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# Acid Promoted-Cascade Cyclization to Produce 2-(4'-Alkoxyaryl)-3,4-Fused Tricyclic Dihydrobenzopyrans via a Vinylidene *para*-Quinone Methide Intermediate

Dongil Choi,[a] Naoki Shiga,[a] Robert Franzén,[b] and Tetsuhiro Nemoto*[a,c]

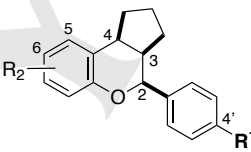
**Abstract:** We developed a novel method for synthesizing 2-(4-hydroxyaryl)-3,4-fused tricyclic dihydrobenzopyrans with 2,3-*syn* and 3,4-*syn* motif based on the acid-promoted cascade cyclization via vinylidene *para*-quinone methide intermediates. Using easily prepared linear substrates, TFA-promoted cascade cyclization proceeded in the presence of triethylsilane, affording a series of five to seven-membered ring-fused dihydrobenzopyran derivatives in moderate to excellent yield in a highly diastereoselective manner. The developed method provided new access to potent and selective ERβ agonists.

## Introduction

Flavan (i.e., 2-aryl dihydrobenzopyran) skeletons are ubiquitous structures in various bioactive natural products. In particular, highly oxygenated flavans typified by catechin and related compounds exhibit a wide variety of bioactivities, such as anticancer activity and antioxidant activity, and are recognized as useful scaffolds for drug discovery studies. Therefore, the development of an efficient and flexible synthetic method to produce functionalized flavan derivatives is an attractive research topic in the field of synthetic organic and medicinal chemistry.[1, 2]

In 2006, researchers at Eli Lilly and Company reported that 3,4-cyclopentane-fused 2-(4-hydroxyaryl)-dihydrobenzopyrans exhibit potent estrogen receptor (ER) agonist activity (Figure 1).[3] Structure activity relationship studies revealed that phenol groups on the aromatic rings are important for the binding affinity, as well as the selectivity of ER subtypes. Removing the phenolic hydroxyl group at the 4'-position dramatically affects the affinity for ERs, indicating the importance of this phenol in the ER pharmacophore.

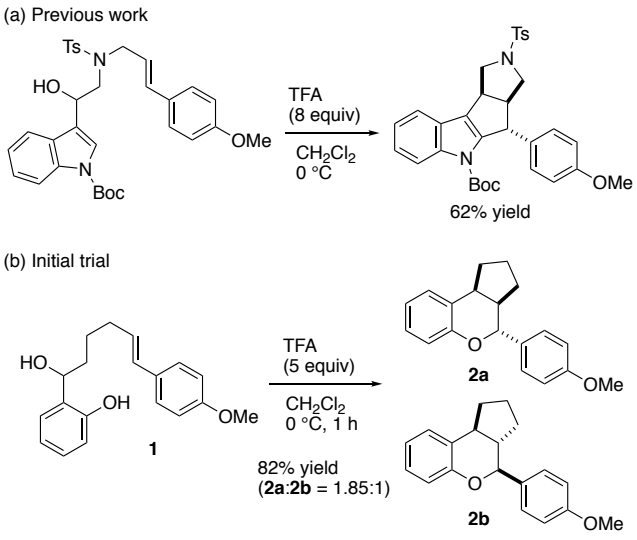
As part of our ongoing studies aimed at developing acid-promoted cascade reactions based on a phenol dearomatization process,[4,5] we recently reported the synthesis of fused-polycyclic indole derivatives via an intramolecular ene-type addition of the double bond of *para*-alkoxystyrene to 3-alkylidene indolenium cations followed by Friedel-Crafts-type addition of the indole to the *para*-quinone methide intermediate (Scheme 1a).[4b,6] The reaction sequence of this process is potentially applicable to the construction of the core structure of 2-aryl-3,4-fused tricyclic dihydrobenzopyrans, leading us to examine an acid-promoted cascade cyclization using **1** as the substrate. The reaction gave a mixture of diastereomers **2a** and **2b** in 82% yield and compound **2a** bearing a 2,3-*anti* and 3,4-*syn* structure was obtained as a major isomer (**2a**:**2b** = 1.85:1) (Scheme 1b). In Eli Lilly's synthesis, reductive cyclization of a 1,2-*cis*-disubstituted cyclopentane derivative was used to construct three contiguous stereocenters. We thus hypothesized that diastereoselective construction of the 2,3-*syn* and 3,4-*syn* motif could be realized by designing a cascade reaction using a vinylidene *para*-quinone methide intermediate, which have been rarely explored in organic synthesis.[7] Herein we report our results.



