# An Expeditious Synthesis of Lasofoxifene and Nafoxidine via the Novel Three-component Coupling Reaction

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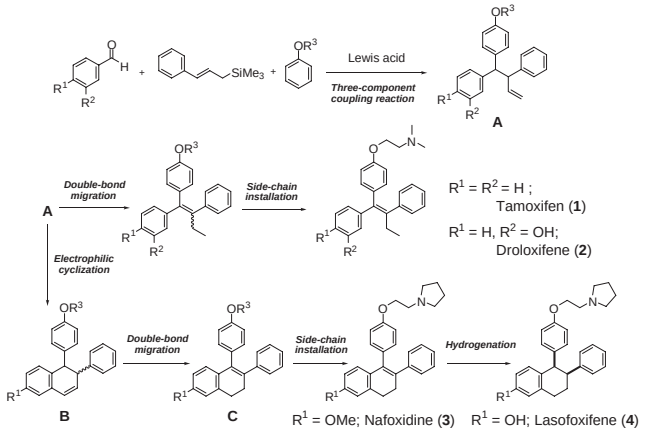
The simple and efficient synthesis of lasofoxifene (**4**), a possible candidate for alleviating osteoporosis, via the novel three-component coupling reaction among 4-pivaloyloxybenzaldehyde (**5**), cinnamyltrimethylsilane (**6**), and anisole in the presence of $HfCl_4$ is illustrated. The successive cationic cyclization of the coupling product, olefin formation, and migration of the double-bond are performed to afford the common synthetic intermediate of lasofoxifene (**4**) and nafoxidine (**3**) via a very concise procedure.

We have recently established a novel three-component coupling reaction among aromatic aldehydes, allylsilanes, and aromatic nucleophiles in the presence of a Lewis acid catalyst.[1] This sequential one-pot allylation and the Friedel–Crafts type alkylation affords 3,4,4-trisubstituted butene (**A**) via the intermediate homoallyl silyl ether. Furthermore, it has been demonstrated that the coupling reaction could be effectively used for the preparation of SERMs (selective estrogen receptor modulators), such as tamoxifen (**1**), idoxifene, and droloxifene (**2**) (Scheme 1).[2]

It is assumed that the structure of the 3,4,4-triarylbutene intermediate **A** generated from the three-component coupling reaction would also be a suitable molecule as a precursor of lasofoxifene (**4**), a hopeful candidate for the treatment of osteoporosis,[3] and nafoxidine (**3**);[4] that is, the terminal olefin part in **A** could react with one of the two aromatic rings at the 4-position by an appropriate electrophilic cyclization to produce a dihydronaphthalene structure **B**. The successive base-induced double-bond migration of **B** and installing the side-chain onto **C** might produce **3**. Since it is already known that **3** could be easily converted to **4** by hydrogenation of the double-bond as shown in the above instances,[3] establishment of the method for the preparation of **3** will be equivalent to the completion of the formal total synthesis of **4**. According to this synthetic plan, we started to develop a novel method for the preparation of **3** and **4** through the three-component coupling reaction as part of our continuous efforts to apply this novel synthetic methodology to afford new types of SERMs.



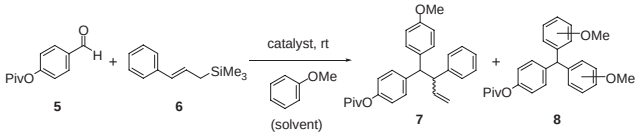

**Scheme 1.** Newly developed synthetic pathway of tamoxifen derivatives via the novel three-component coupling reaction.

We first investigated the three-component coupling reaction among 4-pivaloyloxybenzaldehyde (**5**), cinnamyltrimethylsilane (**6**), and anisole under several reaction conditions to optimize the suitable ratio of catalysts to substrates based on the former results reported for the synthesis of tamoxifen (**1**) and droloxifene (**2**).[2] These results are summarized in Table 1.

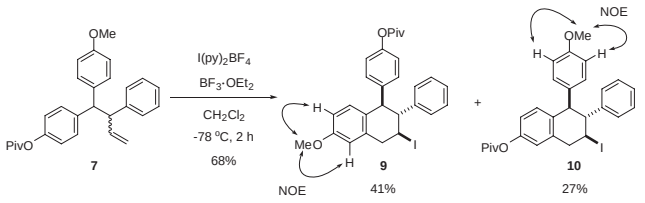
The three-component coupling reaction smoothly proceeded at room temperature in the presence of $HfCl_4$ without the co-catalyst to give the coupling product **7** in high yield using a two-fold amount of **6** to **5** (Entries 4–6). On the other hand, the combined use of $HfCl_4$ and TMSOTf as a co-catalyst, preferentially increased the yields of triarylmethanes **8**, which were produced from a 1 molar amount of **5** and 2 molar amounts of anisole (Entries 1–3); therefore, aldehyde **5** was apparently over-activated by the addition of the co-catalyst. As shown in Entry 6, the coupling reaction with high concentrations of the reactants decreased the yield of the desired compound because the concentration of anisole simultaneously decreased in the reaction conditions.

