Acknowledgment. We wish to thank Dr. J. Bell for valuable technical assistance with the high-pressure LC experiments and Professor J. San Filippo for the use of his high-pressure LC equipment. We also thank Dr. A. Hagedorn for his technical assistance and helpful comments throughout the course of this work and acknowledge the assistance of Dr. B. Wagner in obtaining the ESR spectrum.

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Registry No. 1 (R = CH_2OH), 72784-93-1; 1 (R = CH_2Cl), 72784-94-2; *endo*-**2a**, 52747-94-1; *exo*-**2a**, 52747-95-2; *endo*-**2b**, 72784-95-3; *exo*-**2b**, 72784-96-4; *endo*-**2c**, 72784-97-5; *exo*-**2c**, 72784-98-6; *endo*-**2d**, 72784-99-7; *exo*-**2d**, 72785-00-3; *endo*-**2d** picrate, 72785-01-4; *exo*-**2d** picrate, 72785-02-5; *endo*-**2e**, 824-60-2; *exo*-**2e**, 824-61-3; 2-butyne-1,4-diol, 110-65-6; cyclopentadiene, 542-92-7; benzyl mercaptan, 100-53-8; diethylamine, 109-89-7; dibenzyl disulfide, 150-60-7.

Fluorocarbanion Chemistry. Octafluorofluorene and Companions

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Octafluoro-9-fluorenone (**2**) is obtained by reaction of 2-bromooctafluorobiphenyl-2′-carboxylic acid (**4**) with *n*-butyllithium. The reaction illustrates an unusual intramolecular nucleophilic arylation involving attack at a carboxylate salt. Catalytic reduction gives octafluoro-9-fluorenol, rather than octafluorofluorene (**1**). **1** is synthesized by a six-step procedure from 2-bromononafluorobiphenyl (**7**). The key step involves an intramolecular nucleophilic alkylation to form ethyl octafluorofluorene-9-carboxylate (**12**), which rapidly undergoes decarboxylative hydrolysis in both alkaline and acidic media to form **1**. Relative to the 9-fluorenyl system and open-chain polyfluorinated analogues, **1** and **12** exhibit anomalous reaction chemistry, owing to the exceptional stabilities of their anions.

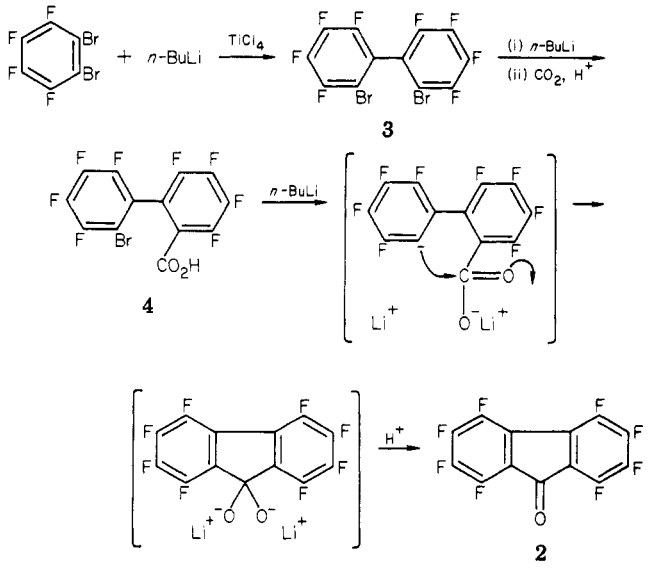
Introduction

The noteworthy effects of high aryl fluorination on reactivity have been elaborated in a recent review.[1] Of special relevance to this paper are the observations that polyfluoroaryl groups strongly stabilize carbanions by both inductive and resonance effects, as evidenced by marked enhancement of hydrocarbon acidities[2-4] and acceleration of carbanionic rearrangements.[5,6] This stabilization may also lead to anomalous reaction chemistry relative to all-hydrogen systems. One of the most revealing manifestations of this dichotomy between fluoro and hydrogen analogues is found in the chemistry of 1,2,3,4,5,6,7,8-octafluorofluorene (**1**) and its congeners.

Discussion

In preliminary communications[7,8] we described two synthetic routes to gain entry into the octafluorofluorene series. In the first approach,[7] we prepared octafluoro-9-fluorenone (**2**), as shown in Scheme I. The strategy required the availability of a suitable 2,2′-bifunctional octafluorobiphenyl which would readily undergo the desired cyclization. To this end, 2,2′-dibromooctafluorobiphenyl (**3**) was prepared from 1,2-dibromotetrafluorobenzene.[9]

Scheme I



Reaction of **3** with an equimolar concentration of *n*-butyllithium in ether at −78 °C gave the bromocarboxylic acid **4** after carbonation. This is a very sensitive reaction, since even under the most favorable conditions **4** was contaminated with small quantities of the octafluorodiphenic acid[10] (**5**), which, fortunately, did not interfere in the subsequent reaction. Rapid carbonation with dry ice favored formation of **4**, whereas slow bubbling of CO_2 gas provided only **5** and **3**, probably via metal–halogen ex-

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(2) A. Streitwieser, Jr., J. A. Hudson, and F. Mares, *J. Am. Chem. Soc.*, **90**, 648 (1968).
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(10) S. C. Cohen and A. G. Massey, *J. Organomet. Chem.*, **10**, 471 (1967).