2-Aryl-3,4-fused tricyclic dihydrobenzopyrans

| R¹ | R² | Binding Affinity | |
|---|---|---|---|
| | | ERβ (nM) | ERα (nM) |
| **H** | 6-OH | 51 ± 11 | 267 ± 112 |
| **OH** | H | 22.1 ± 7.3 | 40 ± 27 |
| **OH** | 6-OH | 0.47 | 4.34 |
| **OH** | 5-OH | 0.66 | 0.35 |

**Figure 1.** 2-(4-Hydroxyaryl)-3,4-Fused Tricyclic Dihydrobenzopyrans with an Estrogen Receptor Agonist Activity.




**Scheme 1.** Initial Trial based on the Previous Work.

## Results and Discussion

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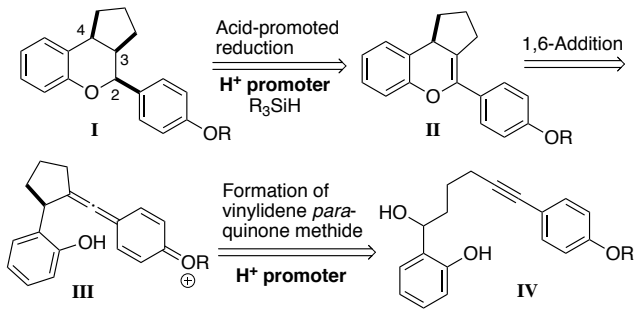
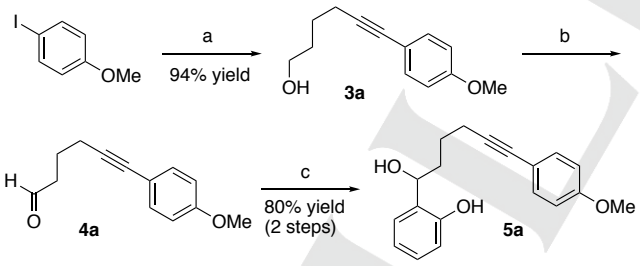
Our synthetic plan for the synthesis of 2-aryl-3,4-fused tricyclic dihydrobenzopyranes with a 2,3-*syn* and 3,4-*syn* structure is outlined in Scheme 2. We envisioned that compound **I** could be constructed by an acid-promoted reduction of enol ether derivative **II**, which in turn would be obtained by 1,6-addition of phenol to vinylidene *para*-quinone methide intermediate **III**. This intermediate could be prepared from compound **IV** by intramolecular dearomative nucleophilic addition of 4-alkynylphenol to *ortho*-quinone methide generated from the *ortho*-hydroxy benzylalcohol moiety. Both processes are promoted by an acid promoter, indicating that the target transformation can be performed in a cascade manner.




**Scheme 2.** Reaction Design.

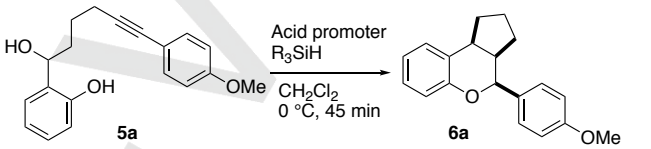
Our investigation started with the synthesis of a model substrate (Scheme 3). 4-Iodoanisole was first coupled with 5-hexyn-1-ol in the presence of 5 mol % of $PdCl_2(PPh_3)_2$ and 5 mol % of CuI in triethylamine, providing compound **3a** in 94% yield. After oxidation of the primary alcohol, the obtained **4a** was reacted with 2 equiv of aryllithium reagent generated from 2-bromophenol to give compound **5a** in 80% yield from **3a**.




**Scheme 3.** Synthesis of Model Substrate. (a) 5-hexyn-1-ol (1.2 equiv), CuI (5 mol %), $PdCl_2(PPh_3)_2$ (5 mol %), $NEt_3$ (0.2 M), rt, 2.5 h; (b) Dess-Martin Reagent (1.6 equiv), $CH_2Cl_2$ (0.1 M), 0 °C to rt, 1.5 h; (c) 2-bromophenol (2 equiv), *n*-BuLi (4.0 equiv), $Et_2O$ (0.1 M), –20 °C, 0.5 h.

