行政院國家科學委員會專題研究計畫成果報告

八十七年度抗高血壓藥物合成之研究

The Synthesis of Potential Anti-Hypertensive Drugs

計畫編號：NSC 87-2113-M-002-023
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一、中文摘要

我們已發展了一條可行的路徑，合成 ET-1 受體拮抗劑 SB209670 的構型固定類似物，此法最主要是利用一個分子內的 Stille 偶合反應，將 SB209670 兩邊的苯環以一個乙烯架橋相連。

關鍵詞：受體、拮抗劑、Stillle 偶合、SB209670

Abstract

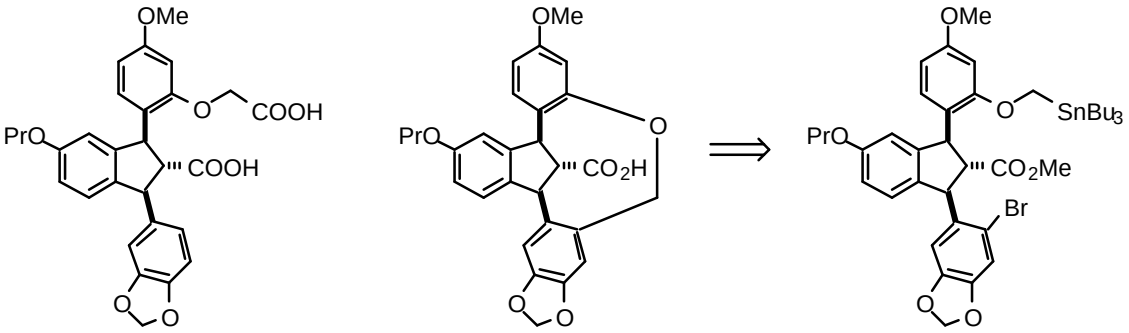
A conformationally rigid analog of SB209670 (**1)**, a potent endothelin receptor antagonist, was prepared featuring a key step involving Stille coupling.

Keywords: SB209670, Stille coupling, receptor antagonist

二、緣由與目的

Endothelin-1 (ET-1), a 21 amino acid peptide, isolated from endothelial cells exhibits profound endogenous vasoconstriction and mitogenic activities.[1] Intensive efforts were put on the search for the endothelin receptor antagonists.[2] Recently, based partly on the molecular modeling of ET-1, SmithKline Beecham Pharmaceuticals reported the finding of (1*S*,2*R*,3*S*)-3-[2-(carboxymethoxy)-4-methoxyphenyl]-1-[3,4-(methylenedioxy)phenyl]-5-(prop-1-yloxy)indan-2-carboxylic acid (**1**; SB 209670) as a highly potent antagonist,[3] selective for the endothelin receptors. The SB researchers used the 1- and 3-aryl groups to mimic the aromatic side chains of Tyr-13, Phe-14 of ET-1. Electron-donating substituents on these two phenyl moieties were designed to have better binding affinity with the receptors. The 2-carboxylic group was considered to function as the Asp-18 of ET-1. The carboxylic acid side chain on the 3-aryl group was designed to mimic the C-terminal carboxyl of the peptide. The propyloxy group was introduced only for the convenience of the synthesis. Removal of this group basically had no effect on the biological activities.

Scheme 1



1
SB209670

2

3

Based on the SB findings, we wish to synthesize acid **2** as the conformationally rigid analog of **1** in order to understand more about the role of the 1- and 3-aryl groups in **1**. Retrosynthetically, we planned to employ a Stille coupling[4] of stannane **3** to construct a methyleneoxy bridge connecting the two flanking aromatic rings on the indane skeleton.

