

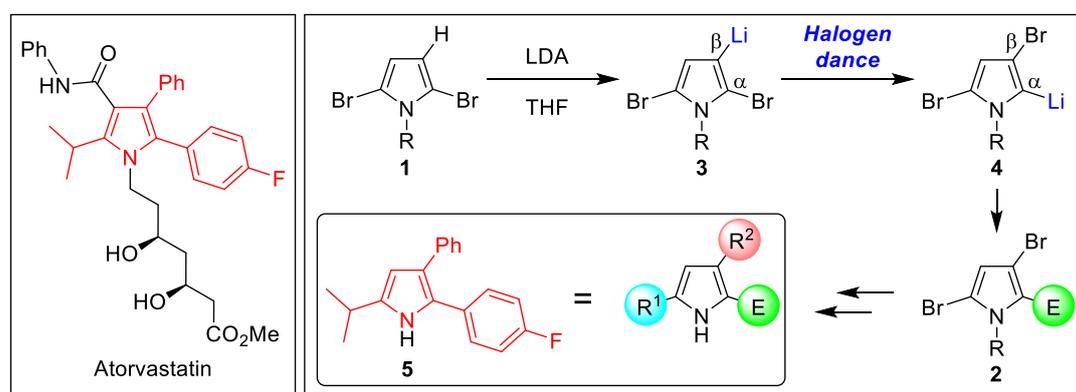
A Formal Synthesis of Atorvastatin through Halogen Dance of Pyrrole

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The pyrrole substructure is involved in pharmaceuticals such as atorvastatin, tolmetin, and ketorolac. We have recently achieved a total synthesis of lamellarins using a halogen dance reaction of an α,β -dibromopyrrole.¹ Herein we developed the halogen dance of α,α' -dibromopyrrole to expand the scope of this reaction and applied the method to a formal synthesis of atorvastatin.

In a preliminary experiment 2,5-dibromopyrrole **1** bearing an ethyl group on nitrogen underwent halogen dance to provide the corresponding product **2** in low yield after electrophilic trapping. The reaction was sluggish compared to that of 2,5-dibromothiophene.² We next investigated the effects of a substituent on nitrogen to promote the formation of β -pyrrolyllithium **3** and halogen dance to generate α -pyrrolyllithium **4**. Electron-withdrawing groups such as a Ts or a Boc group resulted in better yields of the products. After extensive optimization, we found a sulfonyl group, which have been rarely used as a protecting group of pyrroles, facilitated the halogen dance. The two bromo groups in dibromopyrrole **2** possessed distinct reactivities, which allowed the stepwise transformation to give a trisubstituted pyrrole. The synthetic utility of the newly established method was demonstrated by a synthesis of the pyrrole subunit of atorvastatin **5**. The detail of the substituent effects on halogen dance will be discussed.



- 1) Morikawa, D.; Morii, K.; Yasuda, Y.; Mori, A.; Okano, K. *J. Org. Chem.* **2020**, 85, 8603-8617.
- 2) Okano, K.; Sunahara, K.; Yamane, Y.; Hayashi, Y.; Mori, A. *Chem. Eur. J.* **2016**, 22, 16450-16454.