500 μL of DCC suspension and were mixed for 15 min and centrifuged. Supernatants (500 μL) were counted in a liquid scintillation counter.

Sets of tubes also containing 10^{-6} M DHT were used to determine nonspecific binding, which was subtracted from all values. Nonspecific binding was typically 20% of total [^{3}H]DHT bound. Results were plotted and RBAs determined as described earlier. The RBA values reported here are the average of three or more determinations.

The RBAs of these newly synthesized compounds were also determined for AR from MCF-7 human breast cancer cells. To prepare AR cytosol from this cell line, 0.05 mL packed cells per milliliter of TEDGM buffer were homogenized in a Dounce glass-teflon homogenizer with a motor driven pestle at 0-4 °C. The homogenate was centrifuged at 100000g for 30 min and the clear supernatant (cytosol) was collected. Endogenous steroids were removed with DCC and RBAs were determined as above.

To check the receptor specificity, these compounds were also tested for their ability to bind PgR. RBAs for PgR (from T47D human breast cancer cells) were thus determined with respect to [^{3}H]R5020 as described earlier.[15] Nonspecific binding was typically 4% of total [^{3}H]R5020 binding.

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Registry No. 1, 481-29-8; 2, 131545-84-1; 3, 131545-85-2; 4, 131545-86-3; 5, 131545-87-4; 6, 13611-96-6; 7, 131611-97-7; 8, 131545-88-5; 9, 129163-98-0; 10, 1162-60-3; 11, 131545-89-6; but-3-yn-1-yltetrahydropyranyl ether, 40365-61-5; alkynyllithium, 67654-73-3; trimethylsilylacetylene, 1066-54-2; (5α,17α,20E)-21-(tributylstannyl)pregn-20-ene-3β,17β-diol, 131545-90-9.

Perfluorinated Analogues of Poison Ivy Allergens. Synthesis and Skin Tolerogenic Activity in Mice

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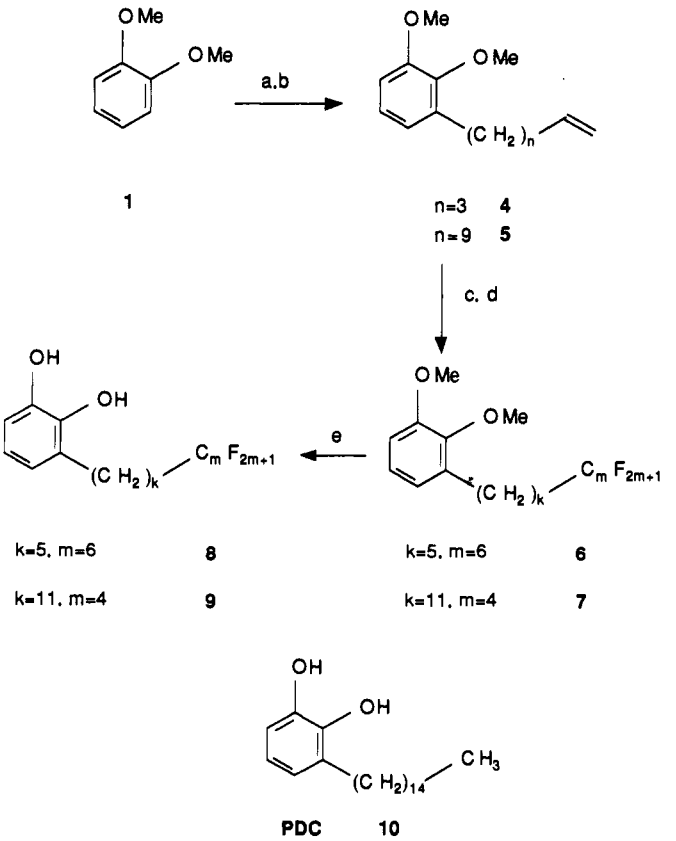
3-(Tridecafluoroundecyl)catechol (8) and 3-(nonafluoropentadecyl)catechol (9), perfluorinated analogues of pentadecylcatechol (PDC), a constituent of poison ivy, have been synthesized. These compounds were nonsensitizers in mice. Compounds 8 and 9, however, were elicitors of allergic contact dermatitis in PDC-sensitized animals. Moreover, compound 9 exhibited tolerogenic properties to sensitization by poison ivy allergens, i.e. mice pretreated with perfluorinated compounds could not be sensitized to PDC.

