Total Synthesis of Terprenin, a Novel Immunosuppressive *p*-Terphenyl Derivative

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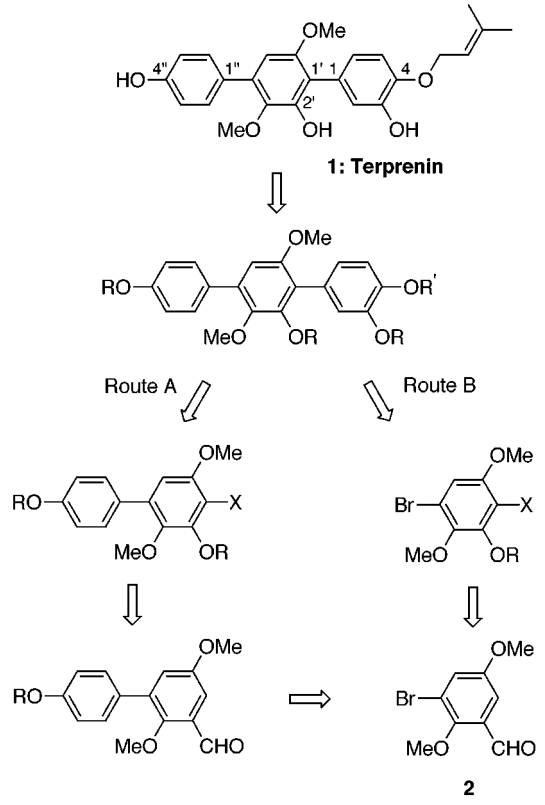
We achieved a total synthesis of terprenin, a novel potent immunoglobulin E antibody suppressant which was obtained from the fermentation broth of *Aspergillus candidus* RF-5672 and has a highly oxygenated *p*-terphenyl skeleton with a prenyloxy side chain. The key steps relied on the Suzuki reaction to construct the terphenyl skeleton and on regioselective halogenations to selectively combine the aromatic rings. The highly efficient and practical production of this important natural product offers promise for the development of a new type of antiallergic drug.

Introduction

Terprenin (**1**, Scheme 1) was discovered in the fermentation broth of *Aspergillus candidus* RF-5672 during our screening of natural products aimed at discovering new immunosuppressants from natural products.[1,2] Terprenin has a novel highly oxygenated *p*-terphenyl structure with a prenyloxy side chain.[3] Although several natural cytotoxic *p*-terphenyl compounds have been isolated from fungi, no derivative with an alkenyl side chain has been reported.[4] The impressive feature of immunosuppressive activities of terprenin is its highly potent in vitro and in vivo suppressive effect on immunoglobulin E (IgE) antibody production without any toxicological signs.[5] IgE is known to play a central role in a variety of allergic diseases including atopic dermatitis, bronchial asthma, allergic rhinitis, allergic conjunctivitis, and anaphylaxis.[6] Although FK506 and cyclosporin A, which are known to be strong immunosuppressants, are established drugs in the management of human organ transplantation, they have been reported to potentiate IgE production in mice.[7]

Scheme 1



To develop a new type of immunosuppressive drug for use against allergic diseases, we first sought to develop a total synthesis of terprenin. Here, we report the highly efficient and practical total synthesis of terprenin with significant new results.[5]

Results and Discussion

Since biaryls are important core components in natural products, organic materials, and molecules of medicinal interest, a number of procedures have been developed for the formation of an aryl−aryl linkage,[8] including modern catalytic cross-coupling reactions such as the Negishi,[9] Stille,[10] Hiyama,[11] and Suzuki reactions.[12] Among them,

(1) Kamigauchi, T.; Sakazaki, R.; Nagashima, K.; Kawamura, Y.; Yasuda, Y.; Matsushima, K.; Tani, H.; Takahashi, Y.; Ishii, K.; Suzuki, R.; Koizumi, K.; Nakai, H.; Ikenishi, Y.; Terui, Y. *J. Antibiot.* **1998**, *51*, 445.

(2) For our previous work in this field, see: (a) Yasui, K.; Tamura, Y.; Nakatani, T.; Kawada, K.; Ohtani, M. *J. Org. Chem.* **1995**, *60*, 7567. (b) Yasui, K.; Tamura, Y.; Nakatani, T.; Horibe, I.; Kawada, K.; Koizumi, K.; Suzuki, R.; Ohtani, M. *J. Antibiot.* **1996**, *49*, 173.

(3) Only 70 mg of terprenin was isolated from 2 L of the fermentation broth.

(4) For natural *p*-terphenyl compounds, see: (a) Marchell, R.; Vining, L. C. *J. Chem. Soc. Chem. Commun.* **1973**, 555. (b) Takahashi, C.; Yoshihira, K.; Natori, S.; Umeda, M. *Chem. Pharm. Bull.* **1976**, *24*, 613. (c) Cutler, H. G.; LeFiles, J. H.; Crumley, F. G.; Cox, R. H. *J. Agric. Food Chem.* **1978**, *26*, 632. (d) Kurobane, I.; Vining, L. C.; McInnes, A. G.; Smith, D. G. *J. Antibiot.* **1979**, *32*, 559. (e) Kobayashi, A.; Takemoto, A.; Koshimizu, K.; Kawazu, K. *Agric. Biol. Chem.* **1985**, *49*, 867. (f) Tringali, C.; Piattelli, M.; Geraci, C.; Nicolosi, G.; Rocco, C. *Can. J. Chem.* **1987**, *65*, 2369.

(5) For a preliminary account of the biological activities and total syntheses of terprenin, see: Kawada, K.; Arimura, A.; Tsuri, T.; Fuji, M.; Komurasaki, T.; Yonezawa, S.; Kugimiya, A.; Haga, N.; Mitsumori, S.; Inagaki, M.; Nakatani, T.; Tamura, Y.; Takechi, S.; Taishi, T.; Kishino, J.; Ohtani, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 973.

(6) For a general review, see: Plant, M.; Zimmerman, E. M. Allergy and Mechanisms of Hypersensitivity. In *Fundamental Immunology, 3rd ed*; Pawl, W. E., Ed.; Raven Press: New York, 1993; pp 1399−1425.

(7) Nagai, H.; Hiyama, H.; Matsuo, A.; Ueda, Y.; Inagaki, N.; Kawada, K. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 321.

