Total Synthesis of Terprenin, a Highly Potent and Novel Immunoglobulin E Antibody Suppressant**

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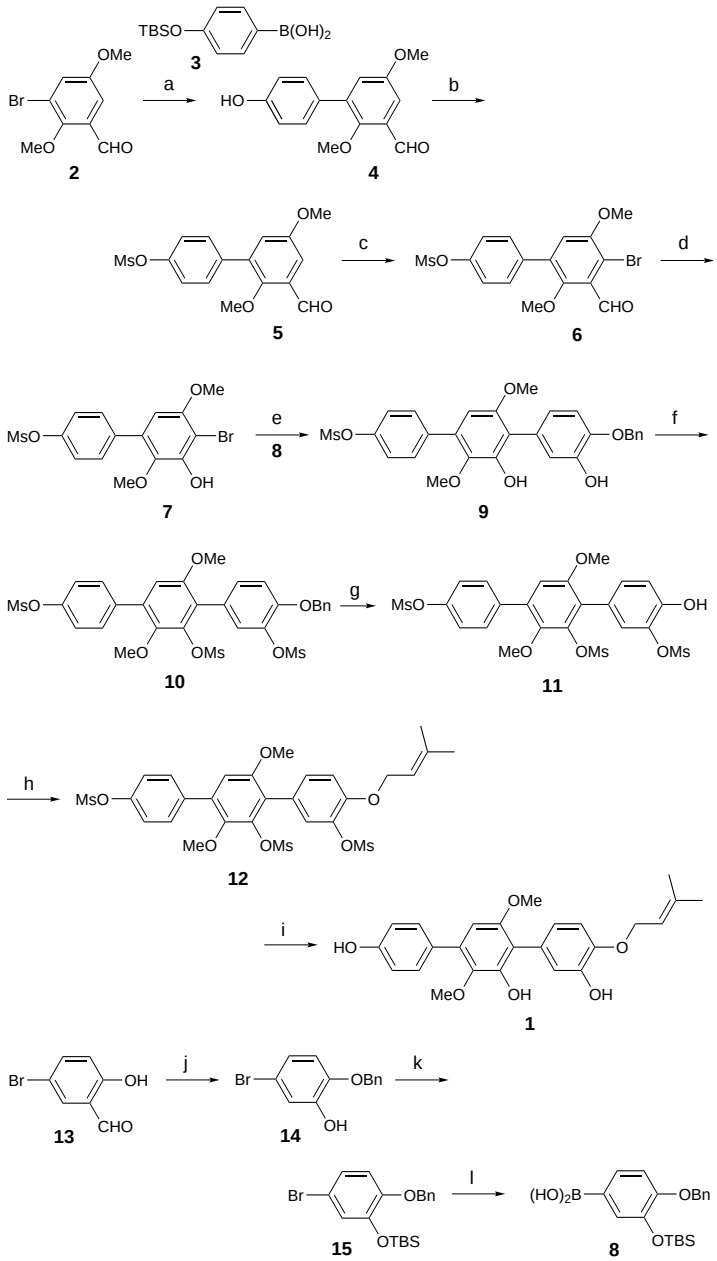
Immunoglobulin E (IgE) antibody is known to play a central role in allergic diseases such as atopic dermatitis, bronchial asthma, allergic rhinitis, allergic conjunctivitis, and anaphylaxis; these disorders are caused by the binding of antigens to specific IgE on mast cells and/or basophiles.[1] Thus, an effective orally active IgE suppressant would be of considerable therapeutic value. FK506 and cyclosporin A are known to be strong immunosuppressants, but they potentiate IgE production in mice.[2] At present, no potent clinically useful IgE suppressant is available.[3]

In the course of our screening program aimed at new immunosuppressants from natural products, terprenin (**1**, see Scheme 1), a highly oxygenated terphenyl compound with a prenyloxy side chain, was discovered in the fermentation broth of *Aspergillus candidus*. The structure of terprenin was established on the basis of spectral data and an X-ray crystallographic analysis.[4]

Terprenin exhibits a remarkable suppressive effect on the in vitro IgE production of human lymphocytes stimulated with anti-CD40 and IL-4 (IC_{50} value of 0.18 nM). In contrast, FK506 shows little or no inhibition even at the high concentration of 1000 nM. The effects of terprenin on in vivo IgE synthesis were examined by immunization of mice by an intraperitoneal injection of ovalbumin (OVA) with alum. Antiserum was collected, and the anti-OVA IgE antibody titer was determined by passive cutaneous anaphylaxis on rats for 24 h. Terprenin was found to suppress antigen-specific IgE production in mice by oral administration in a dose-dependent manner. Even after immunization with OVA, when the IgE value had reached a high level, terprenin exhibited a significant suppressive effect at 20 and 40 mg kg^{-1} without any toxicological signs. FK506, unlike terprenin, enhanced the IgE level at low doses (0.1 – 3 mg kg^{-1}) and showed toxicity at 10 mg kg^{-1} in the form of decrease in body weight and thymus weight.