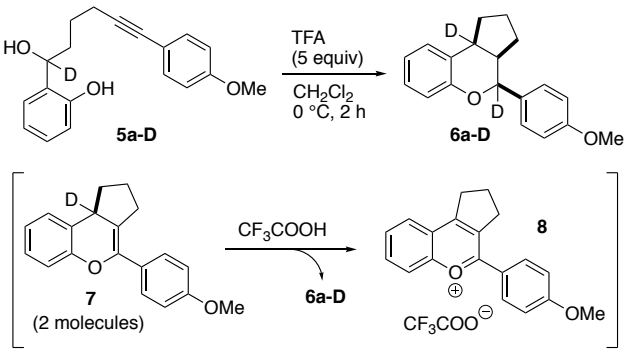
The reaction conditions were optimized using **5a** as a substrate (Table 1). We first examined the reaction using 1 equiv of trifluoroacetic acid (TFA) and 1 equiv of triethylsilane in $CH_2Cl_2$ at 0 °C. The desired product **6a**, however, was not obtained and 65% of **5a** was recovered (entry 1). Increasing the amount of TFA improved the yield of **6a**. When the reaction was performed using 5 equiv of TFA, the product was obtained in 69% yield (entry 3). The yield was further improved to 87% yield using 5 equiv of triethylsilane (entry 5). The use of other hydride sources such as triisopropylsilane and triphenylsilane gave less satisfactory results (entries 7 and 8). We thus selected the reaction conditions in entry 5 as optimal for this cascade process. Interestingly, the present cascade reaction also proceeded in the absence of triethylsilane, affording **6a** in moderate yield (entry 9). To specify the hydride source in the reaction without triethylsilane, compound **5a-D** was prepared and treated with 5 equiv of TFA in $CH_2Cl_2$ at 0 °C (Scheme 2). Product **6a-D** bearing two deuterium atoms in the C2 and C4 positions was obtained in 37% yield, revealing that the disproportionation reaction of 2 molecules of **7** into **6a-D** and **8** unexpectedly promoted the reaction, even in the absence of triethylsilane.