The allergenic principles contained in poison ivy (*Rhus toxicodendron* or *Toxicodendron radicans*), poison oak (*Rhus diversiloba* or *Toxicodendron diversilobum*), and poison sumac (*Toxicodendron vernix*) are the main causes of allergic contact dermatitis in the United States.[1,2] The allergens in these plants have been shown to be a catechols with linear 3-*n*-alkyl chains containing 15 (such as pentadecylcatechol, PDC) or 17 (such as heptadecylcatechol, HDC) carbon atoms, commonly referred to as urushiols.[2,3] Until now, there have been only a few studies directed at induction of immune tolerance to allergic contact dermatitis; tolerance can be induced by modifying the chemical structures of urushiol allergens.[3] The importance of the 3-alkyl carbon chain, number of atoms in the side chain,[4] and influence of branching and rigidity[5] has been evaluated. It was found that the sensitizing power (the contact allergy inducing capacity) was strongly dependent on the nature of the side chain.

In view of the expected biological effect of replacing hydrogen by fluorine, it seemed to us that, by introduction on the side chain of a perfluorinated segment, some interesting biological properties might result. For instance, it has been shown that perfluorinated alkyl chain of the fatty acids exhibited detergent-like activity in human and murine B cell, by physically altering cell membranes.[6] We have investigated the sensitizing power of PDC (10) and side-chain perfluorinated catechol analogues 3-(tridecafluoroundecyl)catechol (8) and 3-(nonafluoropentadecyl)catechol (9) in mice. Although guinea pigs are usually a better animal model of human skin than mice, evaluation of biological data is *qualitative* and based on

Scheme I[a]



[a] *n*-BuLi, THF; (b) bromo-1-undecene 2 or bromo-1-pentene 3; (c) IC_mF_{2m+1} (m = 4 or m = 6), AIBN, reflux 3 h; (d) Bu_3SnH, AIBN, reflux 3 h; (e) BBr_3, CH_2Cl_2.

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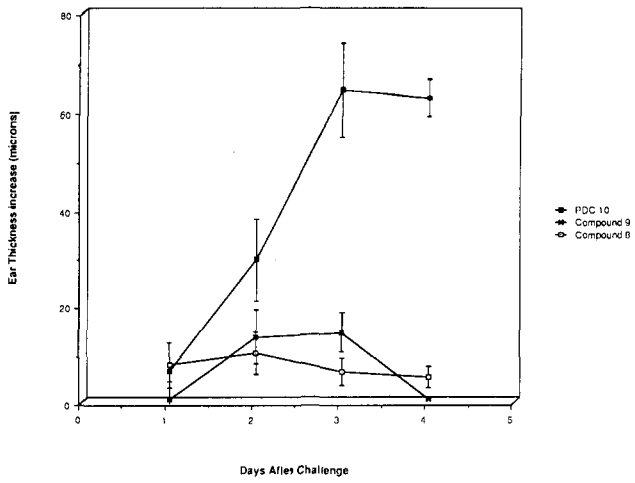

Figure 1. Primary sensitization. The maximum ear swelling was observed 72 h after challenge on the right ear with PDC, nonafluoro-PDC (**9**) and tridecafluoro-PDC (*8*), respectively. Perfluorinated derivatives did not show any evidence of primary sensitization.

a 0–3 test intensity scale.[7,8] Mice provide a well-established immunological model and the importance of induced contact sensitivity (allergic contact dermatitis or ACD) is measured by ear thickening, thus providing a *quantitative evaluation*.[9,12] We describe in this paper the synthesis of two fluoro analogues of PDC, **8** and **9**, and the study of their biological activity: ACD induction, cross-reaction, and immune tolerance induction, in mice.

