dropwise added to a stirred mixture of 2,6-dimethylhydroquinone (28.0 g), 85% H_3PO_4 (23 mL), and petroleum ether (60 mL) over a period of 2.5 h, and the mixture was vigorously stirred for 3 h. The oily residue, obtained after workup, was chromatographed on silica gel (135 g) with petroleum ether to give a crystalline product, which was recrystallized from petroleum ether to yield **12** (13.1 g, 31%) as colorless crystals: mp 92–93.5 °C (lit.[14] mp 91–92 °C). The ^1H NMR, IR, and UV spectra were in accord with those reported for **12**.[14]

By adaptation of the procedure described for the preparation of 5-(chloromethyl)-4-methoxy-2,3,6-trimethylphenol from 4-methoxy-2,3,6-trimethylphenol,[6] a mixture of **12** (5.00 g), 37% HCHO (4.30 g) and concentrated HCl (50 mL) was stirred vigorously for 24 h. Filtration of the mixture afforded a colorless solid (5.63 g): ^1H NMR ($CDCl_3$) δ 4.69 (s, unexchangeable with D_2O); IR (CCl_4) 3605, 3420 (br) cm^{-1}. Attempted purification by recrystallization proved unsuccessful. This crude product (5.63 g) was dissolved in methanol (30 mL), and the solution was kept at room temperature for 20 min. The mixture was poured into water and extracted with ether. The extract was washed successively with water, aqueous $NaHCO_3$, and water, dried, and evaporated. Column chromatography of the oily residue on silica gel (140 g) with benzene yielded **11** (3.47 g) as colorless crystals, identical with that described above (melting point, TLC, ^1H NMR, and IR).

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Synthesis of Perfluorotetraalkyl Orthocarbonates Using Elemental Fluorine

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An extraordinarily significant application of direct fluorination is in the synthesis of oxygen-containing fluorocarbons that are inaccessible by other techniques. Thus, recent research on the synthesis of "spherical" fluorocarbons in our laboratory has led to the preparation of perfluorotetraalkyl orthocarbonates [$C(OCR_f)_4$] by controlled direct elemental fluorine reactions.

Hydrocarbon orthocarbonates are generally synthesized by the action of sodium alkoxides on trichloronitromethane or trichloromethanesulfenyl chloride.[1] Perfluorotetraalkyl orthocarbonates are inaccessible via conventional fluoroorganic techniques. While fluorinated alkoxides are known, they are very weak nucleophiles and, at the temperatures required for reaction, are highly dissociated or undergo competing side reactions.[2] The main difficulty in the fluorination of ester compounds lies in the susceptibility of the ester linkage toward attack by hydrogen fluoride. The direct fluorination method employed by our laboratory has been very successful in fluorination of other acid-sensitive compounds such as crown ethers,[3] branched dialkyl ethers,[4] and polyesters.[5]

