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Efficient synthesis of a multi-substituted diphenylmethane skeleton as a steroid mimetic

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ABSTRACT

Steroids are important components of cell membranes and are involved in several physiological functions. A diphenylmethane (DPM) skeleton has recently been suggested to act as a mimetic of the steroid skeleton. However, difficulties are associated with efficiently introducing different substituents between two phenyl rings of the DPM skeleton, and, thus, further structural development based on the DPM skeleton has been limited. We herein developed an efficient synthetic method for introducing different substituents into two phenyl rings of the DPM skeleton. We also synthesized DPM-based estrogen receptor (ER) modulators using our synthetic method and evaluated their ER transcriptional activities.

Introduction

Steroids are a type of organic compound with four rings arranged in a specific configuration. Many different types of steroids exist in the human body. Certain steroids such as cholesterol are important components of cell membranes that affect membrane fluidity,[1] and many steroids are signaling molecules that regulate physiological functions through the activation of steroid hormone receptors.[2,3] On the other hand, the dysregulation of steroid hormone receptors has been implicated in the pathogenesis of several diseases. For example, 70% of human breast cancers are hormone-dependent and ERα-positive,[4,5] and hypersensitivity to $1\alpha,25(OH)_2D_3$, an endogenous VDR ligand, causes Paget's disease of bone.[6] Therefore, steroid hormone receptor modulators have been attracting increasing attention as therapeutic agents for these diseases and several steroidal derivatives have been developed.[7–9] However, steroidal derivatives may non-selectively act on several steroid hormone receptors and, as a consequence, cause side effects. Moreover, the synthesis a steroidal or secosteroidal skeleton requires time and effort, and substitution positions are limited because of the complex synthetic route.

In 1999, LG190178 was reported as a non-secosteroidal ligand for Vitamin D receptors (VDR).[10] The co-crystal structure between VDR and LG190178 revealed that LG190178 bound to VDR, similar to $1,25(OH)_2D_3$.[11] Hashimoto et al. developed several ligands for steroidal hormone receptors.[12–14] Compound **1** exhibited strong anti-estrogen receptor (ER) antagonistic activity. As shown in Fig. 1, compound **1** and LG190178 are composed of diphenylmethane (DPM) skeletons as a common structure. These findings indicate that the DPM skeleton has potential as a substitute of the steroid skeleton or secosteroid skeleton, and is a key structure in the development of several nuclear receptor ligands with the appropriate introduction of substituents. Based on these findings, we designed and synthesized a series of VDR ligands and ER-selective down-regulators (SERD) based on the DPM skeleton.[15,16] The DPM skeleton was previously synthesized by mixing phenol and 3-pentanone or 4-heptanone under acidic conditions.[16] However, difficulties are associated with efficiently introducing different substituents between two phenyl rings of the DPM skeleton by this method, and, thus, further structural development based on the DPM skeleton has been limited. Therefore, efficient synthetic methods to introduce different substituents into two phenyl rings of the DPM skeleton are needed. In the present study, we described a practical method to synthesize various multi-substituted DPM derivatives. Furthermore, we synthesized a set of DPM derivatives based on our synthetic method and evaluated their ER transcriptional activities. As described above, ER is an attractive target for breast cancer therapy and DPM derivatives may bind to ER and exert their antagonistic activities.[14] Based on these findings, we investigated the structure-activity relationship of DPM derivatives as ER antagonists in order to demonstrate the utility of our synthetic method.

In order to achieve this, we attempted to develop a synthetic method for the construction of a multi-substituted DPM skeleton. We used 4-(3-hydroxypentane-3-yl)-2-methylphenol and catechol as model substrates in order to obtain optimal conditions. We

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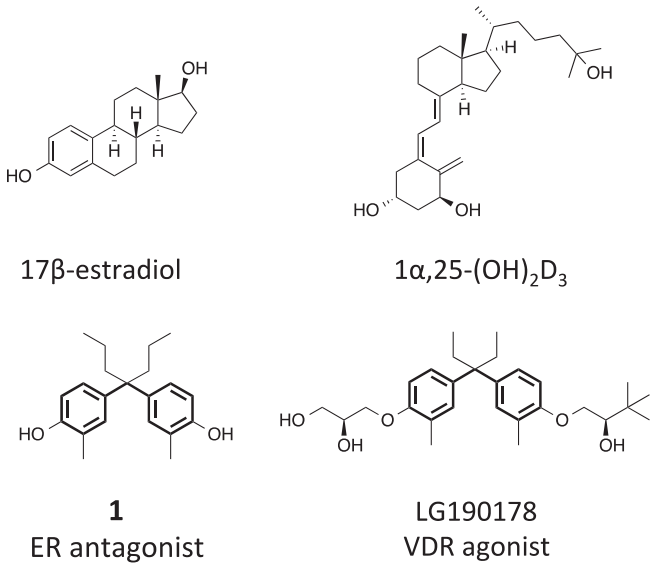
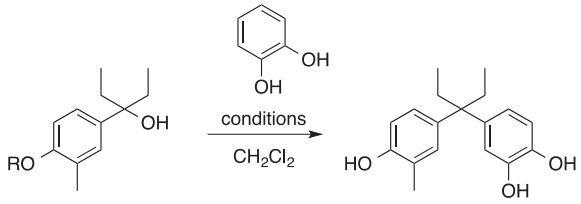


Fig. 1. Chemical structures of 17β-estradiol, 1α,25(OH)$_2$D$_3$, ER antagonist **1**, and LG190178. The DPM skeleton is shown as bold lines.

