Expeditious Synthesis of Vialinin B, an Extremely Potent Inhibitor of TNF- α Production

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ABSTRACT



A first total synthesis of vialinin B, a powerful inhibitor (IC_{50} 20 pM) of TNF- α production, is described. The key reactions include a double Suzuki–Miyaura coupling of electron-rich aryl bromide with a couple of phenylboronic acids, a Cu-mediated Ullmann reaction, and a LHMDS-promoted phenylacetylation. This synthesis proceeded in 11 steps with 18% overall yield from a known sesamol derivative.

Vialinin B (1) is a highly oxygenated dibenzofuran bearing *p*-hydroxyphenyl and phenylacetoxy groups that was isolated by us from the dry fruiting bodies of an edible Chinese mushroom, *Thelephora vialis*, and shows an extremly potent inhibitory activity against tumor necrosis factor (TNF)- α production in rat basophilic leukemia (RBL-2H3) cells (IC₅₀ = 20 pM vs. 0.25 nM for FK-506).¹ TNF- α is a potent multifunctional cytokine that mediates a variety of biological actions with a central role in the pathogenesis of inflammatory diseases such as rheumatoid arthritis (RA).² Thus, inhibitors of TNF- α production in activated mast cells and basophils are promising candidates for a new type of antiallergic agent. The mode of action of **1** and its inhibition mechanism, however, still remain unresolved. Its occurrence

in nature was also limited. To clarify the target molecule of **1** and synthesize new antiallergic drugs, development of an efficient method for the synthesis of **1** is required. Although many oligoarenes including *p*-terphenyls have been synthesized so far,³ no paper has appeared dealing with the synthesis of highly oxygenated dibenzofurans.⁴ Described herein is the first total synthesis of vialinin B (**1**), thus providing a general method for the synthesis of this family.

In the synthetic study of this unique molecule, construction of the dibenzofuran skeleton and selective protection of

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hydroxyl groups in the central core are the main problems throughout the synthetic course. To resolve such problems, we designed a synthetic strategy as shown in Scheme 1.



Removal of two phenylacetyl groups in the target molecule leads to the *O*-protected dibenzofuran catechol **2**. Cleavage of the internal ether linkage can revert **2** back to the desymmetrical *p*-terphenyl **3**. This would be synthesized by Suzuki–Miyaura coupling⁵ of bromide **4** with a couple of boronic acids **5** and **6**.⁶ The methylene acetal moiety in **4** was expected to resist many reagents until the later stage of total synthesis, and the formyl group was introduced for a regioselective coupling as well as for an equivalent of a masked hydroxyl group. These retrosynthetic analyses allowed us to select sesamol (**7**) as the starting material.

Synthesis began with preparation of the central core 4 (Scheme 2). According to De Kimpe's procedure,⁷ sesamol (7) was transformed into 8 in 2 steps. The hydroxyl group in 8 was protected as methoxymethyl (MOM) ether to give 4. This compound seems to be a potential precursor and a versatile starting material for the synthesis of *p*-terphenyls bearing a variety of substituents on the central ring as well as 1 provided that a regioselective Suzuki–Miyaura coupling of 4 with different types of boronic acids is possible. The



first successful example was demonstrated by the coupling of 4 with 5 and 6 as follows. We initially examined a coupling with a simple boronic acid 5, and found that reaction with Pd(PPh₃)₄ in the presence of cesium carbonate afforded a coupling product **9** in 84% yield.⁸ The position of the newly introduced phenyl group was determined by the ¹H NMR analyses including HMBC and NOE experiments (Scheme 2).⁹ Second coupling was achieved by the action of $Pd(OAc)_2$ in the presence of the lignad 13,¹⁰ giving desymmetrical p-terphenyl 11 in 84% yield. Encouraged by the above results, we next changed the order of the coupling partner. Reaction of 4 and 6 under the same conditions (Pd(PPh₃)₄cesium carbonate) gave 10 in moderate yield (\sim 54%) whereas a combination of Pd(OAc)₂ and 13 or 2-di-tertbutylphosphino-2',4',6'-triisopropylbiphenyl resulted in no reaction or a complex mixture. The best results were obtained by the use of $Pd(OAc)_2$ and triphenylphosphine instead of the sterically hindered ligands to give **10** in 78% yield.⁸ The ring connectivity was also confirmed by the ¹H NMR analysis. As anticipated, the second coupling did not proceed by using a system of Pd(OAc)₂-triphenylphosphinepotassium phosphate. But an exchange of the phophine from triphenyl phosphine to 13 dramatically improved the reaction, providing 12 in 91% yield. This compound was also obtained through a one-pot Suzuki-Miyaura coupling. Thus, after completion of the first coupling between 4 and 6 (TLC analyses), 5, 13, and Pd(OAc)₂ (0.05 equiv) were added in

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⁽⁸⁾ Although several spots were observed on TLC, a double coupling product could not be isolated.