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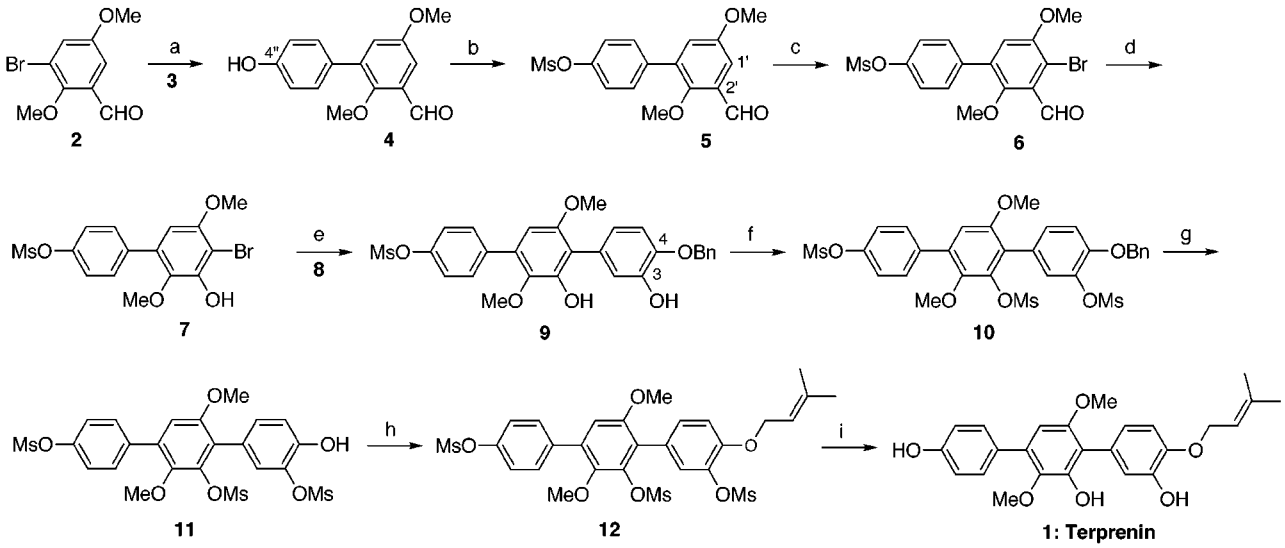
Scheme 2[a]

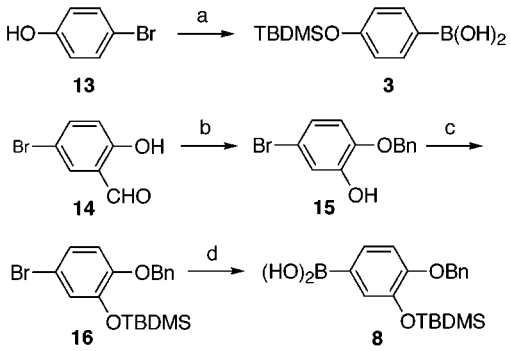


[a] (a) $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, EtOH (100%); (b) MsCl, Et_3N, CH_2Cl_2 (94%); (c) Br_2, NaOAc, HOAc (81%); (d) *m*-CPBA, CH_2Cl_2 followed by 4 N HCl, dioxane (85%); (e) $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, EtOH; (f) MsCl, Et_3N, CH_2Cl_2 (68% for steps e, f); (g) H_2, $Pd(OH)_2$-C, dioxane (92%); (h) prenyl bromide, K_2CO_3, DMF (99%); (i) 3 N KOH, dioxane, MeOH (97%).

the Suzuki reaction, which is based on the palladium-catalyzed cross-coupling of aryl halides or triflates with boronic acids, offers several advantages, such as being unaffected by the presence of water and tolerating a variety of functional groups, which have led to its increased use for a wide range of molecules.[13] We chose the Suzuki reaction to construct the terphenyl skeleton. In considering the palladium-catalyzed elimination reaction of allylic phenyl ethers[14] as well as the instability of the prenyloxy group under acidic and hydrogenous conditions,[15] we decided to construct a C-4 side chain moiety at the last step in the synthetic sequence. Additional consideration of a conveniently available starting material, 3-bromo-2,5-dimethoxybenzaldehyde (**2**), guided the design of our retrosynthetic analysis as shown in Scheme 1. The crucial step in the synthesis was the regioselective functionalization of the aromatic ring. We also needed to be able to discriminate the six oxygen functions using an appropriate protection method.

The first synthesis (route A in Scheme 1) relied upon the stepwise Suzuki reaction as shown in Scheme 2. The starting material **2** was prepared from 2-hydroxy-5-methoxybenzaldehyde according to a known procedure.[16] The Suzuki reaction of **2** with boronic acid **3**[17] (Scheme 3) proceeded almost quantitatively to afford the biphenyl compound **4**. In this reaction, the *tert*-butyldimethylsilyl (TBDMS)-protected group of **3** was cleaved to give the corresponding phenol **4** in the presence of water. A similar palladium-catalyzed desilylation of phenolic silyl ethers has been reported recently by Wilson and Keay.[18]

Scheme 3[a]



[a] (a) ref. 17; (b) ref. 19; (c) TBDMS-Cl, imidazole, DMF (90%); (d) *n*-BuLi, $B(Oi\text{-}Pr)_3$, THF followed by H_2O (64%).

After protection of the C-4″ hydroxyl group of **4** as the mesylate, bromination of **5** with molecular bromine led exclusively to regioselective functionalization to give the desired bromide **6**. In this bromination, the C-2′ formyl group seems to play an important role in the regioselectivity, since the desired C-1′ brominated compound could not be obtained selectively by using the C-2′ phenol or mesylate as a substrate. Next, the formyl group of **6** was converted to the hydroxyl group by Baeyer−Villiger oxidation followed by acidic hydrolysis. Catechol-type boronic acid **8** was prepared from 5-bromosalicylaldehyde

(8) For general reviews, see: (a) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3359. (b) Bringmann, G.; Walte, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (c) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.

(9) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

(10) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. *Org. React.* **1997**, *50*, 1.

(11) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845.

(12) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(13) For the synthesis of terphenyl compounds, see: (a) Iwema Bakker, W. I.; Haas, M.; den Hertog, H. J., Jr.; Verboom, W.; de Zeeuv, D.; Bruins, A. P.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 972. (b) Todd, M. H.; Balasubramanian, S.; Abell, C. *Tetrahedron Lett.* **1997**, *38*, 6781. For recent works in this area, see: (c) Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718. (d) Anderson, N. G.; Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 9556. (e) Sengupta, S.; Bhattacharyya, S. *J. Org. Chem.* **1997**, *62*, 3405. (f) Su, D. S.; Meng, D.; Bertinato, P.; Balog, A.; Sorenson, E. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 757. (g) Ruhland, B.; Bombrun, A.; Gallop, M. A. *J. Org. Chem.* **1997**, *62*, 7820.

(14) For a palladium-catalyzed hydrogenolysis of allylic compounds, see: Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1.

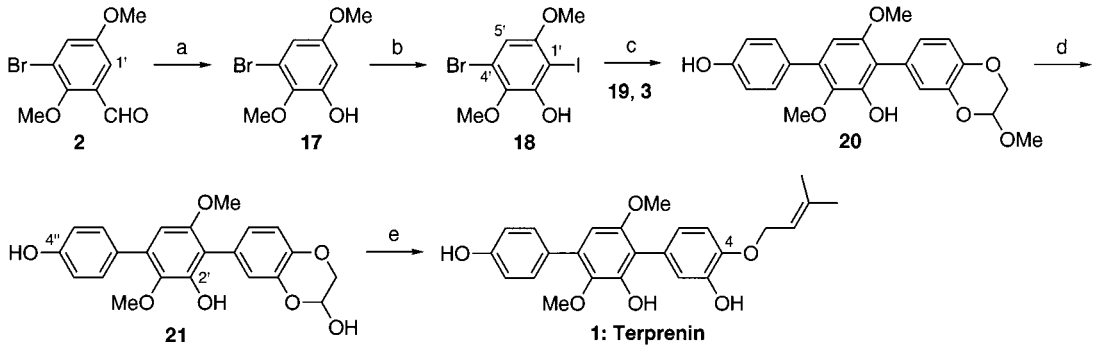
(15) About 50% of the prenyl group of terprenin was cleaved when treated with 3% TFA−MeOH−H_2O for 1 h at 25 °C.

