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# First Total Synthesis of Vialinin A, a Novel and Extremely Potent Inhibitor of TNF-α Production

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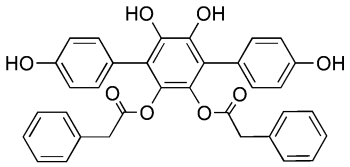
## ABSTRACT




Vialinin A

**Vialinin A, a powerful inhibitor ($IC_{50}$ 90 pM) of TNF-α production, was synthesized from sesamol in 11 steps with 28% overall yield. The key reactions include a double Suzuki coupling of electron-rich aryl triflate with phenylboronic acid and an oxidative deprotection of bis-MOM ether. In addition, the related synthetic studies also suggest the necessity for structural revision of ganbajunin C, a positional isomer of vialinin A.**

The incidence of an immediate hypersensitive allergy (type I) caused by immunoglobulin E, for example, food allergy, pollinosis, asthma, drug-induced allergy, etc., is increasing worldwide,[1] and several therapeutic agents that inhibit the release of chemical mediators such as histamine from mast cells and basophils are currently used as therapeutic agents.[2] Mast cells and basophils, which are high-affinity IgE receptors (FcεRI), are activated by a specific antigen (IgE) through cross-linking of the IgE−FcεRI complex. Cell activation induces the degranulation and release of chemical mediators such as histamine and leukotrienes and subsequently causes the release of cytokines including TNF (tumor necrosis factor)-α, which have important roles in the late phase inflammation of type I allergy. TNF-α is a potent multifunctional cytokine that mediates a variety of biological actions with a central role in the pathogenesis of many inflammatory diseases.[3] Thus, inhibitors of TNF-α production in the activated mast cells and basophils are promising candidates for a new type of anti-allergic agent.

In our search for bioactive compounds from edible Chinese mushrooms, we isolated vialinin A (**1**) from the dry fruiting bodies of *Thelephora vialis* and reported that it had a powerful 2,2-diphenyl-1-picrylhydrazyl (DPPH) free-radical-scavenging activity with an $EC_{50}$ value of 14 μM (cf. $EC_{50}$ = 10 μM for BHT).[4] Asakawa et al. also reported isolation of the same compound from *Thelephora terrestris* and named it terrestrin A.[5] Recently, we found that this compound strongly inhibited TNF-α production in rat basophilic leukemia (RBL-2H3) cells: the $IC_{50}$ was 90 pM when the clinical immunosuppressant FK-506 was used in the same

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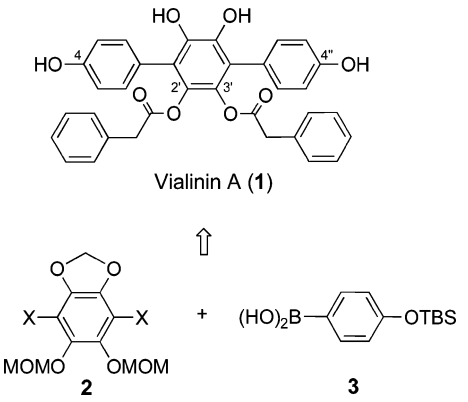
run as a positive standard ($IC_{50}$ = 0.25 nM).[6] The extremely potent biological activity and the unique structure have prompted us to develop an efficient method for preparing this natural product. Herein, we describe the first total synthesis of **1** and structural revision of its positional isomer, ganbajunin C.

In the synthetic study of this unique molecule, selective protection of hydroxyl groups in the central core and construction of the terphenyl skeleton are the main problems throughout the synthetic course. We envisioned densely functionalized benzene **2** as a key intermediate and planned a double Suzuki coupling[7] of it with 4-(*tert*-butyldimethylsilyloxy)phenylboronic acid (**3**) (Scheme 1). The methylene