We describe here the first two total syntheses of terprenin, which permit highly efficient and practical production of this important natural product. The strategy for constructing the terphenyl skeleton was based on two Suzuki reactions,[5] in one case stepwise (first synthesis, see Scheme 1) and in the other as a one-pot reaction (second synthesis, see Scheme 2). Regioselective functionalization of the aromatic ring in the starting material 3-bromo-2,5-dimethoxybenzaldehyde (**2**)[6] was considered to be the crucial step. Because of the characteristic palladium-catalyzed elimination reaction of allylic phenyl ethers[7] as well as the instability of the prenyloxy group under acidic and hydrogenous conditions,[8]



Scheme 1. First synthesis of terprenin (**1**). 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) MCPBA, 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 and 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 %); j) ref. [11]; k) TBSCl, imidazole, DMF (90 %); l) *n*BuLi, $B(OiPr)_3$, THF followed by H_2O (64 %). DME = dimethoxyethane, DMF = dimethylformamide, MCPBA = 3-chloroperoxybenzoic acid, Ms = mesyl, TBS = *tert*-butyldimethylsilyl.

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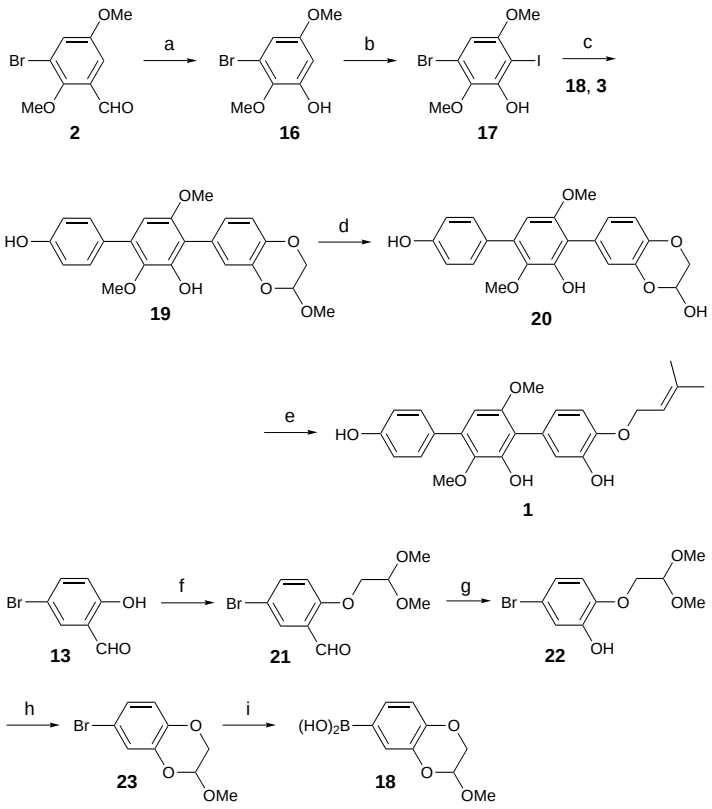
[**] We wish to thank Dr. H. Arita for his encouragement and valuable advice, Dr. R. Suzuki for biological discussions, and Dr. T. Konoike for large-scale preparations.

we decided that construction of the side-chain moiety should be the last step in the synthetic sequence. It was also necessary for us to be able to discriminate between six oxygen functionalities with the aid of appropriate protecting groups.