(16) Rubenstein, L. *J. Chem. Soc.* **1925**, 1998.

(17) Oxford, A. W.; Clitherow, J. W. UK Patent GB 2276162 A, 1994; *Chem. Abstr.* **1994**, *121*, 300771z.

(18) Wilson, N. S.; Keay, B. A. *Tetrahedron Lett.* **1996**, *37*, 153.

Scheme 4[a]



[a] (a) *m*-CPBA, CH_2Cl_2 followed by 1 N KOH, MeOH (81%); (b) I_2, *t*-$BuNH_2$, toluene, 48 h (92%); (c) $Pd_2(dba)_3$, 2 M Na_2CO_3, DME, EtOH followed by $Pd(PPh_3)_4$ (70%); (d) *p*-TsOH, H_2O, acetone (83%); (e) $Me_2CHP^+Ph_3\ I^-$, *n*-BuLi, THF (87%).

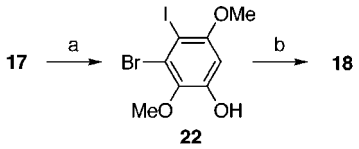
(**14**), as shown in Scheme 3, through a sequence involving conversion of **14** to the phenol **15**,[19] protection of the hydroxyl group of **15** as the TBDMS ether **16**, and borylation of **16** using triisopropyl borate. Although aryl halides or triflates containing electron-withdrawing functional groups have been known to be more favorable for the Suzuki reaction,[12] the reaction of the highly oxygenated, electron-donating, and sterically hindered bromide **7** with **8** proceeded smoothly to afford the expected terphenyl compound **9**.

Formation of the terphenyl skeleton set the stage for the introduction of the side chain at the C-4 position. Since employing acetyl or silyl protecting group at the C-3 hydroxyl group caused migration of the protecting group to the C-4 free hydroxyl group produced at the next hydrogenolysis step, the free hydroxyl groups of **9** were protected as mesylates which would be sensitive to basic deprotection. After deprotection of the benzyl ether of **10** by hydrogenolysis, the prenyl group was introduced to the desired position of terphenyl compound **11** using prenyl bromide. Finally, deprotection of the mesyl groups of **12** by potassium hydroxide led to completion of the total synthesis of terprenin. Spectroscopic data and biological activities of the synthetic compound were identical in all respects to the natural product from *A. candidus*.

In this first total synthesis, the yield of each step was quite high and the overall yield from **2** was 40%. Moreover, since the purification of each product was performed by simple crystallization, no chromatography was needed throughout the manipulation. Therefore, this procedure would be suitable for large-scale and practical production of terprenin.

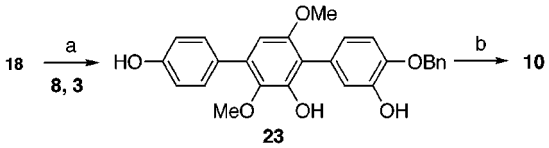
The second synthesis (route B in Scheme 1) was based on the one-pot Suzuki reaction starting from the same bromobenzaldehyde **2** as shown in Scheme 4. To perform the Suzuki reaction regioselectively, we tried to introduce an iodo group to the C-1′ position of the aryl bromide **2**. First, since the iodination of **2** did not proceed selectively,[20] the aldehyde was converted to phenol **17**. Treatment of **17** with iodine in the presence of *tert*-butylamine for 48 h led to regioselective iodination to give the desired C-1′ iodide **18** in 92% yield.[21] A small amount of C-5′ iodide **22** (Scheme 5) was also obtained, and the regioselectivity was 15:1. The success of this reaction was attributed to *tert*-butylamine, without which no iodination occurred. Employing other amines such as diisopropylamine and triethylamine led to lower regioselectivity. We also observed that the isolated **22**, which was obtained as the major product after the reaction of 15 min, was converted to **18** under the above reaction conditions for 48 h as shown in Scheme 5. Namely, the reaction is thermodynamically controlled, and **18** becomes the predominant product when the reaction reaches equilibrium.

Scheme 5[a]



[a] (a) I_2, *t*-$BuNH_2$, toluene, 15 min (64%); (b) *t*-$BuNH_2$, toluene, 48 h (**18**:**22** = 15:1).

Scheme 6[a]



[a] (a) $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, EtOH (67%); (b) MsCl, Et_3N, CH_2Cl_2 (91%).

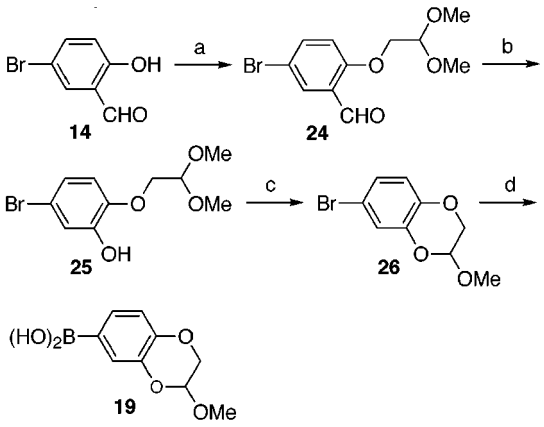
After obtaining compound **18** which had different halogen functionality at the desired C-1′ and C-4′ positions, we examined the various conditions of the one-pot Suzuki reaction. Although the iodo group was located at a more sterically hindered position than the bromo group, as shown in Scheme 6, the catechol-type boronic acid **8** reacted preferentially with the iodo-substituted position using $Pd(PPh_3)_4$ as a catalyst. Without isolation

(19) (a) Schmidt, U.; Meyer, R.; Leitenberger, V.; Griesser, H.; Lieberknecht, A. *Synthesis* **1992**, 1025. (b) Suzuki, K.; Satake, N.; Sugiura, A.; Fujii, T. Japan Patent Kokai 5-213930, 1993; *Chem. Abstr.* **1994**, *120*, 134493t.

(20) Efforts to effect the iododethallation of **2** were unrewarding. For related iodination reactions, see: (a) Taylor, E. C.; Kienzle, F.; Robey, R. L.; McKillop, A.; Hunt, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 4845. (b) Merkushev, E. B. *Synthesis* **1988**, 923. (c) Noda, Y.; Kashima, M. *Tetrahedron Lett.* **1997**, *38*, 6225. (d) Zupan, M.; Iskra, J.; Stavber, S. *Tetrahedron Lett.* **1997**, *38*, 6305.

(21) For the iodination of phenols with iodine and amines, see: (a) Chabrier, P.; Seyden-Penne, J.; Fouace, A. *C. R. Acad. Sci.* **1957**, *245*, 174. For related *ortho*-bromination of phenols, see: (b) Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358. (c) Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576.