Chemistry

Perfluorocatechols **8** and **9** were synthesized, as shown in Scheme I. After lithiation of veratrole at 0 °C, the reaction mixture was reacted at 0 °C with 11-bromoundecene (**2**) or 5-bromopentene (**3**) to give the corresponding alkeneveratroles **4** and **5**,[13] in 54% and 44% yields, respectively. The perfluorinated alkylveratroles were synthesized by refluxing alkeneveratroles **4** and **5** in perfluoroalkyl iodide in the presence of 2,2′-azobis(2-methylpropionitrile) (AIBN).[5] The resulting iodoperfluoro derivative obtained after chromatography was a yellow oil, which was taken up in toluene and refluxed for 3 h in the presence of Bu_3SnH and AIBN.[14] Flash chromatography on silica gel columns gave pure perfluorinated alkylveratroles **6** and **7**. After deprotection of the ether functions with BBr_3,[15] 3-(perfluoroalkyl)catechol **8** and **9** were obtained. Pentadecylcatechol (**10**) was synthesized according to a published method.[3]

Table I. Cross-Sensitivity Reactions in PDC-Sensitized[a] Mice

group	challenged with[b]	ear thickness increase at 48 h, μm
I	PDC	68.5 ± 15
II	compd 8	142 ± 27
III	compd 9	162 ± 32

[a] Mice were sensitized with 15.6 mmol of the test compound in acetone/olive oil 4:1 solution (100 μL) on the shaved abdomen. [b] A challenge dose of 1.56 mmol of the compound in acetone/olive oil solution (25 μL) was applied to the right ear.

Table II. Induction of Nonresponse (Tolerance?) with Fluorinated Compound **9**

group	day 0, pretreatment[a] with	day 4, sensitization[b] to	day 8, challenged[c] with	day 10, result of test,[d] μm
I	**10**	**10**	**10**	64
II	**9**	**10**	**10**	26
III	**9**	**9**	**9**	15

[a] Mice were pretreated with 15.6 mmol of the compound in an acetone/olive oil 4:1 solution (100 μL) on the shaved abdomen. [b] Mice were sensitized with 15.6 mmol of the test compound in acetone/olive oil 4:1 solution (100 μL) on the shaved abdomen. [c] A challenge dose of 1.56 mmol of the compound in acetone:olive oil solution (25 μL) was applied to the right ear. [d] Ear thickness increase measured at 48 h after challenge.

Biological Results

Primary Sensitization. A significant ear swelling increase (50–100 μm thicker than the control ear, i.e. where no allergen was deposited) unambiguously indicates the presence of hypersensitivity. As shown in Figure 1 only PDC (**10**) showed strong allergenic activity. Interesting to note is the fact that the perfluorinated compounds **8** and **9** were not significant sensitizers, as evidenced by a weak ear thickness increase (≪50 μm). The results of the studies of the sensitizing power of compounds **8**–**10** are summarized in Figure 1.

Cross-Sensitivity Reactions. (1) Primary Sensitization to PDC. Surprisingly, mice sensitized to PDC (**10**) gave positive reactions when challenged with its perfluoro analogues **8** and **9**. While the latter are nonsensitizers, they are *elicitors*, i.e. they can evoke an allergic reaction in PDC-sensitized mice. These results are summarized in Table I.

(2) Primary Sensitizations to (Perfluoropentadecyl)catechols 8 and 9. Animals sensitized to **8** and **9** did not show cross-sensitivity reactions to **9** and **8**, respectively (i.e. ear thickness increase was not significant). Animals "sensitized" to **8** and **9** did no react to PDC (**10**) (nonsignificant, i.e. <50 μm ear thickness increase).

Induction of a Nonresponse Reaction (Tolerance?) to PDC. In order to check whether fluoro-PDC **9** could protect the animals against further sensitization to PDC (**10**) itself, three groups of mice were constituted. In group I, animals were sensitized to PDC and tested with PDC. A significant contact sensitivity (ACD) was observed.

In group II, mice were pretreated with fluoro-PDC **9** (on day 0) and received a sensitizing dose (15.6 mmol) of PDC (**10**) on day 4. They were challenged on day 8 with PDC (**10**).

Group III, finally, was constituted with mice that were sensitized to fluoro-PDC **9** on day 4 and elicited with fluoro-PDC **9** on day 8.