In the first synthesis (Scheme 1), bromobenzaldehyde **2** underwent a Suzuki reaction with boronic acid **3**[9] to give the biphenyl product almost quantitatively. The TBS-protected phenol was cleaved in the presence of water to produce phenol derivative **4**.[10] After protection of **4** as mesylate **5**, bromination with molecular bromine led exclusively to regioselective functionalization and the desired bromide **6**. Next, the formyl group of **6** was converted into a hydroxy group by Baeyer–Villiger oxidation. Suzuki reaction of the sterically hindered bromide **7** with boronic acid **8**, readily prepared from 5-bromosalicylaldehyde (**13**),[11] proceeded smoothly to afford the expected terphenyl compound **9**. After completion of the terphenyl skeleton, the free hydroxy groups of **9** were protected as mesylates **10**, chosen because they would be susceptible to removal under basic conditions. Other protecting groups such as acetyl or silyl groups were considered impractical because they would have migrated to the free hydroxy groups produced in the subsequent hydrogenolysis step. After cleavage of the benzyl ether functionality of **10** by hydrogenolysis, a prenyl group was introduced at the desired position in terphenyl compound **11** by reaction with prenyl bromide. Finally, removal of the mesyl groups of **12** with potassium hydroxide completed the first total synthesis of terprenin. The synthetic material was identical in all respects to the natural product from *Aspergillus candidus*, including biological activity.

The advantage of this synthesis is its applicability to large-scale production. The overall yield from **2** was 40%, and no chromatographic steps were required because of the high yield at each step; each product was purified by simple crystallization.

The second total synthesis (Scheme 2) was based on a one-pot process involving two successive Suzuki reactions. To ensure the desired regioselectivity, a functionality other than bromine was required in the *para* position of the starting material, bromobenzaldehyde **2**. Because iodination of **2** did not proceed selectively, the aldehyde was converted into phenol **16**. Treatment of **16** with iodine in the presence of *tert*-butylamine led to regioselective iodination and the desired iodide **17** in 92% yield.[12] Although the iodine atom in **17** is located at a more sterically hindered position than the bromine atom, boronic acid **18**, conveniently prepared from **13**, reacted preferentially at the iodine-substituted position with $[Pd_2(dba)_3]$ as catalyst. The Suzuki reaction in this case proceeded rather sluggishly and unselectively with $[Pd(PPh_3)_4]$ as catalyst. Without isolation of the biphenyl compound, boronic acid **3** and $[Pd(PPh_3)_4]$ were added to the reaction mixture, and the expected terphenyl compound **19** was obtained in 70% yield. Hydrolysis of the protected hemiacetal in **19** with *p*-toluenesulfonic acid in aqueous acetone followed by a Wittig reaction of **20** with excess isopropyltriphenylphosphonium iodide afforded terprenin (**1**) in 87% yield. Since this second synthesis does not require protection–deprotection of phenol groups, the synthetic sequence is sufficiently short for efficient production of terprenin by this route as well.



Scheme 2. Second synthesis of terprenin (**1**). a) MCPBA, CH_2Cl_2 followed by 1N KOH, MeOH (81%); b) I_2, tBuNH$_2$, toluene (92%); c) $[Pd_2(dba)_3]$, 2M Na_2CO_3, DME, EtOH followed by $[Pd(PPh_3)_4]$ (70%); d) *p*-TsOH, H_2O, acetone (83%); e) $[Ph_3PCHMe_2]I$, nBuLi, THF (87%); f) 2-bromo-1,1-dimethoxyethane, K_2CO_3, DMF (92%); g) MCPBA, EtOAc followed by 1N NaOH; h) *p*-TsOH, CH_2Cl_2, MeOH (70% for steps g and h); i) nBuLi, B(OiPr)$_3$, THF followed by H_2O (60%). dba = dibenzylideneacetone, Ts = 4-methylphenylsulfonyl (tosyl).

We have thus developed two practical syntheses of terprenin (**1**), a potent IgE antibody suppressant. Sufficient supplies of this important natural product should now become available to aid in the development of a new type of antiallergic drug as well as in the clarification of its interesting mechanism of action.

Received: December 8, 1997 [Z11235IE]
German version: *Angew. Chem.* **1998**, *110*, 1015–1017

Keywords: cross-coupling · immunosuppressants · natural products · terprenin · total synthesis

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A Molecular Chameleon: Chromophoric Sensing by a Self-Complexing Molecular Assembly**

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In supramolecular chemistry[1]—the domain of chemistry where noncovalent bonding interactions[2] become important—the concept of self-assembly[3] is being increasingly exploited to create molecular-based architectures at the nanoscale level. Over the last decade, numerous researchers have harnessed the power of the noncovalent bond to produce aesthetically pleasing molecular assemblies[4] as well as supramolecular arrays. In recent years, we have employed the molecular recognition[2] that exists between π electron rich aromatic rings (e.g. hydroquinone, 1,5-dioxynaphthalene) and π electron deficient aromatic units (e.g. bipyridinium, diazapyrenium) coupled with C–H···O and O–H···π interactions to assist in the self-assembly of catenanes,[5] rotaxanes,[6] and pseudorotaxanes.[7]