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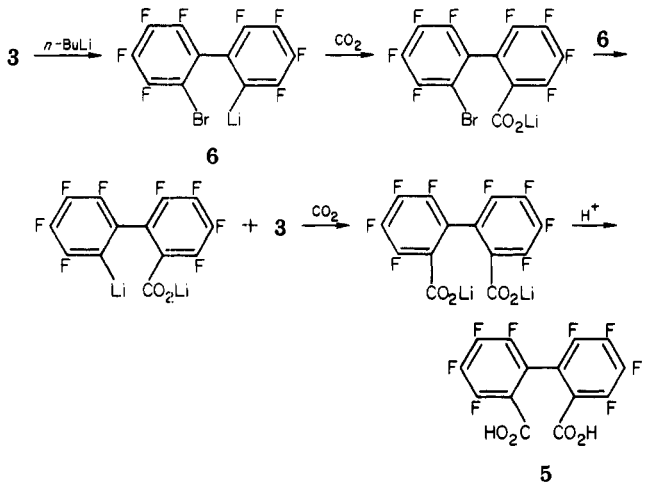
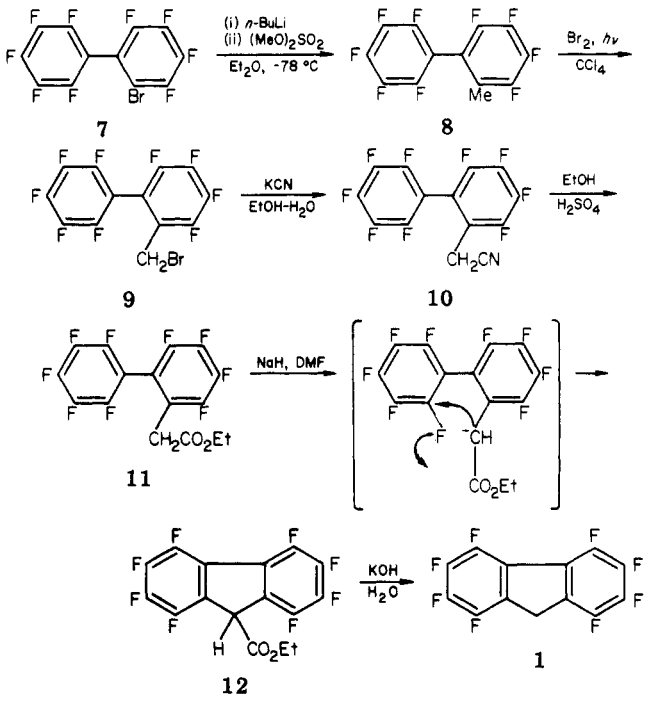
Scheme II



Scheme III



change,[11] as shown in Scheme II.

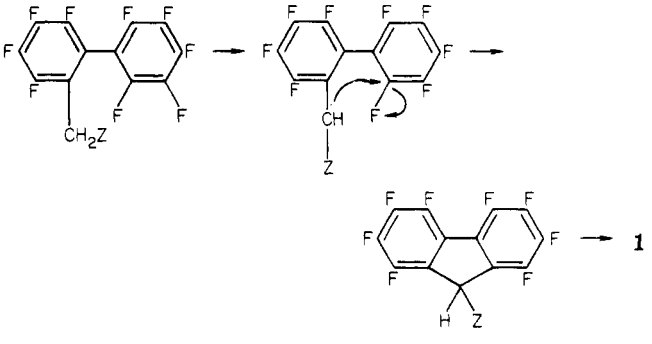
Since pyrolysis of the barium salt[12] of **5** afforded only a trace of the desired octafluoro-9-fluorenone (**2**), the bromo acid **4** was treated with 2 equiv of *n*-butyllithium at −78 °C and acidified to yield **2** in 53% yield. This final step is an extension of the reactions of aliphatic lithium carboxylates with organolithium reagents[13] and perfluoroalkyl carboxylic acids with phenyllithium[14] and Grignard reagents[15] to form ketones. However, ours is the first example of this reaction to yield a completely fluorinated ketone.

In contrast to the behavior of **4**, the hydrogen analogue, 2′-bromobiphenyl-2-carboxylic acid, failed to yield 9-fluorenone under comparable conditions. We suggest that reaction with **4** was successful primarily because the tetrafluorophenyl group substantially enhances the electrophilicity of the carbonyl carbon, thus encouraging nucleophilic attack by the incipient carbanionoid species. Several other features of the cyclization merit comment: (1) to our knowledge, this is the first report of an *intramolecular* nucleophilic arylation involving attack on a carboxylate salt; (2) the favorable transition-state geometry facilitates the 5-exo-trig[16] carbon-to-carbon ring closure; (3) the cyclization is unusual in that the attacking terminal sp^2 carbon is part of an aromatic ring.

Octafluoro-9-fluorenone has also been prepared by the closely related reaction of 2,2′-dilithiooctafluorobiphenyl with dimethyl carbonate[17] and as a minor byproduct in the pyrolysis of silver tetrafluorophthalate.[18] Chambers and Spring[19] have conducted a detailed study of the behavior of **2** with methoxide ion.

Having successfully achieved entry into the fluorene nucleus, we sought to obtain **1** by catalytic reduction of **2**, a standard procedure for the preparation of fluorene. Instead of forming **1**, the reaction stopped at the intermediate octafluoro-9-fluorenol stage and all attempts to effect hydrogenolysis failed. This difficulty in cleaving the carbon–oxygen bond was not unexpected, since the bond is greatly strengthened by the adjacent electron-withdrawing C_6F_4 groups.

We then turned to the second approach in which the strategy was to construct a suitably substituted nonafluorobiphenyl. The side chain should readily form a saturated carbanion, which would effect ring closure by nucleophilic attack at the ortho position of the adjacent ring, with displacement of fluoride ion. A number of such cyclizations involving nucleophilic displacement of aromatic fluoride by heteroatoms[20] and unsaturated carbanions[21] have been reported. One further restriction was required. Group Z, if not H, must be readily convertible to H in the final step.



Our objective was achieved by the preparation of the key intermediate **11** (Z = CO_2Et), the subsequent 5-exo-trig ring closure,[16] and decarboxylative hydrolysis, as summarized in Scheme III.