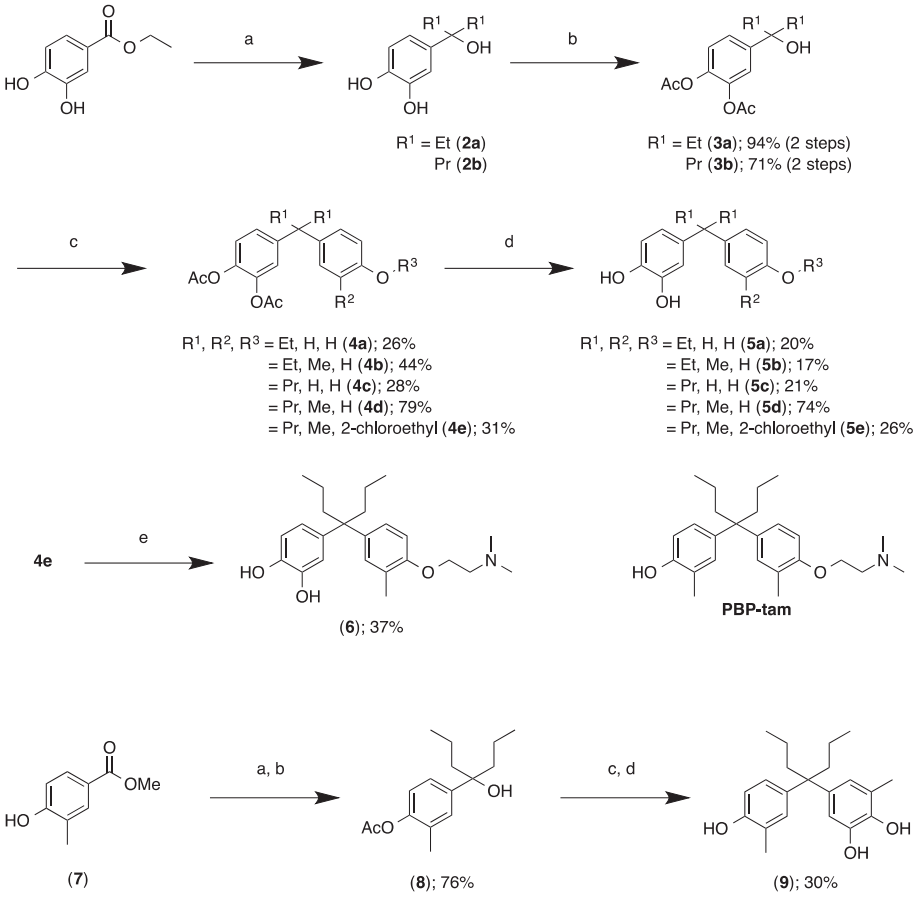
initially investigated the effect of acids on achieving improvements in the yield. As shown in Table 1, a treatment with Brønsted acid such as trifluoroacetic acid (TFA) and acetic acid (AcOH) provided the target compound with a low yield (Entry 1; 13%, Entry 2; trace). Furthermore, a treatment with Lewis acid, BF_3-OEt_2 gave the product in a low yield (Entry 3; 7%). On the other hand, the yield of the product was increased by a treatment with $SnCl_4$ (Entry 4; 50%). The acetylation of the hydroxy group on the aromatic ring markedly improved the yield (Entry 5; 96%). The electron-withdrawing ability of the acetyl group was considered to increase the electrophilicity of the tertiary carbon at the benzyl position and, consequently, the yield of the target compound that formed increased.[17]

Table 1
Optimization of reaction conditions to construct the multi-substituted DPM skeleton.



Entry	R	Conditions	Yield (%)
1	H	TFA (1 Eq.), rt, 5 days	13
2	H	AcOH (1 Eq.), H_2SO_4 (cat.), rt, 24 hr	Trace
3	H	BF_3-OEt_2 (1 Eq.), rt, 24 h	7
4	H	$SnCl_4$ (1 Eq.), rt, 24 h	50
5	Ac	$SnCl_4$ (1 Eq.), rt, 24 h	96

We then designed and synthesized a set of multi-substituted DPM derivatives as an ER antagonist using our synthetic method.



Scheme 1. (a) R^1MgBr, THF, rt., overnight; (b) Ac_2O, pyridine, DCM, rt. overnight; (c) Aryl compounds, $SnCl_4$, DCM, rt., overnight; (d) HCl, MeOH, rt., overnight; (e) Dimethylamine, MeOH, 100 °C, 3 h.