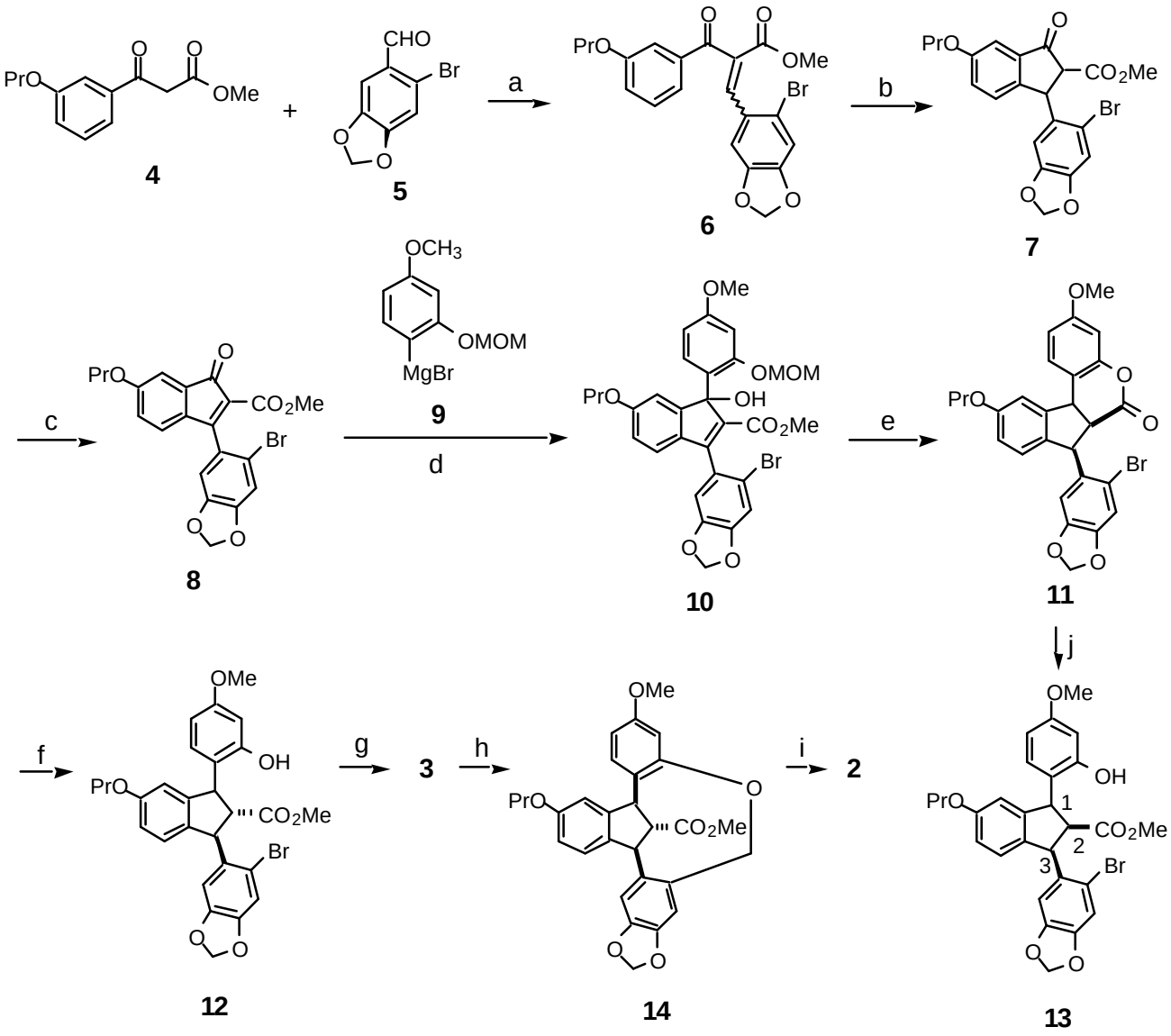
三、研究報告內容

Our synthesis of the cyclic ether **2** was realized as shown in Scheme 2. The preparation of ester **10** followed the same strategy as reported by Elliott *et al.* The Knoevenagel coupling of β-ketoester **4**[3] with the known bromoaldehyde **5**[5] gave enone **6** in 80% yield as a mixture of *E/Z*-isomers. Cyclization of enone **6** in TFA gave the β-ketoester **7** (97%) as a mixture of *cis*- and *trans*-isomers which was oxidized with DDQ to give indenone **8** (58%). Coupling of **8** with the Grignard reagent **9** prepared from the corresponding bromide[3,6] gave the alcohol **10**. Interestingly, alcohol **10** exists as a separable 3:1 mixture of two conformers presumably due to the hindered rotation of the bromo containing 3-aryl group. The relationship of the two isomers was confirmed by heating the minor isomer of **10** in benzene at 80 °C for 2 h to give back a mixture of the two conformers.

Attempted catalytic hydrogenation (H_2, Pd/C, EtOAc/EtOH) of alcohol **10** was not successful even at 80 °C. The sluggishness of this reaction was probably due to the steric hindrance imposed by the 2-bromo-4,5-methylenedioxyphenyl group. Without the bromo group in alcohol **10**, the catalytic hydrogenation can be accomplished at room temperature.[3] To solve this problem, we switched to the use of triethylsilane in TFA at 60 °C. Under this condition we were able to isolate the *cis*-lactone **11** in 40% yield. The MOM protecting group was removed during the initial 5 min period of the reaction. Treatment of the lactone **11** with potassium carbonate in methanol at room temperature gave the ester **13** in 68% yield. That the ester **13** is the all *cis*-isomer was confirmed by NOE experiments. Irradiation of H(2) resulted in 8% and 8% enhancement of the ^{1}H NMR signals of H(1) and H(3), respectively. Therefore, the stereochemistry of the lactone **11** should also be the all *cis*-isomer. When

lactone **12** was treated with one equivalent of sodium methoxide in methanol under refluxing temperature, the lactone ring opening was accompanied with epimerization at C(2) to give the all *trans*-isomer in 70% yield. While the ^{1}H NMR signals of H(2) in ester **13** and lactone **11** appeared at δ 4.1, the corresponding signal in ester **12** appeared at δ 3.2. This chemical shift difference also indicated the difference of stereochemistry at C(2) between esters **12** and **13**.

Scheme 2



Reagents and conditions : (a) AcOH (cat), piperidine (cat), PhH, 80 ^{o}C, 6 h; 80%. (b) TFA, rt, 12 h; 97%. (c) DDQ, dioxane, 70 ^{o}C, 2.5 h; 58%. (d) THF, 0 ^{o}C → rt, 5 h; 70%. (e) Et_3SiH, TFA, 60 ^{o}C, 24 h; 40%. (f) NaOMe, MeOH, reflux, 5 h; 70%. (g) ICH_2SnBu_3, K_2CO_3, DMF, 70 ^{o}C; 75%. (h) $Pd(PPh_3)_4$, $AsPh_3$, Toluene, 100 ^{o}C; 80%. (i)NaOH, dioxane, H_2O, rt, 12 h; 85%. (j) K_2CO_3, MeOH, rt; 68%.

Alkylation of ester **12** with tributyl(iodomethyl)stannane[7] in DMF gave the ether **3** in 75% yield. Stille coupling[7] with palladium tetrakis(triphenylphosphine) in the presence of triphenylarsine[8] afforded the cyclized ether **14** in 80% yield.[9] Finally, the saponification of cyclic ether **14** was accomplished with sodium hydroxide in wet dioxane to afford the acid **2** (85%).

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