The starting compound (**7**) was prepared in 70% yield from bromopentafluorobenzene and pentafluorophenyl-

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(12) J. F. Thorpe and G. A. R. Kon, "Organic Syntheses", Collect. Vol. I, 2nd ed., Wiley, New York, 1932, p 192.
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(19) (a) R. D. Chambers and D. J. Spring, *Chem. Commun.*, 713 (1968); (b) R. D. Chambers and D. J. Spring, *Tetrahedron*, **25**, 565 (1969).
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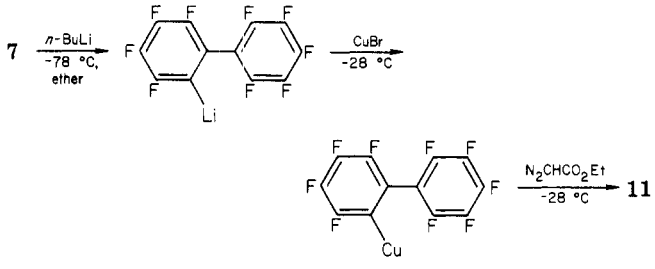
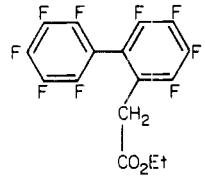
lithium (via tetrafluorobenzyne).[22] 11 was also obtained less reliably by insertion into the carbon–copper bond[23] of [2-(pentafluorophenyl)tetrafluorophenyl]copper with ethyl diazoacetate.

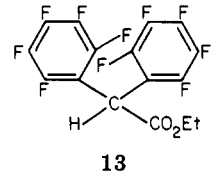


Treatment of 11 with an excess of sodium hydride in dimethylformamide or HMPA generated the stabilized carbanion which underwent intramolecular nucleophilic alkylation to give 12. By contrast, cyclization failed when either 8 or 10 was similarly treated, although the corresponding carbanions appeared to be generated.

Comparative Reaction Chemistry. We have already noted the difference in behavior of 9-fluorenone and octafluoro-9-fluorenone on catalytic hydrogenation. The anomalous reactivity of 1 and 12 relative to their open-chain analogues and to the corresponding 9-fluorenyl systems is especially noteworthy. Thus, mild alkaline hydrolysis of 12 was accompanied by a very facile decarboxylation to afford 1 in quantitative yield, after acidification, as shown in Scheme III. Under even more stringent conditions, 9-carboethoxyfluorene was hydrolyzed to fluorene-9-carboxylic acid. 11 and 13 (prepared by etha-



11



13

nolic acidic hydrolysis of $(C_6F_5)_2CHCN$[24]), the open-chain nonafluoro and decafluoro analogues of 12, also behaved normally to give the corresponding carboxylic acids. These results are a reflection of the exceptional stability of the octafluoro-9-fluorenyl anion.

Further evidence of this stability and lack of reactivity was observed when the pale greenish-yellow anion, generated directly from 1 by using sodium hydride in DMF or organometallic reagents (*n*-BuLi or CH_3MgI), failed to undergo carboxylation or to react with dimethyl sulfate or methyl iodide, in contradistinction to the 9-fluorenyl anion.

Even under acidic conditions, hydrolysis of 12 afforded 1 exclusively. To date, octafluorofluorene-9-carboxylic acid has not been prepared.

The anion derived from 12 should exhibit even greater stabilization than the octafluoro-9-fluorenyl anion because of delocalization through the carboethoxy function. This prediction was confirmed by the total failure to effect the usual reduction of the ester functionality to the primary alcohol with lithium aluminum hydride and other complex metal hydrides. In contrast to ethyl 9-fluorenylcarboxylate and 13, proton abstraction was completely dominant. The remarkably stable, delocalized anion did not exhibit sufficient carbonyl character, and only 12 was recovered on acidification.

Experimental Section[25]

2,2′-Dibromooctafluorobiphenyl (3). *n*-Butyllithium [93 mL (9.62 g, 0.150 mol) of a 15.2% solution in hexane] was added slowly to 38.5 g (0.125 mol) of 1,2-dibromotetrafluorobenzene in 500 mL of anhydrous ethyl ether cooled in a dry ice–acetone bath. After the solution was stirred for 30 min, 20 mL (34.5 g, 0.182 mol) of titanium tetrachloride was added to the orange solution. The reaction was stirred in the cold for an additional 3 h before the dry-ice bath was removed and the flask was left to warm up overnight. The reaction mixture was hydrolyzed with 450 mL of water. The violet aqueous layer was separated from the yellow ether layer and the aqueous layer was extracted three times with ether. The ethereal extracts were washed three times with water, dried ($MgSO_4$), and evaporated in vacuo to yield an orange oil which solidified on standing. Crystallization from Skellysolve B, with dry ice–acetone cooling, gave 14.7 g (51.5%) of 3 as a white microcrystalline solid: mp 93.5–95.5 °C (sealed capillary) (lit.[9] mp 97.5–98.5 °C); IR ($CHCl_3$) 1627 (w, aromatic C=C), 1502 (vs, aromatic ring), 1482 and 1468 (s, aromatic ring), 1033 (s, C–F), and 949 cm^{-1} (m, C–F).

2,2′-Octafluorodiphenic Acid (5). To a solution of 7.18 g (15.8 mmol) of 3 in anhydrous ethyl ether (250 mL) cooled in a dry ice–acetone bath was added 20 mL of a 15.2% solution of *n*-butyllithium in hexane (2.07 g, 32.2 mmol of *n*-BuLi) over 1.1 h. The reaction mixture was allowed to stir in the cold for 2 h before it was swept over, under nitrogen pressure, into another flask containing a well-stirred slurry of powdered dry ice in anhydrous ether. The solution was allowed to stand overnight before it was hydrolyzed with 50 mL of 6 N hydrochloric acid. The resulting layers were separated and the aqueous phase was extracted three times with ether. The combined ethereal phases were washed three times with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo to leave 4.95 g (81.3%) of fairly pure octafluorodiphenic acid: mp 236.5–238.0 °C (lit.[10] mp 239.5–241 °C); IR (Nujol mull) 3300–3000 and 2725–2480 (many broad weak bands, bonded OH), 1752 (s, C=O), 1664 (m, aromatic C=C), and 1517–1445 cm^{-1} (numerous vs bands, aromatic ring).