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The results are summarized in Table II. The ear thickness increase measured was nonsignificant in groups II and III. Clearly, group II did not react to PDC. Studies of induction of nonresponse to PDC were effected with fluoro-PDC **9**. This compound was chosen because it has the same chemical structure as PDC except for substitution of hydrogens by fluorine atoms in part of the side chain.

Discussion

The results of the experiments described above as shown in Figure 1 and Tables I and II can be summarized as follows.

1) PDC (a constitutent of urushiol, the allergenic extract of poison ivy) is a sensitizer in Balb/c mice.

2) Its perfluorinated analogues, namely nonafluoro-PDC (**9**) and tridecafluoro-PDC (**8**), are *nonsensitizers* in mice.

3) Animals "sensitized" to **9** and **8** do not "recognize" PDC (**10**).

4) Animals sensitized to PDC (**10**) do recognize its perfluoro analogues **8** and **9**.

5) When pretreated with fluoro-PDC **9**, Balb/c mice *could not be sensitized* to PDC (**10**).

The last result is probably the most interesting and significant one, as it could indicate induction of immune tolerance to potent natural allergens poison ivy and poison oak urushiols. The animals nonresponders to PDC do not have a depleted system. This was shown when six mice were pretreated with fluoro-PDC **9** and then sensitized and challenged with a potent allergen, methyl dodecanesulfonate (CH_3OSO_2R) (Fraginals, R.; et al. *Arch. Dermatol. Res.* in press). When challenged with the latter, the skin reaction intensity was similar to primary sensitization to methyl dodecanesulfonate. Although, at the moment, it is difficult to demonstrate active immune tolerance, it is evident that the animals have been protected against sensitization to PDC (**10**). This result might show some promise of future application to protect against poison ivy and poison oak. Allergenic activity and cutaneous toxicity of compounds containing perfluorinated alkyl chains is not known. There are some results in the literature describing the biochemical toxicity of perfluorinated compounds containing 8–10 carbon length chain.[16,17] These compounds, originally considered to be metabolically inert, may have some toxic effects at high dose in laboratory animals, possibly by altering membrane lipid composition. However, the mechanism of their toxicity remains unclear. It has been suggested that these substances alter membrane function by changing both fatty acid composition and the oxidative status in the cellular membranes. The detergent-like properties of perfluorinated chains could also alter cell membrane composition and membrane-associated biosynthetic pathways.[17] Such membrane alterations could interfere with ion channel functions, thereby destabilizing osmotic integrity of the cells. It is also possible that, at noncytotoxic doses, skin penetrability of the perfluorinated side chains compounds could be different from those of similar nonfluorinated chains substances. Many perfluorinated compounds (not only those with a perfluorinated side chain) are nontoxic and have been proposed for medical use.[18]

In order to find an appropriate dose to test the perfluorinated compounds in the ACD experimental model, we determined the maximal nontoxic concentration (15.6 mM) and all sensitization tests were done with this concentration. We found that epicutaneous applications of fluorinated-PDC **9** at 32 mM concentrations resulted in cutaneous irritation at 24 h. These animals, 72 h later, showed hypophagia, a depressed nervous system, and locomotion disorder, and we observed a loss of body weight in mice 2 weeks after these applications.

Conclusion

The introduction of fluorine atoms into the side chain of pentadecylcatechol (PDC, **10**) has resulted in complete change of its biological properties, transforming a hapten (allergen) into a compound with protecting properties (a tolerogen or a tolerizer?). Previous chemical changes in PDC such as acetylation of the phenol functions[1] or introduction of a methyl group in position 5 of the aromatic ring[19] have also given encouraging results in the search for skin tolerogens.

Experimental Section

General Procedures. Proton NMR spectra were recorded on a 60-MHz Perkin-Elmer and on a 200-MHz Brucker spectrometer in $CDCl_3$. Chemical shifts (δ) are indicated in ppm with respect to TMS as internal standard ($\delta = 0$), and coupling constants (J) are in hertz. 19-Fluorine NMR spectra were recorded on a 400-MHz Brucker spectrometer in $CDCl_3$. Infrared spectra were obtained on a Beckman Acculab spectrometer using $CHCl_3$ solutions; wavenumbers are indicated in cm^{-1}. Melting points were determined on a Büchi Tottoli 510 apparatus. Mass spectra were recorded on a LKB 9000 S spectrometer. Dry solvents were freshly distilled before use. Tetrahydrofuran (THF) was distilled from sodium benzophenone. Dichloromethane was distilled over P_2O_5. All air- and moisture-sensitive reactions were conducted in flame-dried glassware under an atmosphere of dry argon. Flash chromatographic purifications on silica gel columns were used.