⁽⁹⁾ In the ¹H NMR spectra of **9** and **10**, the up-field shift of the formyl proton due to the shielding effect of the neighboring aromatic ring was observed.

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the same flask, and the reaction was continued for a further 3 h. Standard workup followed by chromatography on silica gel gave a 67% yield of **12**.

In constructing the *p*-terphenyl skeleton, we next turned our attention to the benzofuran formation. Prior to the reaction, the MOM group in 11 was hydrolyzed, giving 14 as an unstable solid (Scheme 3). The intramolecular Oarylation of 14 was investigated under several conditions including $Pd(OAc)_2$ or $Pd_2(dba)_3$ in the presence of 13 or 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl or 2-(ditert-butylphosphino)biphenyl,^{10,11} or Cu catalyst such as Nano-CuO¹² and Cu₂O.¹³ All attempts, however, were unsuccessful, and a desired benzofuran could not be isolated. On the other hand, Bayer–Villiger oxidation^{14,15} of **12** provided the corresponding formate 15, which, upon treatment with base, afforded an unstable phenol 16. The cyclization from 16 to 17 was a troublesome step again. Pdcatalyzed etherification of 16 did not proceed while the Cumediated cyclization reaction gave $17 (\sim 54\%)$ along with an o-quinone without the MOM group ($\sim 25\%$). These results reflected the instability of 16 toward the reaction conditions employed. After extensive experimentation, it was found that treatment of the formate 15 with a Cu catalyst directly produced 17. The use of Cu₂O-pyridine was quite effective; an 88% yield of 17 was attained. Removal of the methyleneacetal moiety was performed by lead tetraacetate (LTA) oxidation,¹⁶ which was previously employed in the total synthesis of natural *p*-terphenyls.¹⁷ Contrary to our expecta-

(15) No presence of potassium fluoride decreased the yield of 15.

tion, the major product was de-MOM product not a desired orthoester when 17 was treated with LTA in benzene.¹⁸ We found that the oxidation was sensitive to the O-protecting group at the C-6 position of 17. For example, the use of ether-type protecting groups such as MOM, Bn, and TBDMS resulted in a complex mixture or no reaction while introduction of electron-withdrawing groups like acetate into 6-OH of 18 gave good results. Consequently, the MOM group in 17 was exchanged to a benzyloxycarbonyl group. LTA oxidation of 19 thus obtained proceeded nicely, giving the corresponding monoacetate 20 in good yield. Exposure of this to mild acidic conditions led to removal of the acetal group, providing an unstable catechol 2 (R = OZ), which was immediately submitted to phenylacetylation. Deprotonation from two hydroxyl groups in 2 was accomplished by the action of lithium bis(trimethylsilylamide) (LHMDS) in THF at -78 °C,¹⁹ and the resulting lithium salt reacted with phenylacetyl chloride to provide 21 in good yield. Finally, all benzyl groups in 21 were removed by hydrogenolysis with $Pd(OH)_2$ to give vialinin B (1). The spectral data of 1 were identical with those of the natural product.²⁰

We have developed a short and efficient method for the synthesis of vialinin B (1) in 13 steps from a commercially available sesamol (7). The key features of this synthesis are as follows: (1) synthesis of a highly functionalized p-terphenyl skeleton based on a Suzuki-Miyaura coupling; (2) construction of a benzofuran skeleton by a Cu-mediated

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⁽¹⁸⁾ LTA oxidation of 5,6-bis(methoxymethoxy)benzo[d][1,3]dioxole as a model compound gave the corresponding orthoester in high yield.

⁽¹⁹⁾ Esterification of 2 in the presence of DMAP in pyridine or triethylamine gave a mixture of 21 and its mono-phenylacetate.

⁽²⁰⁾ The original ¹³C NMR data (δ 119.83 for C-9b) of **1** denoted in ref 1 was a typographical error and should be revised to 119.38 ppm.

intramolecular Ullmann reaction; and (3) LHMDS-promoted phenylacetylation. This method would be quite useful for the preparation of new antiallergic drugs²¹ as well as for bioprobes to clarify the target molecule.

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Supporting Information Available: Experimental procedures and NMR spectra of 1, 4, 9-12, and 14-21. This material is available free of charge via the Internet at http://pubs.acs.org.

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