Scheme 7[a]



[a] (a) 2-bromo-1,1-dimethoxyethane, K_2CO_3, DMF (92%); (b) *m*-CPBA, EtOAc followed by 1 N NaOH, MeOH; (c) *p*-TsOH, CH_2Cl_2, MeOH (70% for steps b, c); (d) *n*-BuLi, B(O*i*-Pr)$_3$, THF followed by H_2O (60%).

of the biphenyl compound, the phenol-type boronic acid **3** and $Pd(PPh_3)_4$ were added to the reaction mixture, and the expected terphenyl compound **23** was obtained in 67% yield. Since the phenol **23** was converted to the mesylate **10**, terprenin could be prepared efficiently using this one-pot Suzuki reaction. We next tried to find a more convenient procedure without using protection−deprotection of the hydroxyl groups at the final stage of introducing the C-4 side chain.

As shown in Scheme 7, we converted **14** to a bicyclic acetal **26** through a sequence involving condensation of the hydroxyl group of **14** with 2-bromo-1,1-dimethoxyethane, Baeyer−Villiger oxidation of **24** followed by alkaline hydrolysis, and acetal formation of **25** by treatment with *p*-toluenesulfonic acid. Borylation of **26** furnished the desired boronic acid **19**. Although the Suzuki reaction of **18** with this acetal-type boronic acid **19** proceeded rather sluggishly and unselectively with $Pd(PPh_3)_4$ as the catalyst, employing $Pd_2(dba)_3$ as the catalyst led to regioselective cross-coupling at the iodo-substituted position to give the biphenyl compound. As a result, the one-pot Suzuki reaction proceeded smoothly on the following addition of the phenol-type boronic acid **3** and $Pd(PPh_3)_4$ to afford the expected terphenyl compound **20** in 70% yield as shown in Scheme 4.[22]

The second total synthesis of terprenin was completed by hydrolysis of the acetal **20** using *p*-toluenesulfonic acid in aqueous acetone and the Wittig reaction of **21** with excess isopropyltriphenylphosphonium iodide without protection of the C-2′ and C-4″ hydroxyl groups. Since this second synthesis needed no protection−deprotection procedure of the hydroxyl groups, the synthetic sequence could be minimized for efficient production of terprenin.

These highly efficient and practical syntheses of terprenin, a potent IgE antibody suppressant, can offer sufficient supplies of this important natural product in order to develop a new type of antiallergic drug as well as to clarify its interesting mechanism of action. These syntheses also provide a convenient method of preparing compounds of this type and suggest that employing the Suzuki reaction can be useful for the construction of these highly oxygenated aromatic molecules.

(22) The second coupling did not proceed with the use of $Pd_2(dba)_3$ as the catalyst.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were determined at 200 or 300 MHz. ^{13}C NMR spectra were determined at 50.3 or 75.5 MHz. High-resolution liquid secondary ion mass spectra (HR-LSIMS) or fast atom bombardment mass spectra (HR-FABMS) were determined using *m*-nitrobenzyl alcohol as a matrix. Fractional moles of water found in some of the analytical samples could not be prevented despite drying in vacuo and were confirmed by their presence in the Karl Fischer method. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere with anhydrous solvents that had been dried over type 4A molecular sieves. Drying of an organic phase over anhydrous sodium sulfate is simply indicated by the word "dried". Column chromatography using Merck Silica gel 60 or a Merck Lobar column is referred to as "chromatography on silica gel".

4′-Hydroxy-2,5-dimethoxy-[1,1′]biphenyl-3-aldehyde (4). To a solution of 18.3 g (74.8 mmol) of **2**[16] in 300 mL of DME and 75 mL of EtOH were added 20.7 g (82.2 mmol) of **3**, 150 mL of 2 M Na_2CO_3 solution, and 4.23 g (3.74 mmol) of $Pd(PPh_3)_4$ under an argon atmosphere. The mixture was refluxed for 20 h. After cooling to 0 °C, the mixture was diluted with 2 N HCl solution and EtOAc and then filtered through a Celite pad. The filtrate was extracted with EtOAc, and then the organic solution was washed with 2 N HCl solution, saturated $NaHCO_3$ solution, and brine. The organic solution was dried and concentrated. The residue was crystallized from (*i*-Pr)$_2$O−hexane to afford 19.3 g (100%) of **4** as colorless crystals: mp 120−122 °C; IR (KBr) 3410, 3256, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3H), 3.85 (s, 3H), 5.24 (s, 1H), 6.94 (m, 2H), 7.16 (d, J = 3.3 Hz, 1H), 7.28 (d, J = 3.3 Hz, 1H), 7.48 (m, 2H), 10.43 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.83, 62.77, 108.52, 115.54 (2C), 124.73, 129.21, 130.02, 130.30 (2C), 136.90, 155.47, 155.60, 156.00, 190.50. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.82; H, 5.55.

4′-(Methanesulfonyloxy)-2,5-dimethoxy-[1,1′]biphenyl-3-aldehyde (5). To a solution of 19.3 g (74.8 mmol) of **4** in 320 mL of CH_2Cl_2 were added 13.1 mL (93.7 mmol) of Et_3N and 6.6 mL (85.9 mmol) of methanesulfonyl chloride at 0 °C. The mixture was stirred for 18 h at 20 °C and diluted with 1 N HCl solution. The mixture was extracted with $CHCl_3$, and then the organic solution was washed with saturated $NaHCO_3$ solution and brine and then dried and concentrated. The crystalline residue was washed with (*i*-Pr)$_2$O−hexane to afford 23.7 g (94%) of **5** as colorless crystals: mp 129−130 °C; IR (KBr) 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.22 (s, 3H), 3.48 (s, 3H), 3.86 (s, 3H), 7.15 (d, J = 3.5 Hz, 1H), 7.34 (d, J = 3.5 Hz, 1H), 7.39 (m, 2H), 7.65 (m, 2H), 10.43 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 37.68, 55.88, 63.27, 109.64, 122.19 (2C), 124.53, 130.24, 130.59 (2C), 135.75, 136.05, 148.80, 155.13, 156.08, 189.83. Anal. Calcd for $C_{16}H_{16}O_6S$: C, 57.13; H, 4.79; S, 9.53. Found: C, 57.32; H, 4.84; S, 9.53.

4-Bromo-4′-(methanesulfonyloxy)-2,5-dimethoxy-[1,1′]-biphenyl-3-aldehyde (6). To a solution of 12.3 g (36.6 mmol) of **5** and 6.0 g (73.3 mmol) of NaOAc in 150 mL of HOAc was added 3.77 mL (73.3 mmol) of bromine. After the mixture was stirred for 18 h at 20 °C, 6.0 g (73.3 mmol) of NaOAc and 3.77 mL (73.3 mmol) of bromine were added. The mixture was stirred for 5 h at 50 °C and then poured into 1 L of ice−water. The mixture was diluted with 50 mL of 1 N $Na_2S_2O_3$ solution and stirred for 30 min. The resulting precipitate was filtered and dissolved in $CHCl_3$, and then the organic solution was washed with saturated $NaHCO_3$ solution and brine and then dried and concentrated. The residue was crystallized from $CHCl_3$−hexane to afford 12.3 g (81%) of **6** as colorless crystals: mp 179−180 °C; IR (KBr) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.22 (s, 3H), 3.45 (s, 3H), 3.94 (s, 3H), 7.04 (s, 1H), 7.39 (m, 2H), 7.64 (m, 2H), 10.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 37.73, 57.03, 62.82, 113.07, 117.52, 122.23 (2C), 130.38, 130.64 (2C), 134.49, 135.92, 148.81, 152.34, 152.86, 191.03. Anal.

