mmol) and

amine (0.50 mmol) was heated at 110 °C for 5 h and then cooled to room temperature. The reaction mixture was purified by flash chromatography on silica gel (methanol: chloroform = 4:1) to obtain the corresponding diol **7** (36-89% yields).

Typical Compound, For 3-(Naphthalen-2-yl)-3-(pyrrolidin-1-yl)propane-1,2-diol (7a): Yield 89%, mp 127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 4H, pyrrolidine-H), 2.61-2.73 (m, 4H, pyrrolidine-H), 3.01 (br.s, 1H, OH), 3.49 (dd, 1H, J = 10.8 Hz, J = 6.9 Hz, CH) 3.53 (dd, 1H, J = 10.8 Hz, J = 5.1 Hz, CH), 3.67 (d, 1H, J = 5.4 Hz, CH), 4.32 (m, 1H, CH), 7.55-7.93 (m, 7H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.04, 51.82, 65.86, 71.32, 72.13, 125.94, 126.08, 127.20, 127.61, 127.73, 127.94, 128.26, 133.05, 134.82.

Synthesis of the Naphtyl 1,3-diamino-propan-2-ol (9) (General Procedure). To a solution of **7** (1.4 mmol) in methylene chloride (10 mL) at 0 °C under N_2 atmosphere was added sequentially triethylamine (2.8 mmol) and methanesulfonyl chloride (1.7 mmol). The reaction mixture was stirred at the same temperature for 3 h. Methylamine (33 wt % solution in ethanol, 1 mL, 10 mmol) or 4-chlorobenzenethiol (1.8 mmol) was added to the mixture and then the reaction mixture was stirred for 12 h at room temperature. The resulting reaction mixture was washed with saturated aqueous $NaHCO_3$ solution and then dried over anhydrous $MgSO_4$. The solvent was removed by evaporation and the crude product was purified by flash chromatography on silica gel (methanol:chloroform = 4:1) to obtain **9** (42-71% yields).

Typical Compound, For 1-(Methylamino)-1-(naphthalen-2-yl)-3-(pyrrolidin-1-yl)propan-2-ol (9a): Yield 53%, mp 100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (m, 4H, pyrrolidine-H), 1.95 (dd, 1H, J = 12.3 Hz, J = 3.3 Hz, CH), 2.26 (s, 3H, NCH_3) 2.29-2.57 (m, 5H, pyrrolidine-H, CH), 3.48 (d, 1H, J = 8.1 Hz, CH), 3.82 (m, 1H, CH), 7.44-7.84 (m, 7H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.57, 34.29, 53.97, 58.89, 70.33, 72.05, 125.72, 125.79, 126.01, 127.43, 127.69, 127.82, 128.27, 133.18, 133.36, 137.92

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Supporting Information. The yields, melting point, ^{1}H NMR data for all the compounds and X-ray crystallographic data for **7a** and **9a**.

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