11-Bromoundecene (2). To a solution of 1-undecen-10-ol (700 mg, 4.12 mmol) in CH_3CN (50 mL) was added CBr_4 (1.93 g, 5.80 mmol), at 0 °C under argon. Then PPh_3 (1.52 g, 5.80 mmol) was added over a 1-h period. After 24 h of stirring at room temperature, ether (20 mL) was added and the reaction mixture filtered over a silica gel column. After removal of the solvents under reduced pressure, a colorless oil was obtained. Flash chromatography on silica gel gave pure **2** (853 mg, 3.66 mmol). Yield: 89%. IR: 1635. ^1H NMR ($CdCl_3$, 200 MHz) δ: 5.35–6.19 (1 H, m, C*H*-10), 4.66–5.12 (2 H, m, CH_2-11), 3.32 (2 H, t, $J_{H\text{-}1,H\text{-}2} = 7$, CH_2-1), 1.94 (2 H, m, CH_2-9), 1.42 (14 H, br s, CH_2-2 to CH_2-8). Anal. Calcd for $C_{11}H_{21}Br$: C, 56.66; H, 9.08. Found: C, 56.8; H, 9.1.

3-Pentenylveratrole (4). To a solution of veratrole (**1**) (6.4 mL, 50.0 mmol) in THF (70 mL) was added, dropwise at 0 °C under argon, *n*-BuLi (32 mL, 51.2 mmol). A heavy yellow precipitate was formed. After stirring for 3 h at 0 °C, the reaction mixture was allowed to reach room temperature. After 1 h of stirring, a solution of 5-bromo-1-*n*-pentene (5.0 g, 33.5 mmol) in THF (20 mL) was added dropwise, at 0 °C under argon. The solution was allowed to reach room temperature and stirred a further 12 h. The reaction was then quenched with 1 N HCl, and extracted with dichloromethane. Flash chromatography on silica gel (eluent hexane/ether 9:1) gave pure compound **4** (3.04 g, 14.8 mmol, colorless oil). Yield: 44%. IR: 1635, 1250. ^1H NMR ($CDCl_3$, 200 MHz) δ: 6.99 (1 H, dd $J = 7.9$, H-5), 6.84-6.76 (2 H, m, H-4 and H-6), 5.93-5.76 (1 H, m, C*H*-4′), 4.95–5.08 (2 H, m, CH_2-5′), 3.87 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 2.69–2.61 (2 H, t, $J_{H\text{-}1,H\text{-}2'} = 7.8$, CH_2-1′), 2.18–2.11 (2 H, m, CH_2-3′), 1.77–1.60 (2 H, m, CH_2-2′). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.5: H, 8.8.

3-(10′-Undecenyl)veratrole (5) was synthesized from veratrole (4.2 mL, 33.0 mmol) and 11-bromoundecene-1 (4.94 g, 21.2 mmol) as described above. 3-(10′-Undecenyl)veratrole (**5**; 3.34 g, 11.5 mmol, colorless oil) was obtained. Yield: 54%. IR: 1640, 1250. ^1H NMR ($CDCl_3$, 200 MHz) δ: 6.99 (1 H, dd $J = 7.8$, *H*-5),

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6.80–6.75 (2 H, m, *H*-4 and *H*-6), 5.92–5.72 (1 H, m, C*H*-10′), 5.04–4.90 (2 H, m, CH_2-11′), 3.86 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 2.66–2.57 (2 H, t $J_{H\text{-}1',H\text{-}2'}$ = 7.7, CH_2-1′), 2.06–2.00 (2 H, m, CH_2-9′), 1.69–1.36 (14 H, m, CH_2-2′, CH_2-3′, CH_2-4′ to CH_2-8′). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.8; H, 10.3.