2-Bromo-2′-carboxyoctafluorobiphenyl (4) with Rapid Carbonation. *n*-Butyllithium (0.836 g, 13.1 mmol, 8.2 mL of 15.0% *n*-BuLi in hexane) was added over a period of 40 min to a stirred solution of 3 (5.97 g, 13.1 mmol) in 250 mL of anhydrous ethyl ether, which was cooled in a dry ice–acetone bath. The mixture was stirred in the cold for an additional 1.5 h before the contents of the flask were swept over, under nitrogen pressure, into another flask containing a stirred dry ice–ether slurry. After standing overnight, the carbonation mixture was hydrolyzed with 60 mL of 6 N hydrochloric acid. The resulting layers were separated and the aqueous layer was extracted three times with ether. The combined ethereal layers were washed three times with water and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 3.63 g of a white solid having a wide melting range. This material was extremely difficult to separate from the contaminating 2,2′-octafluorodiphenic acid. This material is, however, suitable for the synthesis of octafluorofluorenone (2), without further purification. A small sample was tediously crystallized

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(25) **Acidities of octafluoro-9-fluorenyl systems**: in an earlier paper,[4] we reported that substitution of each phenyl group by pentafluorophenyl in diphenylmethane and triphenylmethane results in an enhancement in equilibrium acidities of five to six p*K* units. These changes are due almost exclusively to the inductive influence of the C_6F_5 group. The unusual stabilities of the anions of 1 and 12, in which resonance factors are also significant, strongly suggest that these compounds are far more acidic than $(C_6F_5)_2CH_2$ and $(C_6F_5)_3CH$. We are collaborating with Professor F. G. Bordwell, who has been measuring acidities of carbon acids on an absolute scale in dimethyl sulfoxide.[26] The results of these studies will be published in the near future.
(26) (a) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.*, **97**, 7006 (1975); (b) F. G. Bordwell and G. J. McCollum, *J. Org. Chem.*, **41**, 2391 (1976).

from methanol–water to yield fairly pure 4, mp 158–160 °C (sealed capillary); neutralization equivalent found 415, calcd 421; IR (Nujol mull) 3300–3000 and 2740–2500 (numerous very broad bands, bonded OH), 1714 (s, C=O), 1628 (m, aromatic C=C), 1503 (s, aromatic ring), 1466 (vs, aromatic ring), and 1425 cm^{-1} (s, aromatic ring). Anal. Calcd for $C_{13}HO_2F_8Br$: C, 37.08; H, 0.24. Found: C, 37.21; H, 0.41.

Reaction of 2-Lithio-2′-bromooctafluorobiphenyl with Carbon Dioxide under Conditions of Slow Carbonation. *n*-Butyllithium (0.833 g, 13.0 mmol, 8.0 mL of 15.22% *n*-BuLi in hexane) was added dropwise over a period of 20 min to a stirred solution of 3 (6.00 g, 13.2 mmol) in 500 mL of anhydrous ethyl ether cooled in a dry ice–acetone bath. The mixture was stirred for 25 min before sulfuric acid scrubbed carbon dioxide generated from dry ice was bubbled into the reaction mixture. After the carbonation had proceeded for 1.7 h, the cooling bath was removed from the reaction flask and the carbonation was allowed to proceed for an additional 1.2 h. The reaction mixture was allowed to stand overnight before it was hydrolyzed with 75 mL of 6 N hydrochloric acid. The resulting layers were separated and the aqueous layer was extracted three times with ether. The combined ethereal layers were washed three times with water and dried over anhydrous magnesium sulfate. Evaporation of the ether in vacuo left a crude solid which was partially dissolved in aqueous sodium bicarbonate solution. The bicarbonate mixture was extracted with ether and the ether layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give 2.44 g (40.6%) of crude 3, mp 90.5–95.0 °C (lit.[9] mp 97.5–98.5 °C). The infrared spectrum of this material was identical with that of an authentic sample of 3.

The bicarbonate layer was acidified with hydrochloric acid and extracted with ether. The ethereal layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo to leave 1.57 g (30.9%) of crude 2,2′-octafluorodiphenic acid (5), mp 232–237 °C (after several crystallizations from alcohol–water) (lit.[10] mp 239.5–241 °C). This material had an infrared spectrum identical with that of an authentic sample of 5.

1,2,3,4,5,6,7,8-Octafluoro-9-fluorenone (2). To a solution of crude 2-bromo-2′-carboxyoctafluorobiphenyl (3.57 g, 8.48 mmol) in 250 mL of anhydrous ethyl ether, which was cooled in a dry ice–acetone bath, was slowly added *n*-butyllithium (1.08 g of *n*-BuLi, 16.9 mmol, or 10.6 mL of 15.0% *n*-BuLi in hexane). The addition was carried out over a 35-min period. After the solution was stirred for an additional 1.5 h in the cold, 50 mL of water followed by 50 mL of 6 N hydrochloric acid was added to the cold reaction mixture. The mixture was allowed to warm to room temperature, the layers were separated, and the aqueous layer was extracted three times with ether. The combined ethereal phases were washed three times with water and dried over anhydrous magnesium sulfate. Evaporation of the ether in vacuo left 1.46 g (53.3%) of a light yellow solid. Crystallization from 95% ethanol gave pure 2, mp 250–251 °C (sealed capillary). Further crystallizations from ethanol and vacuum sublimation at 115–125 °C (<1 torr) gave the analytical sample: mp 246.5–247.5 °C (sealed capillary) (lit.[18] 235–236 °C, 195 °C[17]); IR ($CHCl_3$) 1737 (s, C=O), 1721 (w, C=O), 1632 and 1624 (w, aromatic C=C), 1512 (s, aromatic ring), 1491 (vs, aromatic ring), and 988 cm^{-1} (w, C–F). Anal. Calcd for $C_{13}F_8O$: C, 48.17; H, 0.00; F, 46.89. Found: C, 48.02; H, 0.37; F, 47.06. Osmometric mol wt (in benzene) 320, calcd 324; accurate mass (by high-resolution mass spectrometry) 323.981147, calcd 323.9821; prominent peak at mass 296 (M – CO). 2,4-Dinitrophenylhydrazone derivative, mp 239–240 °C dec (from ethanol–ethyl acetate) (lit.[18] 226–227 °C). Anal. Calcd for $C_{19}H_4O_4F_8N_4$: C, 45.26; H, 0.80. Found: C, 45.28; H, 0.96.

