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

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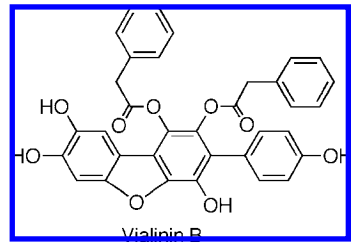
ABSTRACT



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 (IC_{50} = 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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(1) Xie, C.; Koshino, H.; Esumi, Y.; Onose, J.; Yoshikawa, K.; Abe, N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5424–5426.

(2) (a) Vassalli, P. *Annu. Rev. Immunol.* **1992**, *10*, 411–452. (b) Sieper, J.; Braun, J. *Expert Opin. Emerging Drugs* **2002**, *2*, 235–246. (c) Holgate, S. T. *Cytokine* **2004**, *28*, 152–157.

(3) For recent review, see: (a) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440. (c) Doucet, H. *Eur. J. Org. Chem.* **2008**, *201*, 2013–2030. (d) Manabe, K.; Ishikawa, S. *Chem. Commun.* **2008**, *382*, 3829–3838, and references cited therein.

(4) For recent syntheses of simple benzofuran derivatives without polyoxy functions, see: (a) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194–4195. (b) Hussain, M.; Hung, N. T.; Langer, P. *Tetrahedron Lett.* **2009**, *50*, 3929–3932. (c) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 2337–2340. (d) Komine, Y.; Kamisawa, A.; Tanaka, K. *Org. Lett.* **2009**, *11*, 2361–2364. (e) Kawaguchi, K.; Nakano, K.; Nozaki, K. *Org. Lett.* **2008**, *10*, 1199–1202.

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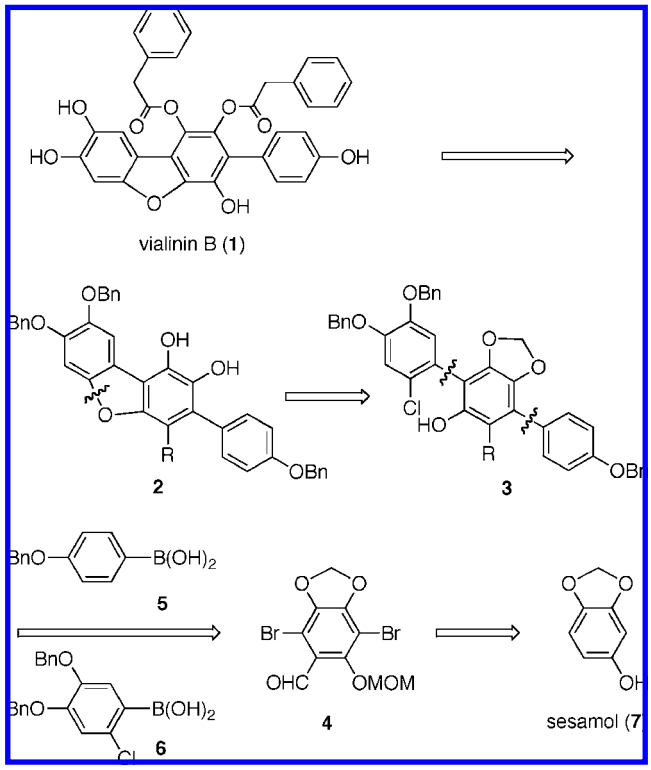
hydroxyl groups in the central core are the main problems throughout the synthetic course. To resolve such problems, we designed a synthetic strategy as shown in Scheme 1.

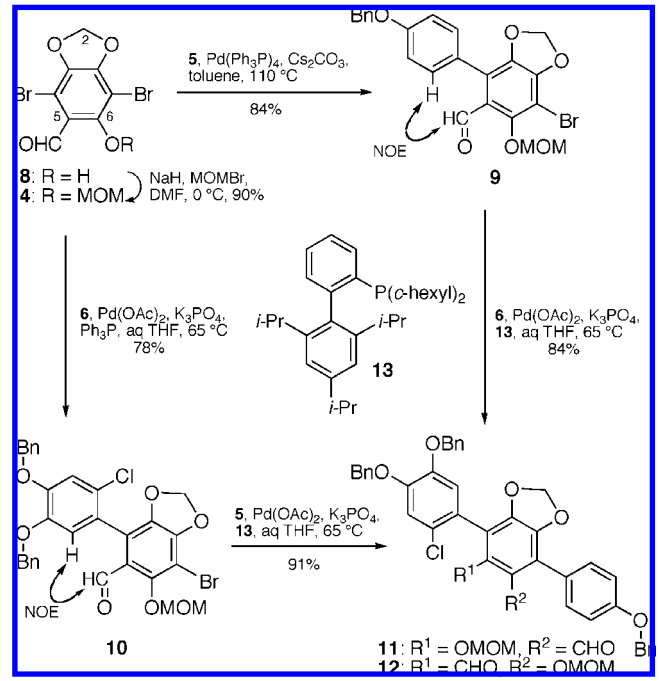
Scheme 1



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 coupling[5] 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

Scheme 2



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 $Pd(PPh_3)_4$ 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 ^{1}H 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 ($Pd(PPh_3)_4$-cesium carbonate) gave **10** in moderate yield (∼54%) whereas a combination of $Pd(OAc)_2$ and **13** or 2-di-*tert*-butylphosphino-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 ^{1}H NMR analysis. As anticipated, the second coupling did not proceed by using a system of $Pd(OAc)_2$−triphenylphosphine−potassium 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

(5) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

(6) Boronic acid **6** was prepared from 4-chlorocatechol via 1,2-bis(benzyloxy)-4-bromo-5-chlorobenzene (**22**) in 3 steps: (1) Br_2, acetic acid, rt; (2) BnBr, K_2CO_3, *n*-Bu_4NI, acetone, 60 °C (86% in 2 steps); (3) *n*-BuLi, (*i*-PrO)$_3$B, THF, −78 to 0 °C (97%); see the Supporting Information.