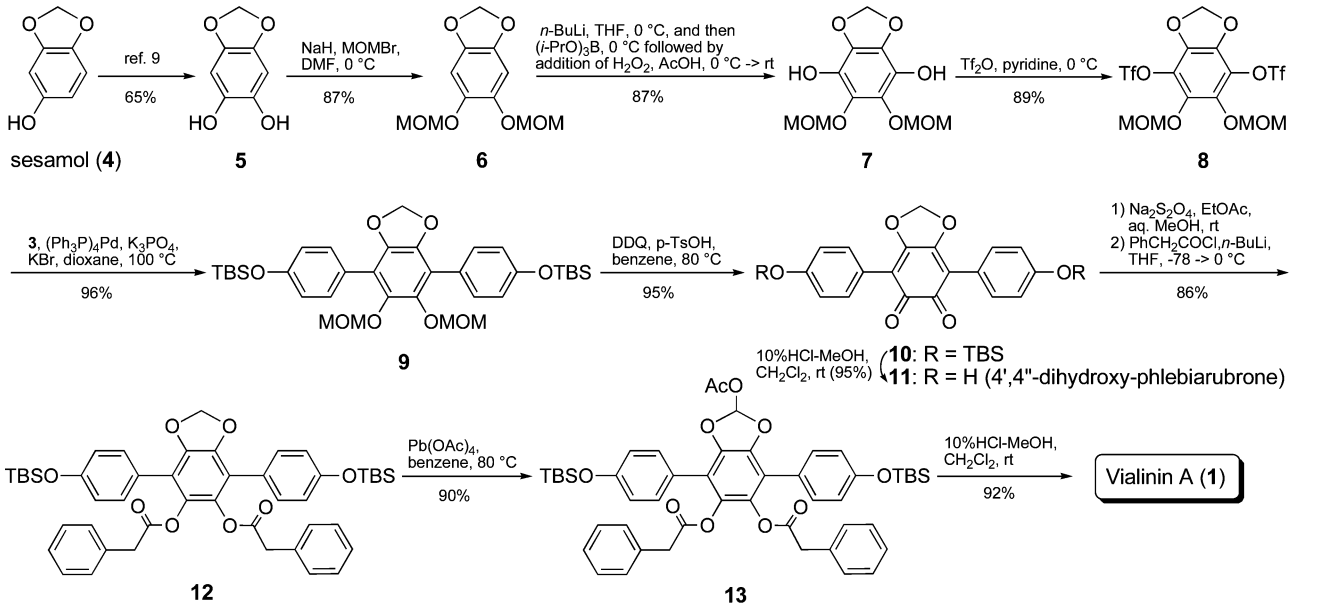
**Scheme 1**




acetal moiety in **2** was expected to resist many reagents until the later stage of total synthesis.

Therefore, we selected sesamol (**4**) as a starting material for the central core (Scheme 2). Preparation of **2** (X = Br) through bromination[8] of an *ortho*-quinone[9] obtained from **4** was not feasible, so the phenol **4** was transformed into catechol **5**[9] and then submitted to methoxymethylation (MOMBr, sodium hydride (NaH)), giving bis-MOM ether **6**. Introduction of two leaving groups into the *para*-position of **6** was accomplished through a double lithiation. Thus, **6** was initially treated with 2.4 equiv of *n*-butyllithium at 0 °C, and then trapping with triisopropyl borate followed by treatment with hydrogen peroxide/acetic acid gave rise to a clean hydroxylation, affording hydroquinone derivative **7**. Upon treatment with triflic anhydride/pyridine, **7** gave triflate **8**. The coupling reaction of **8** with 4.0 molar equiv of **3** proceeded nicely in the presence of tetrakis(triphenylphosphine)palladium (0.05 equiv), potassium bromide (2.1 equiv), and potassium phosphate (4.0 equiv)[10] in dioxane at 100 °C to give terphenyl **9**. At this stage, a selective deprotection of methoxymethyl groups in **9** was needed. After several experiments, we found this transformation could be achieved by the use of 3.0 equiv of DDQ in the presence of *p*-TsOH (1.5 equiv) in benzene at 50 °C,[11] providing *ortho*-quinone **10**. It is noteworthy that two TBS groups were retained under these reaction conditions. This key reaction would enable us to prepare many analogues of terphenyls.[12] For example, **10** underwent hydrolysis under acidic conditions to give 4′,4″-dihydroxyphlebiarubrone (**11**), which was isolated from cultures of *Punctularia atropurpurascens*.[13] The spectral and physical properties of **11** were identical to those of the reported **11**. On the other hand, reduction of **10** with sodium dithionite gave the corresponding catechol, which was immediately submitted to phenylacetylation. We observed that the reaction with phenylacetyl chloride in the presence of organic bases such as pyridine/dimethylaminopyridine and triethylamine was not satisfactory because it proceeded only sluggishly, whereas the use of *n*-butyllithium at −78 °C improved the reaction, and the desired product **12** was

**Scheme 2**



obtained. Hydrolysis of the methylene acetal moiety in **12** was a troublesome step. Conventional methods including the use of boron trichloride or boron tribromide resulted in a complex mixture because of the instability of phenylacetyl groups toward the reaction conditions employed. However, treatment of **12** with 2.5 equiv of lead tetraacetate[14] in benzene at 80 °C provided orthoester **13**. Finally, exposure of **13** to mild acidic conditions led to the removal of two TBS groups concomitant with hydrolysis of the orthoester, giving **1**. The spectral and physical properties of **1** were identical to those of natural **1**.

In previous papers, one of us developed a new stereochemical coding method, CAST (CAnonical representation of STereochemistry)[15] and successfully applied it to a database-oriented $^{13}$C NMR chemical shift prediction system, called CAST/CNMR.[16] In the course of studies applying CAST/CNMR to terphenyls, we found that $^{13}$C NMR data of the terminal aromatic rings of **1** were similar to those of ganbajunin C isolated from edible Chinese mushroom, *Thelephora ganbajun* (Figure 1)[17] and felt that the proposed