Scheme I. Reaction Scheme of Tetraalkyl Orthocarbonates

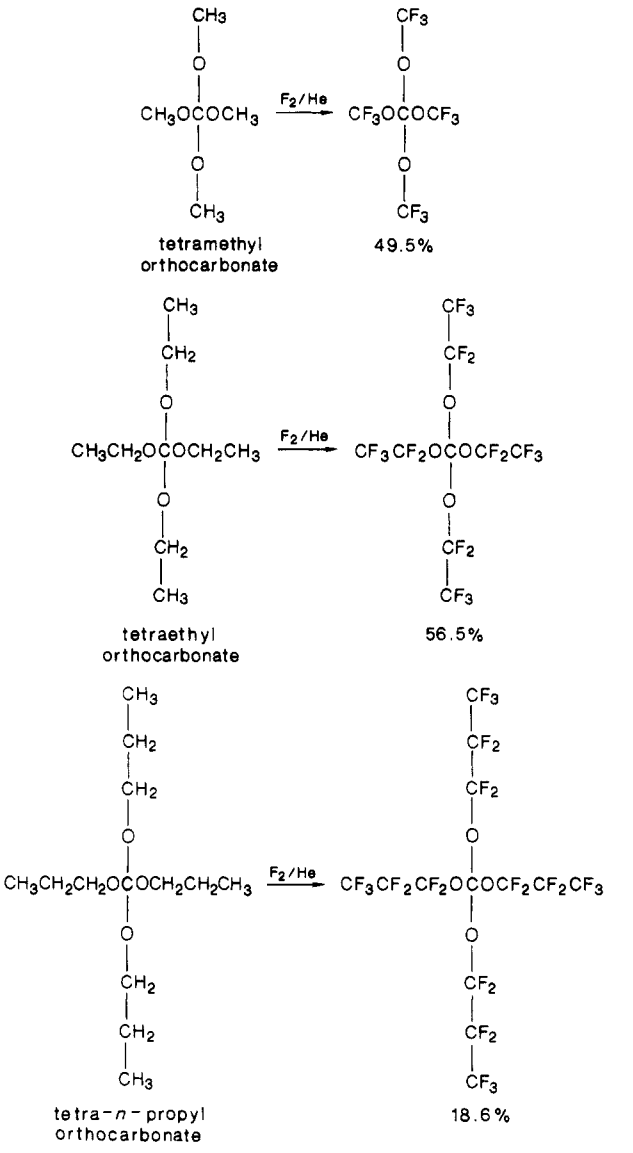

Table I. Comparison of Boiling Points

compound	bp, °C	compound	bp, °C
$C(OCH_3)_4$	114	$C(OC_2F_5)_4$	80
$C(OC_2H_5)_4$	160	$C(OC_3F_7)_4$	132
$C(OC_3H_7)_4$	224	$C(CF_2OCF_3)_4$	130
$C(OCF_3)_4$	20.8	$C(CF_2OC_2F_5)_4$	170

$C(OCF_3)_4$ and $C(OC_2F_5)_4$ were obtained directly from the hydrocarbons in 49.5% and 56.5% yield, respectively. The direct fluorination of $C(OCH_2CH_2CH_3)_4$ yields the compound $C(OCF_2CF_2CF_3)_4$ in an 18.6% yield. It has previously been reported that perfluoro orthocarbonates such as perfluorotetramethyl and perfluorotetraethyl orthocarbonate rearrange during reactions with elemental fluorine and that only very low yields are possible.[6] The reaction scheme appears in Scheme I and a comparison of boiling points appears in Table I. It should be noted

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that the perfluorotetraalkyl orthocarbonates are far more volatile than branched perfluoropolyethers of the same molecular weight.

A number of highly branched perfluoropolyethers prepared by our direct fluorination technique are now under study in the NASA Lewis Research Center's Tribology Department as "spherical" lubricants.[7] It would appear that the new class of "spherical" perfluoro orthocarbonates will also merit consideration as perfluoropolyether lubricants. Such compounds have unusual low temperature properties and low glass transition temperatures characteristic of perfluoropolyethers coupled with thermal stability as high as 430 °C. The low temperature lubrication and liquid properties result from the free rotation around the carbon–oxygen bond at very low temperatures and from vibrational energy storage at higher temperatures.

The high yield of the methyl and ethyl orthocarbonate compounds is a result of the important oxygen "spacer" in the molecule. The fluorination of the structurally similar molecules 3,3-diethylpentane and 4,4-dipropylheptane[8] produces significant amounts of cleavage products as evidence of the steric requirements for four perfluoroalkyl groups attached to a quaternary carbon. The success of this work has prompted us to investigate the synthesis of other similar classes of compounds by the direct elemental fluorination technique. Work is presently in progress on such compounds as perfluoro acetals and perfluoro orthoformates.

Experimental Section

Tetramethyl orthocarbonate and *tetraethyl orthocarbonate* were used as received from Aldrich Chemical Co. Fluorine was technical grade purchased from Air Products and Chemicals. The reactors and fluorination system were previously described.[8-10] Purification of the compounds was accomplished by preparative gas chromatography on a Hewlett-Packard Model 5880A chromatograph equipped with a thermal conductivity detector. The columns used were 10 ft × $^1/_4$ in. stainless steel packed with either 25% fluorosilicone or 25% Fomblin Z on 60/80 mesh Chromosorb A. The carrier gas was helium at 45 mL/min^{-1}. IR spectra were recorded by using a 10-cm pathlength gas cell equipped with KBr windows. MS analyses were performed on a Bell and Howell 21-491 at 70 eV ionizing potential. Fluorine NMR are referenced to $CFCl_3$, with signals at higher field designated as negative. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, NY. The byproducts of the fluorination of orthocarbonates are generally a complex mixture of partially fluorinated material and fragmentation products, with no one compound forming a major fraction of the material other than the perfluoro orthocarbonate. No attempt has been made to optimize the reaction conditions for the production of the maximum amount of perfluorotetraalkyl orthocarbonate.

Fluorination of Tetramethyl Orthocarbonate. A four-zone *cryogenic reactor* was used for the fluorination of tetramethyl orthocarbonate. The first two zones of the reactor were packed with sodium fluoride powder and copper turnings, and the last two zones were packed with copper turnings. Tetramethyl orthocarbonate (2.04 g) was slowly injected into an evaporation coil in line before the reactor. The starting material was condensed into the first zone by the passage of a 60 mL/min^{-1} flow of helium while zones 2, 3, and 4 were cooled to −100 °C. The reactor was then cooled to −120 °C and the fluorination reaction started. Conditions used in the reaction are outlined in Table II. The contents of the dry ice cooled product trap were initially separated on a vacuum line with the majority of the material stopping in a −78 °C trap. Final purification on the Fomblin column at 60 °C produced 2.63 g of perfluorotetramethyl orthocarbonate, corresponding to a 49.5% yield.

