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Jae Wook Lee [a], Ho Jung Son [a], Jae Ho Lee [a], Yeon Eui Jung [a], Geal Jung Yoon [a] & Myung Hwan Park [a]
[a] R&D Center, Dae Woong Pharmaceutical Co., LTD., 223-23 Sangdaewondong, Sungnam, Kyunggi-Do, 462-120, Korea

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AN EFFICIENT SYNTHESIS OF 2,8-DIAZABICYCLO[4.3.0]-NONANE DERIVATIVES VIA INTRAMOLECULAR CYCLIZATION REACTION

Jae Wook Lee,* Ho Jung Son, Jae Ho Lee, Yeon Eui Jung,
Geal Jung Yoon, and Myung Hwan Park+

R&D Center, Dae Woong Pharmaceutical Co., LTD.,
223-23 Sangdaewondong, Sungnam, Kyunggi-Do 462-120, Korea

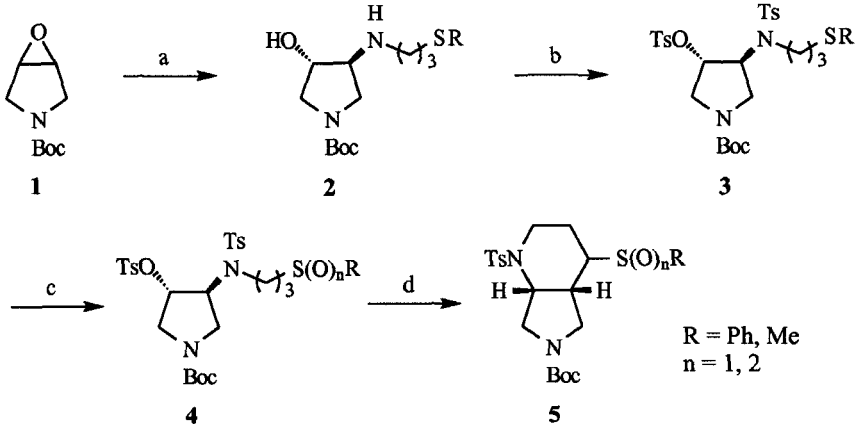
Abstract : Novel 5-functionalized-2,8-diazabicyclo[4.3.0]nonane derivatives **5** were synthesized from epoxide **1** through 4 steps in 46.7~52.6% yield.

Alkaloids that contain saturated five- and six-membered nitrogen heterocycles[1] and diazabicyclic compounds[2] in many natural or unnatural products have been popular synthetic targets due to the array of potent biological activities, the important component in many biologically active compounds, and the variety of structural challenges that are encounted in their construction. In connection with ongoing synthetic programme to develop new methods for novel pyrrolidine ring system and diazabicyclic compounds,[3] we wish to report in this paper a novel method for the construction of 2,8-diazabicyclo[4.3.0]nonane derivatives *via* intramolecular cyclization of sulfone and sulfoxide anions.

*To whom correspondence should be addressed
+Dedicated to Centennial Prof. Koji Nakanishi on the occasion of his 70th birthday

Our strategy, as summarized in the Scheme 1, involves the ring opening of epoxide using thioalkyl amines and intramolecular anionic cyclization of sulfone and sulfoxide anions.

Scheme 1[a]



[a]Reagents and Conditions : (a) $H_2N(CH_2)_3SR$, EtOH, reflux ; (b) TsCl, Pyridine; (c) MCPBA, $CHCl_3$; (d) *t*-BuOK, THF, -10°C.

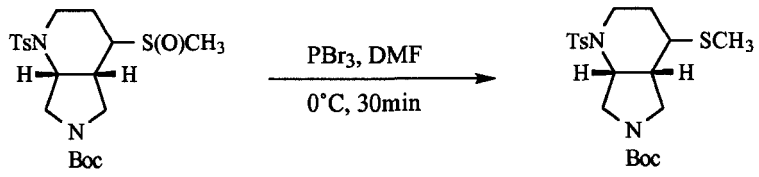
The reaction of epoxide **1** with 3-phenylthiopropylamine or 3-methylthiopropylamine[4] under refluxing ethanol gave β-amino alcohols **2** in good yield. Because we and other[5] have found that the tosylation of hydroxy group of N-Boc derivatives of β-amino alcohols give the oxazolidinones, we selected the tosyl group as a nitrogen protecting group of β-amino alcohols **2**. The reaction of β-amino alcohols **2** with excess *p*-toluenesulfonyl chloride in pyridine followed basic work up[6] provided the crystalline N,O-ditosylated product **3**. It proved to be advantageous to convert **2** to **3**. The oxidation of N,O-ditosylated sulfide **3** using

the appropriate equivalent of MCPBA gave the corresponding sulfoxide and sulfone **4** in excellent yield.

Table 1. Synthesis of diamines **2**, **3**, **4**, and **5**

compound	R	n	Yield(%)	mp(°C)
2a	Ph	-	82.3	84 ~ 86
2b	Me	-	83.5	56 ~ 60
3a	Ph	-	72	136 ~ 138
3b	Me	-	63.3	102 ~ 104
4a	Ph	1	92	146 ~ 148
4b	Ph	2	94.9	138 ~ 142
4c	Me	1	97.7	142 ~ 144
4d	Me	2	94.2	150 ~ 152
5a	Ph	1	94.7	oil
5b	Ph	2	93.6	93 ~ 95
5c	Me	1	93.3	120 ~ 122
5d	Me	2	93.9	139 ~ 141

Just as we considered, the cyclization reaction of N,O-ditosylated sulfoxide or sulfone **4** using *t*-BuOK at -10°C successfully proceeded to give the *cis* cyclized product **5**.[7] The deoxygenation of sulfoxide **5c** with tribromophosphine[8] in DMF at 0°C gave sulfide **6**[9] in 62.5% yield.