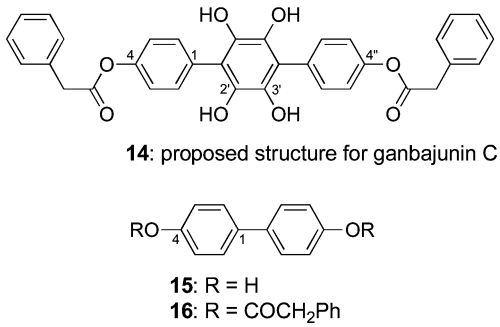



**Figure 1.** Structures of ganbajunin C and biphenyls.

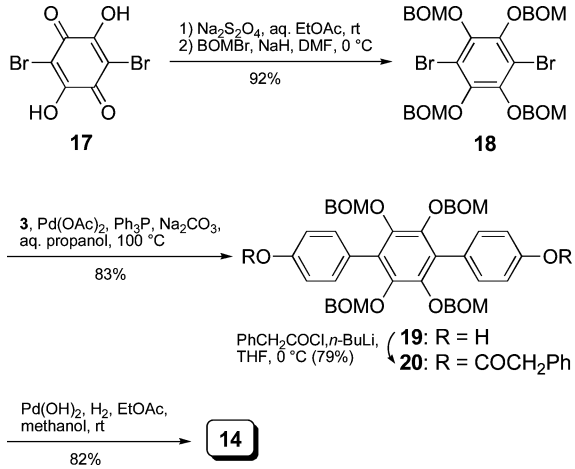
structure **14** was quite strange because two model compounds (**15** and **16**[18]) exhibited clearly different $^{13}$C NMR spectra

**Table 1.** $^{13}$C NMR Data ($\delta$) for Compounds **1**, **14** (natural ganbajunin C), **14** (synthetic), **15**, and **16** in Acetone-$d_6$

| position | **1** vialinin A | **14** (natural) ganbajunin C | **14** (synthetic) | **15** | **16** |
|---|---|---|---|---|---|
| 1 (1″) | 124.3 | 124.8 | 132.7 | 133.3 | 138.5 |
| 2 (2″), 6 (6″) | 132.3 | 132.6 | 133.0 | 128.2 | 128.7 |
| 3 (3″), 5 (5″) | 115.9 | 116.1 | 121.9 | 116.4 | 122.9 |
| 4 (4″) | 157.8 | 158.1 | 150.8 | 157.2 | 151.5 |
| 1′, 4′ | 123.1 | 124.0 | 117.8 | | |
| 2′, 3′ | 134.6 | 142.6 | 136.8 | | |
| 5′, 6′ | 141.7 | 142.6 | 136.8 | | |

(Table 1). The characteristic difference is in the chemical shift of the carbon atom attached to an oxygen atom: the $^{13}$C NMR spectrum of biphenol **15** in acetone-$d_6$ showed one aromatic carbon C-4 at 157.2 ppm, whereas C-4 of the corresponding phenylacetate **16** was observed at $\delta$ 151.5. The low chemical shift (158.1 ppm) of C-4 (4″) in ganbajunin C suggested the 4 (4″)-OH was free. In order to confirm these considerations, the proposed structure **14** was synthesized in a similar strategy (Scheme 3). Bromanilic acid (**17**)

**Scheme 3**




was reduced and then subjected to etherification with benzyloxymethyl chloride (BOMCl) and NaH to give tetrakis-BOM ether **18**. Suzuki coupling of **18** with **3** (2.5 equiv) was effected by the use of palladium acetate[19] (0.05 equiv) and triphenylphosphine (0.15 equiv) in the presence of sodium carbonate in aqueous propanol at 100 °C to afford terphenyl derivative **19**. Coupling reaction using **17** or its dimethoxy analogue instead of **18** failed because of the low solubility of the substrate in the reaction solvent and instability toward the reaction conditions employed. After phenylacetylation of **19**, the resulting diester **20** was hydrogenated over palladium hydroxide under $H_2$ to give **14**.[20,21] As expected, the spectral data of synthetic **14** were completely different from that of reported ganbajunin C. In

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analogy with the case of model compounds (**15** and **16**), synthetic **14** contained one signal for C-4 (4″) at $\delta$ 150.8, which was observed at 158.1 ppm in the $^{13}$C NMR spectrum of the natural product. These results show that the structure of natural ganbajunin C is not **14** as proposed in ref 17. Taking into account the origin and the spectral data, it is likely that the correct structure of ganbajunin C closely resembles that of vialinin A (terrestrin A) (**1**). The $^{13}$C NMR data of the central core of reported ganbajunin C, however, prevent us from stating that **1** and ganbajunin C are identical. To clarify this, a direct comparison of our samples with the authentic natural product would be necessary.

In summary, we developed a short and efficient synthesis of vialinin A (**1**), in only nine steps and with 44% overall yield from a known catechol (**5**). This synthetic process would be quite useful for preparing many analogues of **1** suitable for clinical usage. Furthermore, our synthetic studies suggest the need to reinvestigate the structure of natural ganbajunin C.

(20) It was revealed that **14** was unstable and readily prone to change into the corresponding *p*-quinone on standing at rt.

(21) Tetramethoxymethyl analogue of **20** was also synthesized, but deprotection of the analogue under acidic conditions caused a partial dephenylacetylation and oxidation, resulting in a low yield of **14**.

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**Supporting Information Available:** Experimental procedures, NMR spectra of **1**, **6**−**14**, and **18**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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