Calcd for $C_{16}H_{15}BrO_6S$: C, 46.28; H, 3.64; Br, 19.24; S, 7.72. Found: C, 46.62; H, 3.73; Br, 18.89; S, 8.00.

4-Bromo-4′-(methanesulfonyloxy)-2,5-dimethoxy-[1,1′]-biphenyl-3-ol (7). To a solution of 10.6 g (25.6 mmol) of **6** in 200 mL of CH_2Cl_2 was added 8.28 g (38.4 mmol) of 80% *m*-CPBA at 0 °C. The mixture was stirred for 18 h at 20 °C and then refluxed for 4 h. The mixture was diluted with 1 N $Na_2S_2O_3$ and saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The organic solution was washed with saturated $NaHCO_3$ solution and brine and then dried and concentrated. The residue was dissolved in 200 mL of dioxane, and then 100 mL of 4 N HCl solution was added. The mixture was stirred for 18 h at 50 °C. After cooling to 20 °C, the mixture was diluted with water and extracted with EtOAc, and then the organic solution was washed with saturated $NaHCO_3$ solution and brine and then dried and concentrated. The crystalline residue was washed with 1:1 $(i\text{-Pr})_2O$−hexane to afford 8.81 g (85%) of **7** as colorless crystals: mp 172−174 °C; IR (KBr) 3410 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.21 (s, 3H), 3.47 (s, 3H), 3.89 (s, 3H), 6.15 (s, 1H), 6.42 (s, 1H), 7.36 (m, 2H), 7.63 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 37.64, 56.57, 61.19, 98.79, 104.07, 122.14 (2C), 130.42 (2C), 131.88, 136.79, 138.98, 147.83, 148.66, 153.02. Anal. Calcd for $C_{15}H_{15}BrO_6S$: C, 44.68; H, 3.75; Br, 19.81; S, 7.95. Found: C, 44.58; H, 3.79; Br, 19.59; S, 8.07.

4-Benzyloxy-4″-(methanesulfonyloxy)-3′,6′-dimethoxy-[1,1′:4′,1″]terphenyl-3,2′-diol (9). The procedure described for the preparation of **4** was repeated using 8.79 g (21.8 mmol) of **7**, 110 mL of DME, 23 mL of EtOH, 9.37 g (26.2 mmol) of **8**, 55 mL of 2 M Na_2CO_3 solution, and 1.26 g (1.09 mmol) of $Pd(PPh_3)_4$ to afford **9**, which was used for the next reaction without further purification. Crystallization from EtOAc−hexane afforded pure **9** as colorless crystals: mp 183−185 °C; IR (KBr) 3496, 3465 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.21 (s, 3H), 3.47 (s, 3H), 3.75 (s, 3H), 5.16 (s, 2H), 5.70 (s, 1H), 5.87 (s, 1H), 6.45 (s, 1H), 6.95 (dd, J = 1.8 and 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 1.8 Hz, 1H), 7.35−7.47 (m, 7H), 7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 37.57, 56.05, 61.08, 71.11, 103.78, 111.81, 117.21, 117.32, 122.07 (2C), 122.40, 126.22, 127.92 (2C), 128.47, 128.79 (2C), 130.47 (2C), 131.49, 136.43, 137.48, 138.88, 145.37, 145.59, 147.42, 148.54, 153.64. Anal. Calcd for $C_{28}H_{26}O_8S$: C, 64.36; H, 5.01; S, 6.14. Found: C, 64.22; H, 5.09; S, 6.07.

Methanesulfonic Acid 4″-(benzyloxy)-4,3′-bis(methanesulfonyloxy)-2′,5′-dimethoxy-[1,1′:4′,1″]terphenyl-3″-yl Ester (10). The procedure described for the preparation of **5** was repeated using the above product, 100 mL of CH_2Cl_2 15.2 mL (109 mmol) of Et_3N, and 6.75 mL (87.2 mmol) of methanesulfonyl chloride to afford, after crystallization from MeOH, 10.1 g (68% from **7**) of **10** as colorless crystals: mp 163−165 °C; ^1H NMR ($CDCl_3$) δ 2.68 (s, 3H), 3.13 (s, 3H), 3.21 (s, 3H), 3.56 (s, 3H), 3.78 (s, 3H), 5.19 (s, 2H), 6.84 (s, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.32−7.49 (m, 9H), 7.69 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 37.62, 38.70, 39.57, 56.31, 61.37, 71.14, 111.38, 113.87, 122.13 (2C), 123.97, 125.59, 127.25, 127.75 (2C), 128.54, 128.81 (2C), 130.75 (2C), 130.82, 134.18, 135.75, 136.66, 138.27, 142.04, 144.79, 148.82, 150.41, 153.13; HR-LSIMS m/z 701.0793 $(M + Na)^+$ (calcd for $C_{30}H_{30}NaO_{12}S_3$ m/z 701.0795).

3,2″,4″-Tris(methanesulfonyloxy)-3′,6′-dimethoxy-[1,1′:4′,1″]terphenyl-4-ol (11). A solution of 9.94 g (14.6 mmol) of **10** in 200 mL of dioxane was hydrogenated at ordinary pressure using 2.98 g of 20% palladium hydroxide on carbon for 18 h at 20 °C. The mixture was filtered through a Celite pad, and the filtrate was concentrated. The crystalline residue was washed with $(i\text{-Pr})_2O$ to afford 7.94 g (92%) of **11** as colorless crystals: mp 185−187 °C; IR (KBr) 3503 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.83 (s, 3H), 3.22 (s, 3H), 3.28 (s, 3H), 3.55 (s, 3H), 3.77 (s, 3H), 6.32 (s, 1H), 6.85 (s, 1H), 7.16 (m, 1H), 7.27−7.31 (m, 2H), 7.39 (m, 2H), 7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 37.46, 38.03, 39.35, 56.18, 60.87, 111.53, 117.03, 122.18 (2C), 122.91, 123.99, 126.12, 130.45, 130.53 (2C), 133.19, 135.90, 136.40, 141.49, 144.02, 148.53, 149.23, 152.65. Anal. Calcd for $C_{23}H_{24}O_{12}S_3$: C, 46.93; H, 4.11; S, 16.34. Found: C, 46.63; H, 4.11; S, 16.29.