Octafluoro-9-fluorenone (2) by the Oxidation of 1,2,3,4,5,6,7,8-Octafluorofluorene (1). A solution of 8.00 g (25.8 mmol) of octafluorofluorene in 40 mL of glacial acetic acid was heated to reflux and magnetically stirred. To this solution was added, during 12 min, 12.92 g (43.4 mmol) of sodium dichromate dihydrate dissolved in a mixture of 36 mL of glacial acetic acid and 8 mL of water (warm to dissolve, if necessary). The reaction mixture turned brown-green and a yellow solid began to precipitate. Refluxing and stirring were continued for an additional 2.5 h after which the reaction mixture was poured onto 300 mL of crushed ice. The crude yellow solid was filtered from the dark green solution and was washed successively with dilute aqueous sulfuric acid and water. The dry solid was sublimed at 67–86 °C (0.1–0.08 torr). Recrystallization from benzene–ether gave 3.87 g (46.3%) of 2 as gleaming yellow needles, mp 248.5–250.5 °C (sealed capillary). A second crop of 1.02 g (12.2%), mp 242–247 °C (sealed capillary), was obtained by concentrating the mother liquor. The octafluoro-9-fluorenone obtained by this route was identical in all respects with that prepared by the previous method.

Octafluoro-9-fluorenol. A mixture of 0.50 g (1.54 mmol) of octafluoro-9-fluorenone (2), 50 mg of 5% palladium on charcoal catalyst, and 50 mL of anhydrous ethyl alcohol was shaken under a hydrogen atmosphere (56–60 psi) for 26.5 h. The solution was filtered through a bed of Celite filter-aid and evaporated in vacuo to a light-yellow solid. Crystallization from Skellysolve B with Darco G-60 decolorizing charcoal gave 0.353 g (70.2%) of long white needles, mp 147.5–149 °C. An additional crystallization from Skellysolve B gave 0.301 g (59.8%) of pure material: mp 148–149 °C; IR ($CHCl_3$) 3566 (w, free OH), 3460–3180 (w, br, bonded OH), 1520 (s, aromatic ring), and 1495 cm^{-1} (vs, aromatic ring). Anal. Calcd for $C_{13}H_2OF_8$: C, 47.88; H, 0.62. Found: C, 47.43; H, 0.58. Accurate mass (by high-resolution mass spectrometry) calcd 325.99776, found 325.99786.

Reduction of 10 g (55.5 mmol) of commercial 9-fluorenone in 100 mL of absolute ethanol by hydrogen gas (36–58 psi) in the presence of 5% palladium on charcoal catalyst gave, after two crystallizations from 95% ethanol, 3.22 g (35%) of fluorene, mp 112–115 °C.

2-Bromononafluorobiphenyl (7). This compound was prepared according to a previously described procedure.[22]

2-Methylnonafluorobiphenyl (8). A. From 2-Lithiononafluorobiphenyl and Dimethyl Sulfate. A well-stirred solution of 60.0 g (0.152 mol) of 2-bromononafluorobiphenyl (7) in 400 mL of anhydrous ethyl ether under a nitrogen atmosphere was cooled in a dry ice–acetone bath. To this solution was added 94 mL (9.75 g, 0.152 mol of *n*-BuLi) of a 15.25% solution of *n*-butyllithium in hexane over 0.7 h. The reaction mixture was stirred in the cold for an additional 1 h before 14.7 mL (19.6 g, 0.156 mol) of dimethyl sulfate was added over a period of 9 min. The color of the reaction mixture changed from cloudy brown to cloudy tan to metallic gray. The stirring was continued for 1.1 h before the bath was replaced with a dry ice–carbon tetrachloride bath and the reaction mixture was stirred overnight. Hydrolysis was accomplished by adding 100 mL of 6 N hydrochloric acid to the cloudy pink solution. The layers were separated and the aqueous layer was extracted three times with ether. The combined ethereal layers were washed three times with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo to an oil which rapidly solidified. The resulting crude solid was sublimed at 59–61 °C (0.2–0.3 torr) (**caution**: unreacted dimethyl sulfate may condense in the pump cold trap) and then crystallized twice from 95% ethanol to yield 25.3 g (50.4%) of 8 as white needles: mp 84.5–86.5 °C; IR (CCl_4) 1646 (w, aromatic C=C), 1516, 1503 (sh) and 1487 (vs, aromatic ring), 1453 (w, aromatic ring), and 998 cm^{-1} (w, C–F); ^1H NMR (CCl_4) δ 2.14 [br s (5.4 Hz wide at half-height) with fine structure]. Anal. Calcd for $C_{13}H_3F_9$: C, 47.30; H, 0.92. Found: C, 47.43; H, 0.95.

B. From [2-(Pentafluorophenyl)tetrafluorophenyl]magnesium Bromide and Methyl Iodide. A solution of 31.29 g (79.22 mmol) of 7 in 120 mL of dry tetrahydrofuran was added to 1.93 g (0.0793 mol) of dry magnesium turnings in a flask fitted with a magnetic stirrer and a nitrogen inlet. Initially, a small amount of the bromide–THF solution was added to the flask along with a small crystal of iodine. If darkening and slight warming of the reaction mixture did not occur, additional small portions of the bromide–THF solution and iodine crystals were added. Once reaction commenced, the flask was immersed in an ice bath and the remaining bromide–THF solution was added over a period of 1.6 h. The reaction mixture was stirred in the cold for an additional 1.4 h before 112.5 g (0.793 mol) of methyl iodide was added during 1 h. After addition was complete, the ice bath was recharged and the mixture was stirred overnight. The reaction mixture was hydrolyzed with 100 mL of 10% hydrochloric acid and the layers separated. The aqueous layer was extracted with three portions of ether, and the combined ethereal layers were washed three times with water. After drying over anhydrous magnesium sulfate, the ether was removed in vacuo to leave a

dark semisolid. The dark material was sublimed twice at 66–84 °C (0.09–0.5 torr) to give a white crystalline solid which was recrystallized from 95% ethanol to give 13.18 g (50.4%) of 8 as white plates, mp 82–86 °C. This material was identical with that obtained by method A.