3-(6′,6′,7′,7′,8′,8′,9′,9′,10′,10′,11′,11′,11′-Tridecafluoroundecyl)veratrole (6). To a solution of compound **4** (2.87 g, 13.9 mmol) in dry degassed iodoperfluorohexane (12.4 g, 27.8 mmol) was added AIBN (35 mg, 0.21 mmol). The solution was refluxed for 3 h. After cooling and removal of the excess iodoperfluorohexane, flash chromatography on silica gel (hexane/ethyl acetate 9.5:0.5) gave a pale yellow oil. ^{1}H NMR (60 MHz) showed that all the compound 4 had reacted. The oil was dissolved in dry degassed toluene (25 mL). Then, Bu_3SnH (3.8 mL, 14.0 mmol) as well as some crystals of AIBN were added. The solution was refluxed for 3 h. After cooling and removal of solvents under reduced pressure, flash chromatography on a silica gel column (1.5 L of hexane/ether 9:1) gave compound **6** (5.38 g, 10.0 mmol). Yield: 72%. Mp: 69–70°. IR: 1220. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.99 (1 H, dd J = 7.4, *H*-5), 6.81–6.74 (2 H, m, *H*-4, *H*-6), 3.87 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 2.68–2.61 (2 H, t $J_{H\text{-}1',H\text{-}2'}$ = 7.8, CH_2-1′), 2.15–2.02 (2 H, m, CH_2-5′), 1.72–1.36 (6 H, m, CH_2-2′, CH_2-3′, CH_2-4′). ^{19}F NMR ($CDCl_3$, 400 MHz) δ: −81.3 (3 H, s, CF_3), −114.9 (2 H, s, CF_2), −122.5 (2 H, s, CF_2), −123.4 (2 H, s, CF_2), −124.1 (2 H, s, CF_2), −126.7 (2 H, s, CF_2).

3-(12′,12′,13′,13′,14′,14′,15′,15′,15′-Nonafluoropentadecyl)veratrole (7) was synthesized in the same way as compound **6**. From compound **5** (1.53 g, 5.28 mmol), C_4F_9I (3.60 g, 10.4 mmol), and Bu_3SnH (1.4 mL, 5.28 mmol), product **7** (1.69 g, 3.31 mmol) was obtained as colorless oil. Yield: 63%. IR: 2960, 1220. ^{1}H NMR ($CDCl_3$ 60 MHz) δ: 6.80 (3 H, m, *H*-4, *H*-5, *H*-6), 3.82 (6 H, s, 2-OCH_3), 2.70–2.35 (2 H, m, CH_2-1′), 1.32 (20 H, br s, CH_2-2′ to CH_2-11′). Anal. Calcd for $C_{19}H_{30}O_2$: C, 54.12; H, 6.12. Found: C, 54.4; H, 6.0.

3-(6′,6′,7′,7′,8′,8′,9′,9′,10′,10′,11′,11′,11′-Tridecafluoroundecyl)catechol (8). To a solution of compound **6** (373 mg, 0.87 mmol) in CH_2Cl_2 (25 mL) at −13 °C was added a solution of BBr_3 (2.5 mL, 1 M in CH_2Cl_2, 2.57 mmol). The reaction mixture was allowed to reach room temperature and stirred for 4 h. The reaction was quenched with MeOH (10 mL). Removal of solvent gave a brown oil. Flash chromatography (degassed silica gel and eluent, hexane/ether 5:5) gave white crystals of compound **8** (336 mg, 0.67 mmol). Yield: 77%. Mp: 69–70 °C. IR: 3550, 3300, 2970, 1240. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.72 (3 H, s, *H*-4, *H*-5, *H*-6), 5.24–5.01 (2 H, 2 br s, 2-O*H*), 2.65 (2 H, t, $J_{H\text{-}1',H\text{-}2'}$ = 7.5, CH_2-1′), 2.03 (2 H, m, CH_2-5′), 1.68–1.26 (6 H, m, CH_2-2′, CH_2-3′, CH_2-4′). ^{19}F NMR ($CDCl_3$, 400 MHz) δ: −81.3 (3 H, s, CF_3), −114.9 (2 H, s, C), −122.5 (2 H, s, CF_2), −123.4 (2 H, s, CF_2), −124.1 (2 H, s, CF_2), −126.7 (2 H, s, CF_2). Anal. Calcd for $C_{17}H_{15}F_{13}O_2$: C, 69.72; H, 11.70. Found: C, 69.9; H, 11.7.