Methanesulfonic Acid 4,3′-Bis(methanesulfonyloxy)-2′,5′-dimethoxy-4-(3-methyl-2-butenyloxy)-[1,1′:4′,1″]terphenyl-3″-yl Ester (12). To a solution of 7.75 g (13.2 mmol) of **11** in 65 mL of DMF were added 2.73 g (19.8 mmol) of K_2CO_3 and 1.82 mL (15.8 mmol) of prenyl bromide at 0 °C. The mixture was stirred for 18 h at 20 °C and then diluted with 0.2 N HCl solution at 0 °C. The mixture was extracted with EtOAc, and then the organic solution was washed with 10% citric acid solution, saturated $NaHCO_3$ solution, and brine and then dried and concentrated. The crystalline residue was washed with $(i\text{-Pr})_2O$ to afford 8.54 g (99%) of **12** as colorless crystals: mp 155−157 °C; ^1H NMR ($CDCl_3$) δ 1.76 (d, J = 0.9 Hz, 3H), 1.81 (s, 3H), 2.71 (s, 3H), 3.21 (s, 3H), 3.23 (s, 3H), 3.56 (s, 3H), 3.78 (s, 3H), 4.64 (d, J = 6.6 Hz, 2H), 5.49 (dd, J = 0.9 and 6.6 Hz, 1H), 6.84 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.32−7.40 (m, 4H), 7.69 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.32, 25.81, 37.65, 38.68, 39.61, 56.32, 61.39, 65.94, 111.41, 113.60, 118.78, 122.16 (2C), 124.15, 125.16, 127.31, 130.80 (3C), 134.15, 136.74, 138.37, 139.28, 142.10, 144.87, 148.86, 150.61, 153.20. Anal. Calcd for $C_{28}H_{32}O_{12}S_3$: C, 51.21; H, 4.91; S, 14.65. Found: C, 50.92; H, 4.92; S, 14.39.

3′,6′-Dimethoxy-4-(3-methyl-2-butenyloxy)-[1,1′:4′,1″]-terphenyl-3,2′,4″-triol (terprenin, 1). To a solution of 8.54 g (13.0 mmol) of **12** in 130 mL of 1:1 dioxane−MeOH was added 260 mL of 3 N KOH solution. The mixture was stirred for 18 h at 50 °C and then diluted with 2 N HCl solution at 0 °C. The mixture was extracted with $CHCl_3$, and then the organic solution was washed with 10% citric acid solution, saturated $NaHCO_3$ solution, and brine and then dried and concentrated. The residue was crystallized from $(i\text{-Pr})_2O$ to afford 5.33 g (97%) of **1** as colorless crystals: mp 155.5−156 °C; IR (KBr) 3393 cm^{-1};^1H NMR (acetone-d_6, 600 MHz) δ 1.77 (br s, 3H), 1.79 (br s, 3H), 3.37 (s, 3H), 3.73 (s, 3H), 4.63 (br d, J = 6.6 Hz, 2H), 5.52 (m, 1H), 6.49 (s, 1H), 6.83 (dd, J = 2.2 and 8.2 Hz, 1H), 6.92 (d, J = 2.2 Hz, 1H), 6.94 (m, 2H), 6.96 (d, J = 8.2 Hz, 1H), 7.54 (m, 2H), 7.62 (br s, 1H), 7.78 (s, 1H), 8.64 (br s, 1H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 18.31, 26.00, 56.04, 60.67, 66.18, 103.85, 112.75, 116.06 (2C), 117.61, 118.97, 121.44, 123.15, 127.91, 130.48, 130.85 (2C), 133.54, 137.50, 140.04, 146.23, 146.79, 149.24, 154.51, 157.79; HR-LSIMS m/z 422.1730 $(M)^+$ (calcd for $C_{25}H_{26}O_6$ m/z 422.1728). Anal. Calcd for $C_{25}H_{26}O_6 \cdot 0.6H_2O$: C, 69.30; H, 6.33. Found: C, 69.40; H, 6.41. Karl Fischer Calcd for $C_{25}H_{26}O_6 \cdot 0.6H_2O$: H_2O, 2.50. Found: H_2O, 2.53.

1-(Benzyloxy)-4-bromo-2-(*tert*-butyldimethylsilyloxy)-benzene (16). To a solution of 85.0 g (305 mmol) of **15**[19] in 500 mL of DMF were added 27.0 g (397 mmol) of imidazole and 55.1 g (365 mmol) of *tert*-butyldimethylsilyl chloride. The mixture was stirred for 18 h at 20 °C and then concentrated in vacuo. The residue was diluted with 1 L of EtOAc, 500 mL of water, and 200 mL of 1 N HCl solution. The organic layer was separated and washed with water, saturated $NaHCO_3$ solution, and brine and then dried and concentrated. The crystalline residue was washed with hexane to afford 108 g (90%) of **16** as colorless crystals: mp 34−36 °C; ^1H NMR ($CDCl_3$) δ 0.11 (s, 6H), 0.95 (s, 9H), 5.01 (s, 2H), 6.53 (d, J = 9.0 Hz, 1H), 6.95−7.00 (m, 2H), 7.30−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −4.64 (2C), 18.35, 25.63 (3C), 71.02, 112.84, 115.24, 124.27, 124.42, 127.83 (2C), 128.08, 128.49 (2C), 136.61, 146.40, 149.69. Anal. Calcd for $C_{19}H_{25}BrO_2Si$: C, 58.01; H, 6.41; Br, 20.31. Found: C, 57.98; H, 6.39; Br, 20.16.

4-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)benzeneboronic Acid (8). To a solution of 56.9 g (145 mmol) of **16** in 500 mL of THF was added 100 mL (159 mmol) of 1.59 N *n*-BuLi in hexane dropwise over a 10-min period at −78 °C. The mixture was stirred for 30 min, and then 100 mL (433 mmol) of triisopropyl borate was added. The mixture was allowed to warm to −20 °C and diluted with 30 mL of water. After stirring for 18 h, the mixture was extracted with EtOAc. The organic solution was washed with water and brine and then dried and concentrated. The crystalline residue was washed with hexane to afford 32.9 g (64%) of **8** as colorless crystals: mp 125−126 °C; IR (KBr) 3433 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.17 (s, 6H), 1.01 (s, 9H), 5.14 (s, 2H), 7.04 (d, J = 8.2 Hz, 1H), 7.30−7.50 (m, 5H), 7.67 (d, J = 1.4 Hz, 1H), 7.77

(dd, J = 1.4 and 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −4.48 (2C), 18.42, 25.79 (3C), 70.51, 113.00, 123.00, 127.61, 127.86 (2C), 128.03, 128.48 (2C), 130.19, 136.74, 144.84, 154.12; HR−FABMS m/z 651.2314 (bis(m-nitrobenzyl) ester)$^+$ (calcd for $C_{33}H_{37}{}^{11}BN_2NaO_8Si$ m/z 651.2316).