**Table 1.** Optimization of the Reaction Conditions.



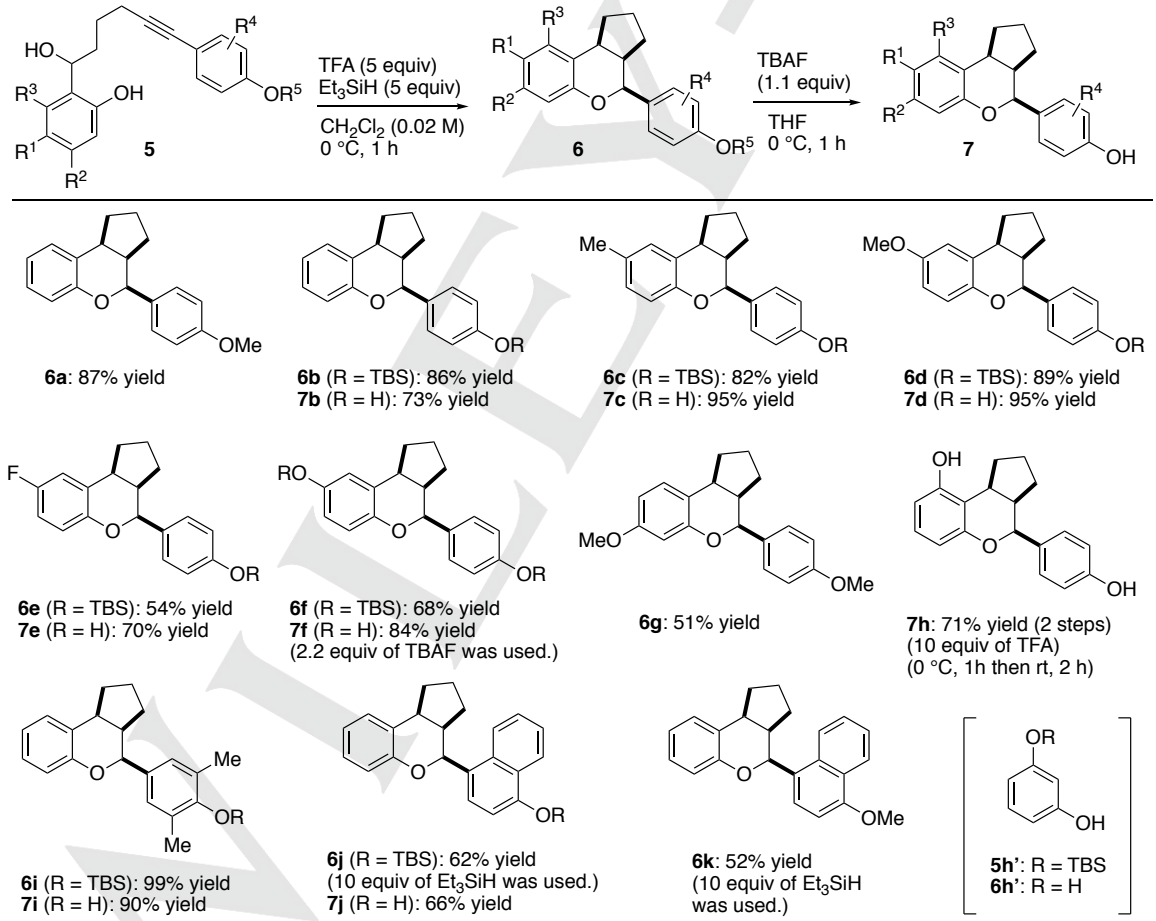

| Entry | Acid Promoter | $R_3SiH$ | Yield[a] |
|---|---|---|---|
| 1 | TFA (1 equiv) | $Et_3SiH$ (1 equiv) | 0% (65%)[b] |
| 2 | TFA (3 equiv) | $Et_3SiH$ (1 equiv) | 37% |
| 3 | TFA (5 equiv) | $Et_3SiH$ (1 equiv) | 69% |
| 4 | TFA (5 equiv) | $Et_3SiH$ (2 equiv) | 82% |
| 5 | TFA (5 equiv) | $Et_3SiH$ (5 equiv) | 87% |
| 6 | TFA (5 equiv) | $Et_3SiH$ (10 equiv) | 87% |
| 7 | TFA (5 equiv) | *i*-$Pr_3SiH$ (2 equiv) | 32% |
| 8 | TFA (5 equiv) | $Ph_3SiH$ (2 equiv) | 37% |
| 9 | TFA (5 equiv) | – | 37% (42%)[c] |

[a] Isolated yield. [b] Recovery of **5a**. [c]Reaction time: 2 h.

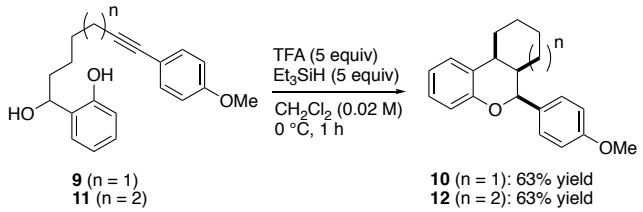



**Scheme 4.** Deuterium Labelling Study.

With the optimized reaction conditions in hand, we next examined the scope and limitations using various substrates (Scheme 5). In addition to model substrate **5a**, TBS-protected 4-alkynyl phenol derivatives were effective substrates for this reaction. Treatment of **5b** under the optimized conditions led to the corresponding product **6b** in 86% yield. The TBS group could be removed using tetrabutylammonium fluoride (TBAF), affording 2-(4-hydroxyphenyl)-3,4-fused tricyclic dihydrobenzopyran derivative **7b** in 73% yield. Substrates with a substituent on the $R^1$ position **5c**–**f** reacted under the same reaction conditions to give the corresponding products **6c**–**f** in 54%–89% yield. Treatment of compound **6f** with 2.2 equiv of TBAF afforded product **7f**, the potent and selective ERβ agonist shown in Figure 1, in 84% yield. A substrate with a methoxy group in $R^2$ was also applicable to this process, providing **6g** in 51% yield. Although substrate **5h** bearing a *t*-butyldimethylsiloxy group in the $R^3$ position was prepared according to the general procedure in Scheme 3, separation of compounds **5h** from **5h'** and **6h** from **6h'** by a silica gel column chromatography was difficult in each reaction. Therefore, the obtained mixture of **5h** and **5h'** was first treated with 4.4 equiv of TBAF and 4.4 equiv of AcOH, and the resulting mixture of **6h** and **6h'** was then allowed to react with 10 equiv of TFA and 5 equiv of triethylsilane, producing compound **7h** in 71% yield for 2 steps. Moreover, substrates with substituents on the alkynylphenyl moiety were examined. When *ortho*-dimethylphenol-type substrate **5i** was used, the corresponding product **6i** was obtained in 99% yield, and could be transformed into compound **7i** in 90% yield. Naphthol derivatives **5j** and **5k** were also examined. The acid-promoted cascade reactions proceeded in the presence of 10 equiv of $Et_3SiH$, affording the corresponding products **6i** and **6k** in 62% yield and 52% yield, respectively, accompanied by the formation of a small amount of the naphthol unit-epimerized product (dr = 20:1). Substrates **9** and **11** bearing a longer tether were also examined (Scheme 6). Both substrates were treated with the optimum conditions and the corresponding products with a six-membered ring or a seven-membered ring **10** and **12** were obtained in 63% yield and 63% yield, respectively, in a highly diastereoselective manner.