5c **6**

In conclusion, we have developed the method for the synthesis of novel 5-functionalized 2,8-diazabicyclo[4.3.0]nonane derivatives through 4 steps in 46.7~52.6% yield. The scope and utility of these reactions are under investigation. Also, the application to biologically active compound is investigated and will be reported in the future.

References and Notes

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4. 3-Thiosubstituted propylamines were prepared by the reaction of 3-chloropropyl amine and the appropriate thiols in water in the presence of NaOH.

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6. A typical procedure is as follows : To a stirred solution of **2b** (2.3 g, 7.92 mmol) in 35ml of pyridine was added TsCl (4.5 g, 23.6 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1h. Pyridine was evaporated, treated with EtOAc (100 ml), and washed with H_2O (50 ml × 2). The EtOAc layer was concentrated, treated with THF (120 ml), and added slowly 1N NaOH (80 ml). The mixture was stirred for 30min, extracted with EtOAc, and washed with brine. The organic layer was dried and concentrated. The residue was crystallized from methanol to give 3 g (63.3 %) of **3b**.

3a : mp 136~138°C ; ^{1}HNMR ($CDCl_3$) δ 1.42(s, 9H), 1.60~1.96(m, 2H), 2.41(s, 3H), 2.44(s, 3H), 2.79(t, J=6.6Hz, 2H), 2.99~3.43(m, 4H), 3.52~3.83(m, 2H), 4.21~4.50(m, 1H), 4.78~5.04(m, 1H), 7.20~7.36(m, 9H), 7.61~7.76(m, 4H).

3b : mp 102~104°C ; ^{1}HNMR ($CDCl_3$) δ 1.42(s, 9H), 1.61~1.95(m, 2H), 2.06(s, 3H), 2.38(t, J=6.5Hz, 2H), 2.43(s, 3H), 2.46(s, 3H), 2.91~3.32(m, 4H), 3.45~3.82(m, 2H), 4.26~4.55(m, 1H), 4.87~5.12(m, 1H), 7.24~7.40(m, 4H), 7.65~7.80(m, 4H).

7. A typical procedure is as follows : To a stirred solution of **4c** (2.51 g, 4.08 mmol) in 40 ml of THF was added dropwise 4.94ml (4.5 mmol) of *t*-BuOK (1M in THF) at -10°C. After stirring for 30min at -10°C, the reaction mixture was quenched with saturated ammonium chloride solution(50 ml) and extracted with chloroform. The organic layer was washed with brine, dried, and concentrated. The residue was crystallized from ethyl ether : n-hexane

system to give 1.68 g (93.3 %) of **5c**.

5a : ^{1}HNMR ($CDCl_3$) δ 1.48(s, 9H), 1.71~2.27(m, 2H), 2.42(s, 3H), 2.59~3.23(m, 2H), 3.31~3.64(m, 2H), 4.06(m, 4H), 5.20~5.33(m, 1H), 7.29(d, J=8.3Hz, 2H), 7.43~7.67(m, 7H).

5b : mp 93~95°C ; ^{1}HNMR ($CDCl_3$) δ 1.48(s, 9H), 1.87~2.22(m, 2H), 2.42(s, 3H), 3.06~3.30(m, 2H), 3.52(t, J=6.6Hz, 2H), 4.06(m, 4H), 5.22~5.37(m, 1H), 7.29(d, J=8.3Hz, 2H), 7.56~7.78(m, 5H), 7.87~7.99(m, 2H).

5c : mp 120~122°C ; ^{1}HNMR ($CDCl_3$) δ 1.47(s, 9H), 1.93~2.25(m, 2H), 2.43(s, 3H), 2.60(s, 3H), 2.70~2.97(m, 2H), 3.50~3.67(m, 2H), 4.12(m, 4H), 5.31~5.41(m, 1H), 7.31(d, J=8.4Hz, 2H), 7.64(d, J=8.4Hz, 2H).

5d : mp 139~141°C ; ^{1}HNMR ($CDCl_3$) δ 1.47(s, 9H), 1.97~2.33(m, 2H), 2.44(s, 3H), 2.96(s, 3H), 3.07~3.26(m, 2H), 3.58(t, J=6.3Hz, 2H), 4.13(m, 4H), 5.33~5.43(m, 1H), 7.32(d, J=8.4Hz, 2H), 7.64(d, J=8.4Hz, 2H).

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9. **6** : ^{1}HNMR ($CDCl_3$) δ 1.47(s, 9H), 1.69~1.96(m, 2H), 2.09(s, 3H), 2.43(s, 3H), 2.32~2.63(m, 2H), 3.51(t, J=6.6Hz, 2H), 4.11(m, 4H), 5.29~5.41(m, 1H), 7.30(d, J=8.4Hz, 2H), 7.66(d, J=8.4Hz, 2H) ; Mass(70 ev), m/z(%) 57(40.7), 171(58.7), 215(100), 426(1.5, M^+).

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