All the coupling reactions listed in Table 1 afforded a ca. 2:3 mixture of the syn and anti diastereomers of the 3,4,4-trisubstituted butenes **7**. The ratio of the diastereomers was determined by $^1$H NMR and HPLC analyses. Because these compounds could not be separated at this stage, a diastereomeric mixture of the coupling products was used for the next carbocyclization

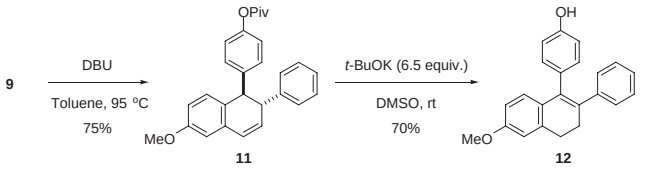
**Table 1.** The three-component coupling reaction among 4-pivaloyloxybenzaldehyde (**5**), cinnamyltrimethylsilane (**6**), and anisole using $HfCl_4$/TMSOTf as the catalyst




| Entry | Catalyst/equiv. | | Molar ratio of **5**/**6** | Time /h | Conc. /M | Yield of **7** /% |
|---|---|---|---|---|---|---|
| | $HfCl_4$ | TMSOTf | | | | |
| 1 | 1.0 | 0.50 | 1/1.2 | 20 | 0.1 | complex mixture |
| 2 | 1.0 | 0.25 | 1/1.2 | 20 | 0.1 | 34 |
| 3 | 1.0 | 0 | 1/1.2 | 20 | 0.1 | 43 |
| 4 | 1.0 | 0 | 1/2 | 20 | 0.1 | 63 |
| 5 | 1.0 | 0 | 1/2 | 2 | 0.3 | 78 |
| 6 | 1.0 | 0 | 1/2 | 20 | 0.8 | 54 |




**Scheme 2.** Iodine-induced cationic carbocyclization.



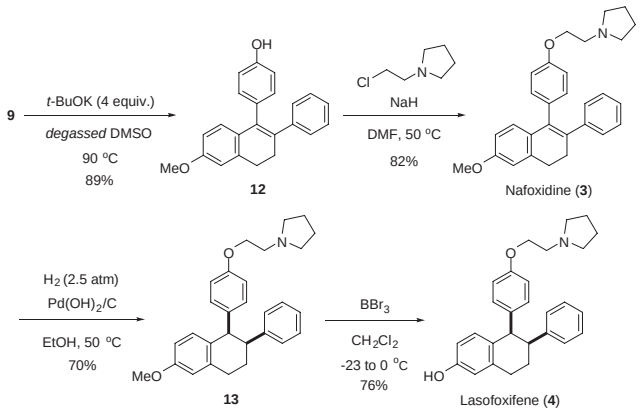

**Scheme 3.** Formation of dihydronaphthalene derivatives.

step. It was anticipated that both compounds might be converted into the corresponding dihydronaphthalene derivatives by the double-bond migration in the later step.

Some electrophilic cyclization reactions were then carried out to transform **7** into the corresponding dihydronaphthalenes. First, no desirable cyclization occurred when the $NBS/BF_3 \cdot OEt_2$-mediated reaction was applied to the electrophilic cyclization of **7**. Therefore, we tried the iodine-induced cationic cyclization of **7** using bis(pyridine)iodonium tetrafluoroborate ($I(py)_2BF_4$), which was developed by Barluenga et al.[5] Fortunately, the desired cyclization smoothly took place in the presence of stoichiometric amounts of $I(py)_2BF_4/BF_3 \cdot OEt_2$, and two carbocyclized products **9** and **10** were predominantly obtained in good yields as shown in Scheme 2. It is noteworthy that the cyclized compounds **9** and **10** have all trans configurations and the reaction exclusively afforded these positional isomers **9** and **10** in 41 and 27% yields, respectively. The ratio of yields of **9** to **10** might correspond to the diastereomeric ratio of the triarylbutene **7** generated by the coupling reaction. The stereochemistry of both cyclized compounds was determined by the coupling constants of the $^1H$ NMR spectroscopy, and the positions of the methoxy and pivaloyloxy groups in **9** and **10** have been deduced by the observation of enhanced NOEs of these compounds as depicted in Scheme 2.

Since **9** has a suitable structure to produce lasofoxifene (**4**) and nafoxidine (**3**), the dehydroiodination of **9** was then attempted using DBU, and the desired dihydronaphthalene **11** was exclusively obtained in good yield (Scheme 3). According to our previous study, the double-bond migration of **11** was successfully attained using *t*-BuOK in DMSO to produce a synthetic intermediate **12** which corresponds to the common framework for preparing **3** and **4**.

During the first attempt for the direct conversion of **9** to the common intermediate **12** using *t*-BuOK in usually dried DMSO, uncharacterized over-aromatized compounds were unfortunately synthesized; however, this conversion was finally and successfully attained using *t*-BuOK in *degassed* DMSO by freeze-and-thaw cycles as shown in Scheme 4. The total syntheses of lasofoxifene (**4**) and nafoxidine (**3**) were finally accomplished via the successive introduction of the 2-pyrroridinoethyl moiety onto the hydroxy group of **12** by the conventional method according to the report of Kapil et al.,[6] followed by hydrogenation and cleavage of the protective group in the methoxy substituent




**Scheme 4.** Synthesis of lasofoxifene (**4**) and nafoxidine (**3**) via direct conversion of iodide intermediate **9** into the common precursor **12**.

in **13** by $BBr_3$ (Scheme 4).

Thus, we developed a novel method to produce lasofoxifene (**4**) and nafoxidine (**3**) using the three-component coupling reaction among 4-pivaloyloxybenzaldehyde (**5**), cinnamyltrimethylsilane (**6**), and anisole in the presence of $HfCl_4$. The intermediary 3,4,4-triarylbutene derivative **7** was effectively transformed into **3** as a precursor of **4** via the successive three-step transformations; namely, cationic cyclization, sequential double-bond formation/migration, and side-chain installation.

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The authors dedicate this paper to Professor Teruaki Mukaiyama on the celebration of his 80th birthday.

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