2-Bromomethylnonafluorobiphenyl (9). A solution of 22.0 g (66.6 mmol) of 2-methylnonafluorobiphenyl (8) in 400 mL of carbon tetrachloride was irradiated and refluxed by means of a 150-W frosted incandescent lamp. A mixture of 12.0 g (75.0 mmol) of bromine and 100 mL of carbon tetrachloride was added dropwise over a period of 95 min. The reaction mixture was refluxed for an additional 5 h and allowed to stand overnight before the carbon tetrachloride was removed in vacuo. The resulting orange oil was dissolved in Skellysolve B and decolorized with Darco G-60 charcoal. The filtrate was cooled in a dry ice–acetone bath to give a white solid, mp 50–54 °C. Crystallization of this material from petroleum ether (30–60 °C) with dry ice–acetone cooling gave 17.4 g (64.0%) of **9**: mp 53–55 °C; IR (CCl_4) 1641 (m, aromatic C=C), 1516, 1502, and 1488 (vs, aromatic ring), 1454 (m, aromatic ring), 1000 and 976 cm^{-1} (m, C–F); ^1H NMR (CCl_4) δ 4.26 (d, J_{HF} = 2.0 Hz). Anal. Calcd for $C_{13}H_2F_9Br$: C, 38.17; H, 0.49. Found: C, 38.43; H, 0.62.

2-(Cyanomethyl)nonafluorobiphenyl (10). A solution of 16.0 g (38.2 mmol) of **9** in 70 mL of absolute ethanol was mixed with 3.32 g (51.0 mmol) of potassium cyanide, dissolved in 30 mL of water. The mixture was stirred vigorously and warmed in an oil bath maintained at 68–70 °C for 2 h. The dark reaction mixture was then poured onto 500 mL of crushed ice. The resulting pink solid was filtered off, washed well with water, dried, and then crystallized twice from benzene–Skellysolve B (once using Darco G-60 charcoal) to yield **10** as heavy white needles, 8.86 g (63.7%): mp 123–125.5 °C; IR ($CHCl_3$) 2258 (w, C≡N), 1664 (m, aromatic C=C), 1514 (sh), 1503, and 1486 (vs, aromatic ring), 1456 (m, aromatic ring), 1003 and 988 cm^{-1} (m, C–F); ^1H NMR ($CDCl_3$) δ 3.61 [br s (3.2 Hz at half-height) with fine structure]. Anal. Calcd for $C_{14}H_2F_9N$: C, 47.35; H, 0.57; N, 3.94. Found: C, 47.69; H, 0.58; N, 3.67. Accurate mass by high-resolution mass spectrometry calcd 355.00432, found 355.00432.

Ethyl 2-(Pentafluorophenyl)tetrafluorophenylacetate (11). A. Via Ethanolysis of 2-(Cyanomethyl)nonafluorobiphenyl (10). Concentrated sulfuric acid (99 mL) was slowly poured (**caution**: exothermic reaction) into a well-stirred solution of 18.5 g (52.0 mmol) of **10** in 225 mL of 95% ethanol. The reaction mixture was then refluxed with external heat for 6 h before it was poured into 600 mL of ice and water. The resulting mixture was extracted four times with ether and the ethereal layer was washed three times with water and dried over anhydrous magnesium sulfate. Removal of the ether in vacuo, followed by distillation of the residue through a 12.5-cm Vigreux column, gave 16.0 g (76.5%) of **11** as a colorless viscous oil: bp 99–102 °C (0.7 torr); n^{23}_D 1.4629; IR (neat film) 1742 (vs, C=O), 1643 (m, aromatic C=C), 1514, 1502, and 1486 (vs, aromatic ring), 1002 and 988 cm^{-1} (w, C–F); ^1H NMR (CCl_4) δ 1.18 (t, 3, J_{HH} = 7.0 Hz, CH_2CH_3), 3.53 (d, 2, J_{HF} = 2.0 Hz, CH_2), and 4.04 (q, 2, J_{HH} = 7.0 Hz, CH_2CH_3). Anal. Calcd for $C_{16}H_7O_2F_9$: C, 47.78; H, 1.75; mol wt, 402. Found: C, 47.58; H, 1.56; mol wt (by low-resolution mass spectrometry) 402.

B. Via [2-(Pentafluorophenyl)tetrafluorophenyl]copper. *n*-Butyllithium (56.7 mmol or 35 mL of a 15.25% solution of *n*-BuLi in hexane) was added over 18 min to a solution of 20.0 g (50.6 mmol) of 2-bromononafluorobiphenyl (**7**) in 400 mL of anhydrous ethyl ether cooled in a dry ice–acetone bath. After the solution was stirred for 1 h in the cold, 9.44 g (65.8 mmol) of cuprous bromide (Fisher Certified Reagent Grade) was added all at once. After 1 h the bath was replaced with a dry ice–carbon tetrachloride bath and the beige-colored solution was allowed to stir for 3.2 h before 6.0 mL (6.45 g, 56.5 mmol) of ethyl diazoacetate was added rapidly to the reaction flask. The cooling bath was well-charged with dry ice, the mixture was stirred overnight under nitrogen and hydrolyzed with 100 mL of 6 N hydrochloric acid, and the resulting layers separated. The aqueous layer was extracted with ether and the ethereal phase was washed with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo to a dark oil. Distillation of the oil through a 10-cm jacketed Vigreux column gave two fractions: (1) 11.2 g boiling at 55–97 °C (0.6 torr) containing diethyl maleate, diethyl fumarate, and 2-hydrononafluorobiphenyl; and (2) 2.85 g (14% yield) boiling at 97–123 °C (0.7–0.8 torr) containing mostly **11**, contaminated with 2-hydrononafluorobiphenyl.