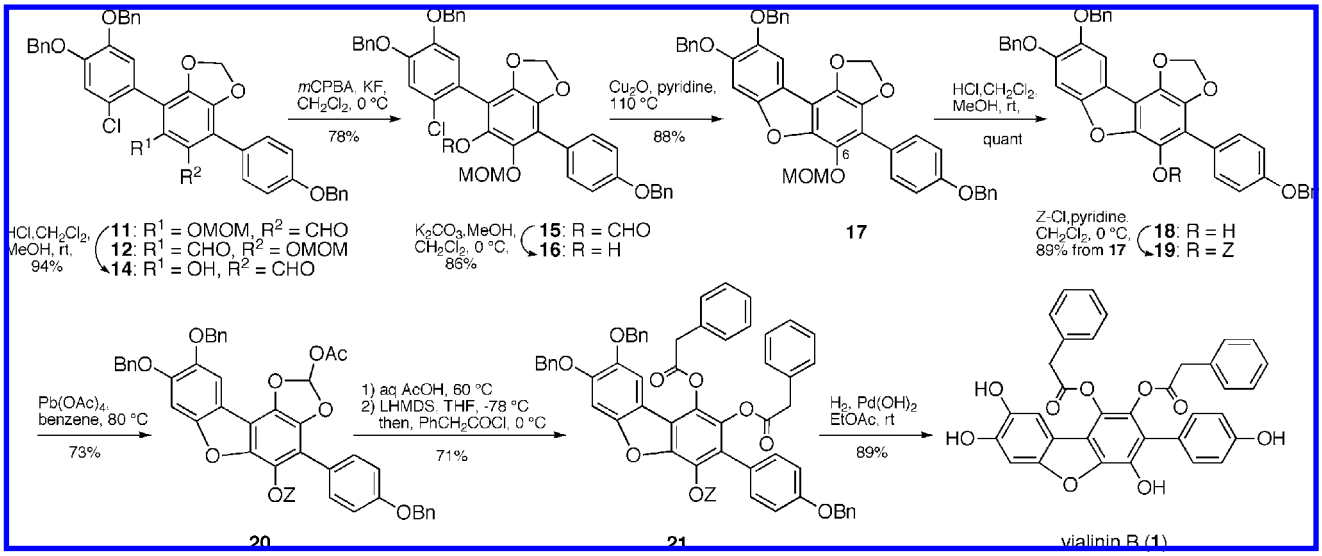
(7) Maes, D.; Vervisch, S.; Debenedetti, S.; Davio, C.; Mangelinckx, S.; Giubellina, N.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 2505–2511.

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

(9) In the ^{1}H 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.

(10) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

Scheme 3



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 *O*-arylation 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-(di-*tert*-butylphosphino)biphenyl,[10,11] or Cu catalyst such as Nano-CuO[12] and Cu_2O.[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. Pd-catalyzed etherification of **16** did not proceed while the Cu-mediated cyclization reaction gave **17** (∼54%) along with an *o*-quinone without the MOM group (∼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 Cu_2O-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 expectation, 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

(11) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321–4326.
(12) (a) Kidwai, M.; Mishra, N. K.; Bansal, V.; Kumar, A.; Mozumdar, S. *Tetrahedron Lett.* **2007**, *48*, 8883–8887. (b) Zhang, J.; Zhang, Z.; Wang, Y.; Zheng, X.; Wang, Z. *Eur. J. Org. Chem.* **2008**, *511*, 5112–5116. (c) Schareina, T.; Zapf, A.; Cotté, A.; Müller, N.; Beller, M. *Tetrahedron Lett.* **2008**, *49*, 1851–1855, and references cited therein.
(13) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319–6337.
(14) Camps, F.; Coll, J.; Messeguer, A.; Pericás, M. A. *Tetrahedron Lett.* **1981**, *22*, 3895–3896.
(15) No presence of potassium fluoride decreased the yield of **15**.
(16) Ikeya, Y.; Taguchi, H.; Yoshioka, I. *Chem. Pharm. Bull.* **1981**, *29*, 2893–2898.
(17) (a) Ye, Y.-Q.; Koshino, H.; Onose, J.; Yoshikawa, K.; Abe, N.; Takahashi, S. *Org. Lett.* **2007**, *9*, 4131–4134. (b) Ye, Y.-Q.; Koshino, H.; Onose, J.; Negishi, C.; Yoshikawa, K.; Abe, N.; Takahashi, S. *J. Org. Chem.* **2009**, *74*, 4642–4645.
(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 ^{13}C NMR data (δ 119.83 for C-9b) of **1** denoted in ref 1 was a typographical errror 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 drugs[21] 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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(21) For recent anti-RA drugs, see: (a) Brennan, F. M.; Chantry, D.; Jackson, A.; Maini, R.; Feldmann, M. *Lancet* **1989**, *334*, 244–247. (b) Maini, R.; St. Clair, E. W.; Breedveld, F.; Furst, D.; Kalden, J.; Weisman, M.; Solen, J.; Emery, P.; Harriman, G.; Feldmann, M.; Lipsky, P. *Lancet* **1999**, *354*, 1932–1939.