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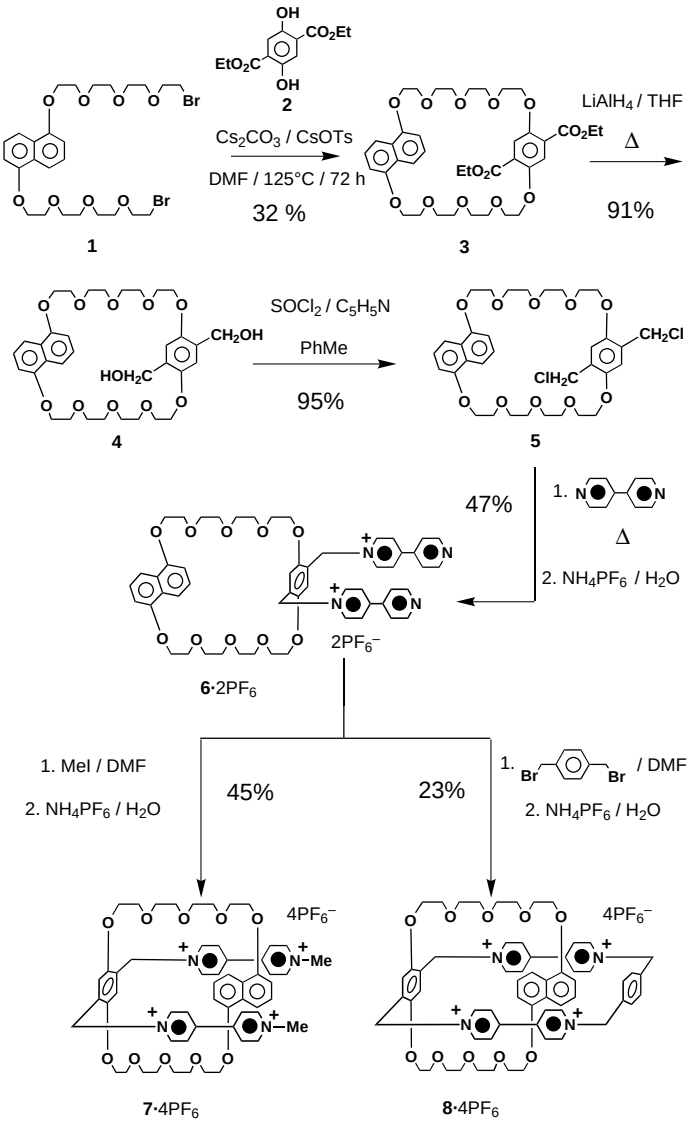
[**] We thank the Eusko Jaurlaritza Unibersitate, Hizkuntza, eta Ikerketa Saila in the Basque Country (Spain) for the award of a predoctoral fellowship (to M.G.-L). The research was funded in the UK by the Engineering and Physical Sciences Research Council.

Here we report the four-step synthesis of an intermediate dicationic salt $\mathbf{6}\cdot 2PF_6$ (see Scheme 1), and the potential of the AB_2-type[8] monomeric tetracation $\mathbf{7}^{4+}$ possessing complementary recognition sites, which is easily obtained from $\mathbf{6}\cdot 2PF_6$, to self-assemble in the shape of a polysupramolecular dendritic wedge (see Scheme 2a).[9] Furthermore, we report on a related attempt to construct from $\mathbf{6}\cdot 2PF_6$ a polycatenane that is reminiscent of an anchor chain; however, the fascinating macrobicyclic tetracation $\mathbf{8}^{4+}$ is formed instead. It is composed of two complementary macrocycles linked together by a common aromatic ring in a manner that allows it to display an intriguing kind of self-complexation,[10] as demonstrated in solution by ^1H NMR spectroscopy and in the solid state by X-ray crystallography. We also describe how $\mathbf{8}^{4+}$ can act in a novel fashion as a chromophoric receptor[11] for tetrathiafulvalene (TTF; see Scheme 3), giving the macrobicyclic tetracation molecular switching[12] properties.

Scheme 1 outlines the synthesis of the key intermediate $\mathbf{6}\cdot 2PF_6$.[13] Reaction of the dibromide **1**[7] with the diester **2**



Scheme 1. The synthesis of the crown ether derivative $\mathbf{7}\cdot 4PF_6$ and the self-assembly of the self-complexing macrobicycle $\mathbf{8}\cdot 4PF_6$. Ts = toluenesulfonyl.

  1433-7851/98/3707-0975 $ 17.50+.50/0