Nucleophilic substitution of one of two catecholic hydroxyl groups with fluorine and its application to the synthesis of novel fluorinated flavonoids

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Introduction of fluorine into candidates of pharmaceuticals and agrochemicals often dramatically improves their chemical and biological profiles such as stability, lipophilicity, and bioavailability. Due to electrochemical similarity of fluorine to oxygen, the substitution of a hydroxyl group with fluorine is widely used in the drug discovery process. On the other hand, ^{18}F-labeled organic compounds are used as in vivo probes for the noninvasive and real time imaging by positron-emission tomography (PET). Various methods have been developed so far to convert aliphatic hydroxyl groups into fluorine using nucleophilic fluorine sources; however, a similar conversion of aromatic hydroxyl groups is limited.

Recently, I have developed a new method for the nucleophilic substitution of catecholic hydroxyl groups with fluorine. The reaction proceeds under mild conditions without using transition metals, and one of two hydroxyl groups of the catechols is selectively converted into fluorine. Catechin, a kind of flavonoids, possesses various beneficial pharmacological properties. Because, it has many phenolic hydroxyl groups, a chemoselective protection of the hydroxyl groups was needed when I applied the above-mentioned fluorination method to catechin. After many unfruitful trials, I finally accomplished the selective protection of its A- and C-ring hydroxyl groups, the fluorination of the B-ring catechol, and the deprotection without any decomposition of the sensitive catechin framework to give unnatural fluorinated catechin derivatives.

In conclusion, I developed a selective protection method of polyphenolic compounds and thereby synthesized novel fluorinated catechin derivatives. Mono-fluorination of two catecholic hydroxyl groups of flavonoids is expected to increase their lipophilicity and stability, and to acquire novel bioactivities. The developed method will also be applicable to the ^{18}F-installation of bioactive compounds, which allows us to monitor their biodistribution by PET. Thus, it will provide a new effective protocol in the drug discovery from naturally-derived flavonoids.