3-(12′,12′,13′,13′,14′,14′,15′,15′,15′-Nonafluoropentadecyl)catechol (9) was synthesized in the same way as compound **8**. From compound **7** (1.04 g, 2.03 mmol) and BBr_3 (6.0 mL, 1 M CH_2Cl_2, 6.0 mmol), compound **9** was obtained as pale yellow crystals (0.848, g, 1.76 mmol). Mp: 42–43 °C. IR: 3550, 3300, 2970, 1240. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.72 (3 H, s, H-4, H-5, H-6), 5.25–5.00 (2 H, b s, 2-O*H*), 2.61 (2 H, t, $J_{H\text{-}1',H\text{-}2'}$ = 7.6, CH_2-1′), 2.06 (2 H, m, CH_2-11′), 1.62–1.29 (18 H, m, CH_2-2′ to CH_2-10′). ^{19}F NMR ($CDCl_3$, 400 MHz) δ: −81.5 (3 H, s, CF_3), −115.1 (2 H, s, CF_2), −125.0 2 H, s, CF_2), −126.5 (2 H, s, CF_2). Anal. Calcd for $C_{21}H_{27}F_9O_2$: C, 52.28; H, 5.64. Found: C, 52.1; H, 5.5.

Biological Assays. Female BALB/C mice, 6–7 weeks of age, were obtained from IFFA CREDO (Lyon, France). They were maintained in an animal care facility at constant temperature (22 °C) and fed with dry food and water ad libitum.

The sensitization procedure consisted of abdominal painting with a solution (100 μL) of 15.6 mmol for each fluorinated compound or PDC in acetone/olive oil (4:1), followed after an appropriate time (generally 4–5 days) by challenge with an acetone solution (25 μL) of the fluorinated compound or PDC, respectively, on the ventral side of the right ear. Ear thickness was measured with an ODITEST engineering micrometer (West Germany). Measurements of ear thickness was recorded 24, 48, 72, and 96 h after ear challenge.

Primary Sensitization. The sensitization procedure consisted of a single painting on the shaved lower abdomen of the mice with compounds **8**, **9**, or **10** in an acetone/olive oil (4:1) mixture on day 0. After 4 days, the mice were challenged with compounds **8**, **9**, or **10** on the dorsal side of the right ear. Measurement of ear thickness was done on days 5–8. Control groups consisted of naive mice "sensitized" with the vehicle alone by exactly the same procedure as described above for the experimental group. After 4 days, they were challenged on the right ear with the compounds, respectively.

Cross-Reaction. Twenty-four Balb/c mice were used. All mice were sensitized to fluoro-PDC **8**. Four days after, challenge was effected in eight mice with PDC (**10**), with compound **8** in another group of eight mice, and, finally, another eight mice were challenged with compound **9**. Every compound was applied in the same way.

Induction of Nonresponse (Tolerance?) by Epicutaneous Application of Perfluorinated Compound 9. Twenty-four mice were used, three groups of eight mice each were constituted. Group I was treated epicutaneously with PDC (**10**) on day 0. A sensitization attempt with PDC (**10**) was done on day 4. Mice were tested on the right ear with a challenging dose of PDC (**10**) on day 8. Ear thickness was measured on days 9–12 (see Table II). Group II was pretreated epicutaneously with perfluorinated compound **9** on day 0. A sensitization attempt with PDC (**10**) was done on day 4. Mice were tested on the right ear with a challenging dose of PDC (**10**) on day 8. Ear thickness was measured on days 9–12 (see Table II). Group III was pretreated epicutaneously with perfluorinated compound **9** on day 0. A sensitization attempt with compound **9** was done on day 4. Mice were tested on the right ear with a challenging dose of compound **9** on day 8. Ear thickness was measured on days and 9–12 (see Table II).

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