**Scheme 5.** Scope and Limitations.




**9** (n = 1)
**11** (n = 2)

**10** (n = 1): 63% yield
**12** (n = 2): 63% yield

**Scheme 6.** Substrate Scope.

## Conclusions

In conclusion, we developed a novel method for synthesizing 2-(4-hydroxyaryl)-3,4-fused tricyclic dihydrobenzopyrans with 2,3-*syn* and 3,4-*syn* motifs based on the acid-promoted cascade cyclization via vinylidene *para*-quinone methide intermediates. Using easily prepared linear substrates, a series of five to seven-membered ring-fused dihydrobenzopyran derivatives were obtained in moderate to excellent yield in a highly diastereoselective manner. The developed method provided new access to potent and selective ERβ agonists. The present work demonstrated the synthetic utility of vinylidene *para*-quinone methide intermediates. Further studies on the application of this intermediate to complex molecule synthesis are in progress.

## Experimental Section

**General Procedure for the Acid-Promoted Cascade Cyclization (Table 1, entry 5):** To a stirred solution of **5a** (29.6 mg, 0.1 mmol) in $CH_2Cl_2$ (5.0 mL) at 0 °C was added $Et_3SiH$ (80 μL, 0.5 mmol) and TFA (38 μL, 0.5 mmol). After being stirred for 1 h at 0 °C, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography to give the desired products **6a** (24.7 mg) in 87% yield. IR (ATR) ν 2952, 2869, 1612, 1582, 1455, 1303, 1175, 1034, 993, 823 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.39 (2H, d, *J* = 8.8 Hz), 7.18 (1H, d, *J* = 8.0 Hz), 7.10 (1H, ddd, *J* = 8.4, 8.4, 2.0 Hz), 6.96–6.88 (4H, m), 5.13 (1H, d, *J* = 2.4 Hz), 3.82 (3H, s), 3.52 (1H, ddd, *J* = 8.0, 8.0, 2.4 Hz), 2.64–2.55 (1H, m), 2.20–2.09 (1H, m), 1.88–1.80 (1H, m), 1.70–1.59 (1H, m), 1.53–1.35 (3H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 158.7, 155.4, 133.4, 129.1, 127.4, 126.8 (2C), 126.7, 121.3, 117.1, 113.6 (2C), 77.2, 55.3, 45.3, 39.6, 34.9, 23.7, 23.5; HRMS (ESI-TOF): m/z: Calcd. for $C_{19}H_{19}O_2^-$ [M-H] $^-$: 279.1391; found: 279.1400.

## Acknowledgements

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**Keywords:** Cascade reaction • dihydrobenzopyrans • synthetic method

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Layout 1:

# COMMUNICATION

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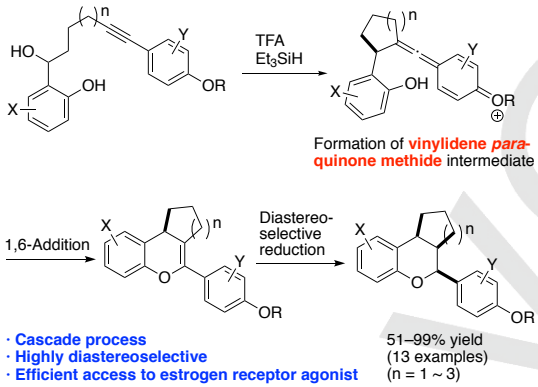


**Cascade Reaction***

*Dongil Choi, Naoki Shiga, Robert Franzén, and Tetsuhiro Nemoto **

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**Acid Promoted-Cascade Cyclization to Produce 2-(4'-Alkoxyaryl)-3,4-Fused Tricyclic Dihydrobenzopyrans via a Vinylidene *para*-Quinone Methide Intermediate**