9-Carboethoxyoctafluorofluorene (12). A. In DMF. A 53.4% mineral oil dispersion of sodium hydride (4.03 g, 89.5 mmol) was washed with approximately 300 mL of anhydrous ethyl ether under a nitrogen atmosphere to remove the mineral oil. After being dried under nitrogen, the sodium hydride was dispersed with magnetic stirring in 100 mL of purified DMF in a nitrogen-purged flask. The flask was immersed in an oil bath maintained at 85–87 °C. When the reaction mixture reached bath temperature, 6.00 g (14.9 mmol) of ethyl 2-(pentafluorophenyl)tetrafluorophenylacetate (**11**) in 50 mL of purified DMF was added over 5 h. The first few drops of the addition produced a pea-green solution. After an additional 1.3 h in the bath, the brown solution was poured slowly onto 300 mL of crushed ice containing 100 mL of 6 N hydrochloric acid. After the solution was allowed to stand overnight, a tan solid was collected by vacuum filtration, washed with a large quantity of water, dried, and sublimed at 48–56 °C (0.07–0.06 torr). The crude solid (3.83 g, 67.2%) was crystallized from ethanol–water to yield 2.89 g (50.6%) of **12** as long white gleaming needles, mp 73–75 °C. A small second crop, amounting to 0.37 g (6.5%) of gleaming off-white long needles, mp 69–74 °C, was obtained by concentrating the mother liquor. An analytical sample had a melting point of 75–76.5° C; IR (CCl_4) 1746 (s, C=O), 1628 (w, aromatic C=C), 1518 (s, aromatic ring), 1493 (vs, aromatic ring), and 988 cm^{-1} (w, C–F); ^1H NMR (CCl_4) δ 1.32 (t, 3, J_{HH} = 7 Hz, CH_2CH_3), 4.24 (q, 2, J_{HH} = 7 Hz, CH_2CH_3), and 5.09 (br s with fine structure, width at half-height = 3.4 Hz, 2, CH_2). Anal. Calcd for $C_{16}H_6O_2F_8$: C, 50.28; H, 1.58. Found: C, 50.21; H, 1.39. Accurate mass (by high-resolution mass spectrometry) calcd 382.02397, found 382.02383.

B. In Hexamethylphosphoramide. Sodium hydride (4.03 g, 98.5 mmol) was dispersed with magnetic stirring in 100 mL of purified hexamethylphosphoramide in a nitrogen-purged flask. The flask was immersed in an oil bath maintained at 87–88 °C. When the flask reached bath temperature, 6.00 g (14.9 mmol) of **11** in 50 mL of purified hexamethylphosphoramide was added over 5 h. The yellow dispersion turned lime green after the first few drops of the addition. After the solution was stirred for an additional 1 h, the brown solution was poured onto 300 mL of crushed ice containing 100 mL of 6 N hydrochloric acid. After the solution was allowed to stand overnight, the crude solid was filtered off, washed with water, dried, and sublimed at 46–63 °C (0.07–0.06 torr). Two crystallizations from ethanol–water gave 4.24 g (74.4%) of **12** as white needles, mp 74–76 °C (sealed capillary).

Octafluorofluorene (1). A. Acid Hydrolysis. A mixture of 1.00 g (2.62 mmol) of **12** and 0.503 g (5.23 mmol) of methanesulfonic acid in 10 mL of 90% formic acid was refluxed for 44.4 h. The reaction mixture was then poured into 100 mL of water and the resulting solid was collected, washed with water, dried, and crystallized from 95% ethanol to yield 0.553 g (68.2%) of **1**, mp 112.5–114.5 °C (sealed capillary).

B. Basic Hydrolysis. A suspension of 1.00 g (2.62 mmol) of **12** in 60 mL of 5% (wt/v) aqueous potassium hydroxide was refluxed for 1 h. On heating, the aqueous layer turned a pale green-yellow. After reflux, the reaction mixture was poured into 200 mL of 6 N hydrochloric acid. The resulting solid was combined with solid which had steam distilled into the condenser during the course of the reaction and washed with water. The dry solid was sublimed at 53–62 °C (0.1–0.08 torr) to give 648 mg (79.9%) of crude **1**, mp 106.5–114 °C. Crystallization from ethanol–water gave 561 mg (69.2%) of gleaming white needles, mp 113.5–115.0 °C (sealed capillary). A small second crop of 48 mg (5.9%), mp 112–114.5 °C, was obtained by concentrating the mother liquor: IR (CCl_4) 1520 (s, aromatic ring), 1495 (vs, aromatic ring), and 968 cm^{-1} (m, C–F); ^1H NMR (CCl_4) δ 4.09 [br s (2.8 Hz wide at half-height) with fine structure]. Anal. Calcd for $C_{13}H_8F_2$: C, 50.35; H, 0.65. Found: C, 50.42; H, 0.65. Accurate mass (by high-resolution mass sectrometry) calcd 310.00285, found 310.00262.

Attempted Base-Catalyzed Hydrolysis of Ethyl [2-(Pentafluorophenyl)tetrafluorophenyl]acetate (11). A mixture of 2.00 g (4.97 mmol) of **11** and 40 mL of 5% (wt/v) aqueous

potassium hydroxide was refluxed for 1.5 h. Starting material was recovered quantitatively.

[2-(Pentafluorophenyl)tetrafluorophenyl]acetic Acid by Acid-Catalyzed Hydrolysis of 11. A mixture of 2.00 g (4.97 mmol) of 11 and 0.96 g (9.94 mmol) of methanesulfonic acid in 20 mL of 90% formic acid was refluxed with magnetic stirring for 23.5 h. The reaction mixture was then poured into 100 mL of water and the oil which formed solidified immediately. The crude white solid was collected by vacuum filtration, washed with water, and finally crystallized twice from ethanol–water to yield 1.31 g (70.4%) of a white microcrystalline acid: mp 151–152.5 °C; IR (CCl_4) 3300–2500 (br, carboxylic acid OH), 1722 (vs, C=O), 1644 (w, aromatic C=C), 1514, 1502, and 1487 (vs, aromatic ring), 1002 and 993 cm^{-1} (w, C–F); ^1H NMR (pyridine) δ 3.83 (d, 2, CH_2, J_{HF} = 1.8 Hz) and 10.12 (m, 1, COOH); neutralization equivalent calcd 374, found 379. Anal. Calcd for $C_{14}H_3O_2F_9$: C, 44.94; H, 0.81. Found: C, 44.50; H, 0.80.