3-Bromo-2,5-dimethoxyphenol (17). To a solution of 2.45 g (10.0 mmol) of **2** in 25 mL of CH_2Cl_2 was added 3.24 g (15.0 mmol) of 80% m-CPBA at 0 °C. The mixture was allowed to warm to 20 °C and stirred for 18 h. The mixture was diluted with $CHCl_3$ and 1 N $Na_2S_2O_3$ solution. The organic solution was washed with saturated $NaHCO_3$ solution and brine and then dried and concentrated. The residue was dissolved in 50 mL of MeOH, and then 1 mL of 1 N KOH solution was added. The mixture was stirred for 1 h at 20 °C and then diluted with 50 mL of EtOAc, 50 mL of water, and 2 mL of 1 N HCl solution. The organic solution was washed with water and brine and then dried and concentrated. The residue was dissolved in 1:2 EtOAc−hexane and filtered through a pad of silica gel. The filtrate was concentrated, and the resulting crystalline residue was washed with hexane to afford 1.89 g (81%) of **17** as colorless crystals: mp 73−74 °C; IR ($CHCl_3$) 3526 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H), 3.85 (s, 3H), 5.72 (s, 1H), 6.50 (d, J = 3.0 Hz, 1H), 6.62 (d, J = 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.76, 61.36, 101.40, 109.81, 115.81, 138.71, 150.30, 157.06. Anal. Calcd for $C_8H_9BrO_3{\cdot}0.1H_2O$: C, 40.91; H, 3.95; Br, 34.02. Found: C, 40.83; H, 3.93; Br, 33.78. Karl Fischer Calcd for $C_8H_9BrO_3{\cdot}0.1H_2O$: H_2O, 0.77. Found: H_2O, 0.63.

3-Bromo-6-iodo-2,5-dimethoxyphenol (18). To a solution of 5.0 mL (47.6 mmol) of *tert*-butylamine in 160 mL of toluene was added 5.94 g (23.4 mmol) of iodine. After stirring for 1 h at 25 °C, 5.46 g (23.4 mmol) of **17** was added at 0 °C. The mixture was allowed to warm to 25 °C, stirred for 48 h, and then diluted with EtOAc. The organic solution was washed with water, 1 N $Na_2S_2O_3$ solution, and brine and then dried and concentrated. The crystalline residue was washed with hexane to afford 7.72 g (92%) of **18**, as colorless crystals: mp 135−136 °C; IR ($CHCl_3$) 3507 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 3.87 (s, 3H), 6.13 (s, 1H), 6.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 57.44, 61.92, 74.85, 107.00, 116.51, 139.13, 151.26, 156.20. Anal. Calcd for $C_8H_8BrIO_3$: C, 26.77; H, 2.25; Br, 22.26, I, 35.35. Found: C, 26.73; H, 2.28; Br, 22.04, I, 35.39.

2,5-Dimethoxy-4-(3-methoxy-2,3-dihydrobenzo[1,4]-dioxin-6-yl)-biphenyl-3,4′-diol (20). To a solution of 500 mg (1.40 mmol) of **18** in 20 mL of DME and 2.8 mL of EtOH were added 292 mg (1.40 mmol) of **19**, 2.8 mL of 2 M Na_2CO_3 solution, and 13.0 mg (0.0140 mmol) of $Pd_2(dba)_3$ under an argon atmosphere. The mixture was refluxed for 2 h. After cooling to 20 °C, 700 mg (2.80 mmol) of **3**, 5.6 mL of 2 M Na_2CO_3 solution, 5 mL of EtOH, and 160 mg (0.14 mmol) of $Pd(PPh_3)_4$ were added. The mixture was refluxed for 18 h. After cooling to 20 °C, the mixture was diluted with saturated NH_4Cl solution and then extracted with EtOAc. The organic solution was washed with saturated $NaHCO_3$ solution and brine and then dried and concentrated. The residue was chromatographed on silica gel using 2:3 EtOAc−hexane to afford 401 mg (70%) of **20** as colorless crystals: mp 103−105 °C; IR ($CHCl_3$) 3595, 3510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 3H), 3.58 (s, 3H), 3.75 (s, 3H), 4.12 (dd, J = 1.8 and 11.4 Hz, 1H), 4.21 (dd, J = 2.4 and 11.4 Hz, 1H), 4.87 (br s, 1H), 5.16 (dd, J = 1.8 and 2.4 Hz, 1H), 5.93 (s, 1H), 6.45 (s, 1H), 6.89−7.03 (m, 4H), 7.07 (d, J = 1.8 Hz, 1H), 7.51−7.56 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 55.19, 55.50, 59.96, 65.36, 94.46, 102.84, 115.12 (2C), 115.48, 116.13, 119.71, 124.34, 127.44, 128.59, 129.66 (2C), 132.69, 139.24, 139.57, 141.64, 148.10, 152.91, 156.74; HR−FABMS m/z 410.1352 (M)$^+$ (calcd for $C_{23}H_{22}O_7$ m/z 410.1366).

4-(3-Hydroxy-2,3-dihydrobenzo[1,4]dioxin-6-yl)-2,5-dimethoxy-biphenyl-3,4′-diol (21). To a solution of 2.50 g (6.10 mmol) of **20** in 20 mL of acetone and 20 mL of water was added 3.50 g (18.3 mmol) of p-toluenesulfonic acid. The mixture was refluxed for 18 h. After cooling to 20 °C, the mixture was diluted with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic solution was washed with brine and then dried and concentrated. The residue was chromatographed on silica gel using 1:1 EtOAc−hexane to afford 2.00 g (83%) of **21** as colorless crystals: mp 183−185 °C; IR ($CHCl_3$) 3691, 3596, 3510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 3H), 3.57 (d, J = 7.8 Hz, 1H), 3.75 (s, 3H), 4.11−4.19 (m, 2H), 5.39 (s, 1H), 5.58 (m, 1H), 5.96 (d, J = 0.6 Hz, 1H), 6.45 (s, 1H), 6.89−6.95 (m, 2H), 6.97−7.06 (m, 3H), 7.50−7.55 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 55.47, 59.95, 66.82, 88.54, 102.82, 115.10 (2C), 115.37, 116.29, 119.51, 123.72, 127.36, 128.60, 129.65 (2C), 132.63, 139.20, 140.60, 141.33, 148.10, 152.92, 156.70; HR−FABMS m/z 396.1211 (M)$^+$ (calcd for $C_{22}H_{29}O_7$ m/z 396.1209).

3′,6′-Dimethoxy-4-(3-methyl-2-butenyloxy)-[1,1′:4′,1″]-terphenyl-3,2′,4″-triol (terprenin, 1). To a solution of 818 mg (1.90 mmol) of isopropyltriphenylphosphonium iodide in 5 mL of THF was added 1.20 mL (1.90 mmol) of 1.57 N n-BuLi in hexane dropwise over a 1-min period at 0 °C. The mixture was stirred for 30 min at 25 °C, and then 50.0 mg (0.130 mmol) of **21** in 3 mL of THF was added at −78 °C. The mixture was stirred for 30 min at the same temperature and then allowed to warm to 25 °C and stirred for 7 h. The mixture was diluted with saturated NH_4Cl solution and then extracted with EtOAc. The organic solution was washed with water and brine and then dried and concentrated. The residue was chromatographed on silica gel using 2:3 EtOAc−hexane to afford 47.0 mg (87%) of **1**, which was identical in all respects with the natural product.

