4-Bromobenzyl Group As a Linker for Chemical Probes

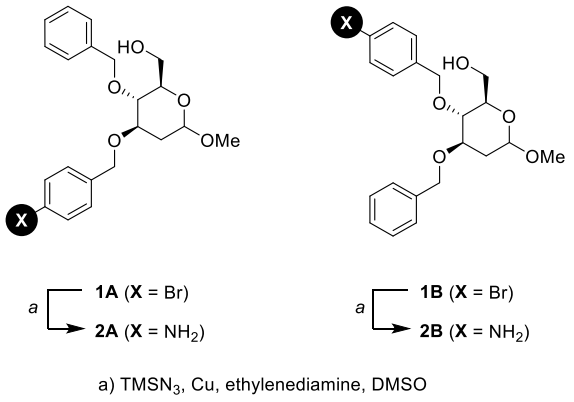
(Graduate School of Nanobioscience, Yokohama City University)

○IWASE, Akira; OUJI, Hoshiyuri; ISHIKAWA, Yuichi; OIKAWA, Masato

Keywords: Bioactive Small Molecule; Chemical Probe; 4-Bromobenzyl Ether; Amination; Copper

Chemical probes of bioactive small molecule are used for studying biological function of target biomolecules. In this study, we planned to develop a methodology wherein benzyl group is used as a linker between bioactive small molecule and various labeling groups. We anticipated that the benzyl linker would be derived from 4–bromobenzyl group *pro re nata*. Although such aryl bromo group can be generally used for cross coupling reactions, we, in this study, decided to explore alternative strategy for chemoselective derivatization wherein the bromo group is first transformed into an amino group which is a highly reactive functionality for introduction of labeling groups.

The 4–bromobenzyl ether can be generally synthesized by etherification of hydroxy group with 4–bromobenzyl bromide. 1,3–Diol can be also monoetherified selectively to give 4–bromobenzyl ether by 4–bromobenzylidenation followed by reduction with DIBAL–H. We have prepared two 4–bromobenzyl ethers **1A** and **1B** from tri–*O*–acetyl–D–glucal over 5 steps each, and explored conditions for amination. After several experiments, copper-mediated reductive amination using $TMSN_3$[1] was found to be the most practical to give rise to amines **2A** and **2B** in high yield. The reaction is highly chemoselective and other functionalities such as hydroxy and acetal groups are not affected. Amines **2A** and **2B** are expected as precursor for chemical probes of γ–secretase inhibitor.[2] Our synthetic study toward this goal will be presented.



1) Maejima, T.; Shimoda, Y.; Nozaki, K.; Mori, S.; Sawama, Y.; Monguchi, Y.; Sajiki, H. *Tetrahedron* **2012**, *68*, 1712.
2) Takahashi, Y.; Fuwa, H.; Kaneko, A.; Sasaki, M.; Yokoshima, S.; Koizumi, H.; Takebe, T.; Kan, T.; Iwatsubo, T.; Tomita, T.; Natsugari, H.; Fukuyama, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3813.