Pentafluorophenylacetonitrile. This compound was prepared in 58% yield from hexafluorobenzene and ethyl cyanoacetate according to a previously described procedure.[27]

Bis(pentafluorophenyl)acetonitrile.[24] To a suspension of 2.2 g (0.092 mol) of sodium hydride in 40 mL of DMF and 21.0 g (0.113 mol) of hexafluorobenzene was added 4.8 g (0.023 mol) of (pentafluorophenyl)acetonitrile at room temperature during 50 min. The resulting dark solution was stirred for 4 h and 40 mL of ether was added, followed by 40 mL of 5% HCl. The organic layer was separated and the aqueous layer extracted three times with ether. The ethereal extracts were combined, washed with water, and dried over anhydrous sodium sulfate. After removal of the ether, the crude material was distilled to afford 2.14 g (25%) of product, bp 120–124 °C (2.8 torr), mp 65 °C (sublimation).

Ethyl Bis(pentafluorophenyl)acetate (13). Bis(pentafluorophenyl)acetonitrile (2.14 g, 0.057 mol) was heated under reflux for 10 h with 5 mL of absolute ethanol and 2 mL of concentrated H_2SO_4. After the solution was cooled, water was added and the product was extracted with ether. The aqueous layer was also extracted with ether. The combined ethereal layers were washed with water, 10% sodium bicarbonate, and again with water and then dried over anhydrous sodium sulfate. After removal of ether, the residue was distilled to give 0.8 g (27%) of ester, bp 108–110 °C (3.5 torr).

Alkaline hydrolysis of the ester with 5% potassium hydroxide gave bis(pentafluorophenyl)acetic acid, mp 108–109 °C (lit.[24] 112.0–112.5 °C); mass spectrum m/e 226 ($C_6F_5CHCO_2H$,$^+$ 181 ($C_6H_5CH_2$),$^+$ 162 (181 – F). A higher melting product (mp 148 °C) containing a phenolic function ($FeCl_3$ test) was also isolated.

Acidic hydrolysis of the ester with *p*-toluenesulfonic acid and 97% formic acid afforded, after 90 h of reflux, a 62% yield of bis(pentafluorophenyl)acetic acid, mp 106–108 °C (heptane).

Bis(pentafluorophenyl)acetic Acid via Decafluorobenzilic Acid. Methyl decafluorobenzilate and decafluorobenzilic acid were prepared according to previously described procedures.[5]

Bis(pentafluorophenyl)acetic Acid. Glacial acetic acid (5 mL), 0.3 g of purified red phosphorus, and 0.1 g of iodine crystals were placed in a round-bottom flask fitted with a reflux condenser. The mixture was stirred (magnetic stirrer) for 20 min and 2.0 g of decafluorobenzilic acid was added. The mixture was heated under reflux, with stirring, for 4 h. Hexane was added and 1.6 g of crystalline acid, mp 108–109 °C, was obtained on cooling the solution. This material did not depress the melting point on admixture with the acid obtained on hydrolysis of 13.

Reaction of Bis(pentafluorophenyl)acetate with Lithium Aluminum Hydride. Lithium aluminum hydride (0.1 g) in 30 mL of ether was placed in a two-necked flask and 1.1 g of ester in 30 mL of ether was added dropwise from a dropping funnel during 30 min. The mixture was heated under reflux for 30 min and excess hydride was decomposed by slowly adding 50 mL of ethyl acetate with magnetic stirring. Then, 20 mL of 3 N HCl was added. After the organic layer was separated, the aqueous layer was extracted with ether and the ethereal layers were combined. After removal of ether, the liquid residue revealed a strong hydroxyl absorption in the 3500–3400-cm^{-1} region.

Registry No. 1, 27053-34-5; 2, 19925-96-3; 2 2,4-dinitrophenylhydrazone, 19925-97-4; 3, 5576-19-2; 4, 19925-95-2; 5, 16583-10-1; 6, 72844-06-5; 7, 1093-66-9; 8, 72844-07-6; 9, 72844-08-7; 10, 72866-24-1; 11, 27053-32-3; 12, 27053-33-4; 13, 42238-45-9; 1,2-dibromotetrafluorobenzene, 827-08-7; octafluoro-9-fluorenol, 72844-09-8; ethyl diazoacetate, 623-73-4; [2-(pentafluorophenyl)tetrafluorophenyl]-acetic acid, 72844-10-1; bis(pentafluorophenyl)acetonitrile, 42238-34-6; (pentafluorophenyl)acetonitrile, 653-30-5; (pentafluorophenyl)acetic acid, 653-21-4; decafluorobenzilic acid, 29688-34-4; methyl decafluorobenzilate, 38449-79-5.

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Polymer-Bound Oxime Esters as Supports for Solid-Phase Peptide Synthesis. Preparation of Protected Peptide Fragments

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A series of polystyrene-bound substituted benzophenone oximes (II) have been synthesized and tested as potential supports for the solid-phase preparation of protected peptide fragments. The polymer-bound *p*-nitrobenzophenone oxime (IID) has been found to be a suitable support for stepwise peptide synthesis. Protected peptides can be assembled on IID by coupling and deprotection steps similar to those employed in the usual Merrifield solid-phase procedures. Cleavage of peptides from IID can be accomplished with hydrazine and amino acid esters under mild conditions which do not affect benzyl ester side-chain protecting groups. The utility of IID has been illustrated in the synthesis of protected peptide hydrazides and esters, several of which have aspartic and glutamic acid side chains protected by benzyl groups.

Introduction

The solid-phase method of peptide synthesis[1] has had many notable successes. However, the preparation of peptides greater than 20 amino acids in length using the solid-phase technique often poses major problems in that very extensive purification of the final product is needed. In contrast to the solid-phase method, the classical solution methods[2] of peptide synthesis are likely to give more homogeneous products since intermediates are usually purified after each coupling step. A major problem though

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