3-Bromo-4-iodo-2,5-dimethoxyphenol (22). The procedure described for the preparation of **18** was repeated for the reaction of 15 min to afford, after chromatography on silica gel using 1:2 EtOAc−hexane, **22** (64%) as colorless crystals: mp 163−165 °C; IR ($CHCl_3$) 3527 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 3.84 (s, 3H), 5.79 (br s, 1H), 6.57 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 57.36, 61.60, 82.92, 98.80, 128.03, 139.48, 150.72, 157.19. Anal. Calcd for $C_8H_8BrIO_3$: C, 26.77; H, 2.25; Br, 22.26, I, 35.35. Found: C, 26.87; H, 2.36; Br, 22.26, I, 35.13.

4-(Benzyloxy)-3′,6′-dimethoxy-[1,1′:4′,1″]terphenyl-3,2′,4″-triol (23). To a solution of 1.08 g (3.0 mmol) of **18** in 12 mL of DME and 3.0 mL of EtOH were added 1.13 g (3.15 mmol) of **8**, 6.0 mL of 2 M Na_2CO_3 solution, and 174 mg (0.15 mmol) of $Pd(PPh_3)_4$ under an argon atmosphere. The mixture was stirred for 6 h for 70 °C. After cooling to 20 °C, 984 mg (3.9 mmol) of **3**, 6.0 mL of 2 M Na_2CO_3 solution, 12 mL of DME, 3.0 mL of EtOH, and 174 mg (0.15 mmol) of $Pd(PPh_3)_4$ were added. The mixture was refluxed for 15 h. After cooling to 20 °C, the mixture was diluted with 10% citric acid solution and then filtered through a Celite pad. The filtrate was extracted with EtOAc, and then the organic solution was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel using 1:2 EtOAc−hexane to afford 893 mg (67%) of **23** as colorless crystals: mp 138−141 °C; IR (KBr) 3367 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 3H), 3.75 (s, 3H), 5.15 (s, 2H), 5.71 (s, 1H), 5.93 (s, 1H), 6.45 (s, 1H), 6.91−7.10 (m, 5H), 7.35−7.55 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 55.99, 60.68, 71.07, 103.75, 111.75, 115.38 (2C), 116.16, 117.37, 122.48, 126.56, 127.88 (2C), 128.39, 128.73 (2C), 130.06 (2C), 130.45, 132.48, 136.45, 138.71, 145.21, 145.41, 147.23, 153.45, 155.22. Anal. Calcd for $C_{27}H_{24}O_6{\cdot}0.45H_2O$: C, 71.65; H, 5.55. Found: C, 71.88; H, 5.63. Karl Fischer Calcd for $C_{27}H_{24}O_6{\cdot}0.45H_2O$: H_2O, 1.79. Found: H_2O, 1.79.

Methanesulfonic Acid 4″-benzyloxy-4,3′-bis(methanesulfonyloxy)-2′,5′-dimethoxy-[1,1′:4′,1″]terphenyl-3″-yl Ester (10). The procedure described for the preparation of **5** was repeated using 893 mg (2.01 mmol) of **23**, 10 mL of CH_2Cl_2, 1.68 mL (12.1 mmol) of Et_3N, and 0.70 mL (9.05 mmol) of methanesulfonyl chloride to afford 1.24 g (91%) of **10** which was identical with the product from **9**.

5-Bromo-2-[2,2-(dimethoxy)ethoxy]benzaldehyde (24). To a solution of 30.0 g (150 mmol) of **14** in 400 mL of DMF were added 21.0 mL (178 mmol) of 2-bromo-1,1-dimethoxyethane and 41.0 g (297 mmol) of K_2CO_3. The mixture was refluxed for 3.5 h. After cooling to 20 °C, the mixture was diluted with saturated NH_4Cl solution and then extracted with EtOAc. The organic solution was washed with water and brine and then dried and concentrated. The residue was chromato-

graphed on silica gel using 1:2 EtOAc−hexane to afford 39.8 g (92%) of **24** as colorless crystals: mp 82−83 °C; IR ($CHCl_3$) 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.48 (s, 6H), 4.10 (d, J = 5.1 Hz, 2H), 4.75 (t, J = 5.1 Hz, 1H), 6.90 (d, J = 8.9 Hz, 1H), 7.62 (dd, J = 2.5 and 8.9 Hz, 1H), 7.93 (d, J = 2.5 Hz, 1H), 10.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 54.65 (2C), 68.75, 102.13, 114.16, 115.00, 126.49, 131.05, 138.30, 159.84, 188.18; HR−FABMS m/z 310.9911 $(M + Na)^+$ (calcd for $C_{11}H_{13}{}^{79}BrNaO_4$ m/z 310.9895).

7-Bromo-2-methoxy-2,3-dihydrobenzo[1,4]dioxine (26). The procedure described for the preparation of **17** was repeated using 39.8 g (138 mmol) of **24**, 400 mL of EtOAc, 59.4 g (275 mmol) of 80% *m*-CPBA, 140 mL of 1 N NaOH solution, and 280 mL of MeOH to afford **25**, which was used for the next reaction without further purification.

To a solution of the above product in 300 mL of CH_2Cl_2 was added a solution of 13.5 g (71.0 mmol) of *p*-toluenesulfonic acid in 10 mL of MeOH. The mixture was stirred for 3 h at 25 °C and then diluted with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic solution was washed with brine and then dried and concentrated. The residue was chromatographed on silica gel using 1:10 EtOAc−hexane to afford 23.5 g (70% from **24**) of **26** as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.55 (s, 3H), 4.04 (dd, J = 1.7 and 11.4 Hz, 1H), 4.19 (dd, J = 2.0 and 11.4 Hz, 1H), 5.12 (dd, J = 1.7 and 2.0 Hz, 1H), 6.77 (d, J = 8.6 Hz, 1H), 6.98 (dd, J = 2.3 and 8.6 Hz, 1H), 7.06 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.08, 65.79, 94.94, 113.22, 118.44, 120.63, 124.85, 141.54, 142.55; HR-FABMS m/z 243.9739 $(M)^+$ (calcd for $C_9H_9{}^{79}BrO_3$ m/z 243.9735).

2,3-Dihydrobenzo[1,4]dioxine-7-boronic Acid (19). The procedure described for the preparation of **8** was repeated using 6.30 g (25.7 mmol) of **26**, 120 mL of THF, 18.0 mL (28.3 mmol) of 1.57 N *n*-BuLi in hexane, and 8.90 mL (38.6 mmol) of triisopropyl borate to afford, after chromatography on silica gel using 2:1 EtOAc−hexane, 3.30 g (60%) of **19** as colorless crystals: mp 94−97 °C; IR ($CHCl_3$) 3684, 3608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (s, 3H), 4.17 (dd, J = 1.7 and 11.3 Hz, 1H), 4.28 (dd, J = 2.2 and 11.3 Hz, 1H), 5.21 (dd, J = 1.7 and 2.2 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 7.74−7.79 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 59.40, 69.48, 98.24, 120.34 (2C), 128.24, 133.40, 143.66, 150.59; HR−FABMS m/z 480.1345 (bis(*m*-nitrobenzyl) ester)$^+$ (calcd for $C_{23}H_{21}{}^{11}BN_2O_9$ m/z 480.1340).

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