Table II. Fluorination Conditions for Tetramethyl Orthocarbonate

He, cm^3 min^{-1}	F_2, cm^3 min^{-1}	time, days	zone temp, °C			
60	1	1	−120	−120	−120	−120
30	1	1	−120	−120	−120	−120
30	2	0.5	−120	−120	−120	−120
10	1	0.5	−120	−120	−120	−120
10	2	0.5	−110	−110	−110	−110
0	1	0.5	−110	−110	−110	−110
0	1	0.5	−90	−90	−90	−90
0	1	1	−80	−80	−80	−80
0	1	0.5	25	−80	−80	−80
0	1	0.5	25	25	−80	−80
0	1	0.5	25	25	25	−80
0	1	1	25	25	25	25

Table III. Fluorination Conditions for Tetraethyl Orthocarbonate

He, cm^3 min^{-1}	F_2, cm^3 min^{-1}	time, days	zone temp, °C			
30	0.5	0.5	−100	−100	−100	−100
30	1	0.5	−100	−100	−100	−100
30	1	0.5	−90	−90	−90	−90
30	1	0.5	−80	−80	−80	−80
30	2	0.5	−80	−80	−80	−80
30	2	0.5	25	−80	−80	−80
15	2	0.5	25	25	−80	−80
0	1	1	25	25	−80	−80
0	1	0.5	25	25	25	−80
0	1	1	25	25	25	25

Perfluorotetramethyl orthocarbonate: bp 20.8 °C. The fluorine NMR spectrum consists of a single peak at −59.0 ppm δ ($CFCl_3$). The $^{13}C\{^{19}F\}$ NMR spectrum shows two peaks at 118.6 ppm and 114.9 ppm with an intensity ratio of 4:1. The electron impact MS contained the following prominent peaks: *m/e* 267 $[C(OCF_3)_3]^+$, 201 $[CF(OCF_3)_2^+$, base peak], 113 $(OCOCF_3)^+$, 85 $(OCF_3)^+$, 47 $(OCF)^+$. The IR spectrum exhibited absorptions at 1170 (vs, br), 1050 (vs, br), 1010 (vs, br), 750 (m), 710 (m) cm^{-1}.

Fluorination of Tetraethyl Orthocarbonate. A 1.6-g sample of tetraethyl orthocarbonate was mixed well with 10 g of dry sodium fluoride and the mixture packed into a 5 in. × 1 in. brass tube. The tube was loaded into the first zone of a four-zone cryogenic reactor. The other three zones were packed with copper turnings. All four zones were cooled to −100 °C and the system was purged with helium for 10 h. Fluorination was started at −100 °C following the conditions outlined in Table III. Fluorinated material (2.86 g) was collected from the glass product trap and purified by preparative gas chromatography using the fluorosilicone column at 80 °C. Perfluorotetraethyl orthocarbonate (2.6 g) was collected to give a 56.5% yield based on starting material.

Perfluorotetraethyl orthocarbonate: bp 80 °C. Anal. Calcd for $C_9F_{20}O_4$: C, 19.58; F, 68.33. Found: C, 19.33; F, 69.05. Mass spectral analysis: *m/e* 301 $[CF(OC_2F_5)_2]^+$, 163 $(OCOC_2F_5)^+$, 119 $(C_2F_5^+$, base peak), 100 $(C_2F_4)^+$, 69 $(CF_3)^+$, 50 $(CF_2)^+$. IR analysis: 1240 (vs, br), 1100 (vs, br), 850 (m), 750 (s, sh), 675 (m) cm^{-1}. The ^{19}F NMR spectrum consisted of two peaks at $\delta(CFCl_3)$ −88.3 (CF_3) and −91.0 (-CF_2-) in a relative ratio of 3:2.

Fluorination of Tetra-*n*-propyl Orthocarbonate. A sample of *tetra-n-propyl orthocarbonate* was synthesized as described by DeWolfe.[1] A 2.89-g sample was prepared for fluorination by mixing well with 10 g of powdered sodium fluoride. The mixture was dispersed onto the copper turnings of a "pancake" reactor[8] and connected to the fluorination system. The reactor was cooled to −80 °C and purged overnight. After cooling the reactor to −100 °C, the fluorination reaction was started. Conditions used in the reaction are listed in Table IV. The product was collected in a dry ice cooled glass trap downstream of the reactor. Approximately 2 mL of a clear liquid was collected from the trap. GC analysis of the liquid on a 25% Fomblin column at 80 °C gave a 18.6% yield of the desired product.

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Table IV. Fluorination Conditions for Tetra-*n*-propyl Orthocarbonate

He, cm^3 min^{-1}	F_2, cm^3 min^{-1}	temp, °C	time, days
100	1	-100	1
100	1	-90	1
100	1	-80	1
50	1	-80	1
50	2	-80	1
20	2	-80	1
20	4	-60	1
10	4	-60	1
0	4	-30	1
0	4	rt	1
0	4	50	1
60	0	50	0.5

Perfluorotetra-*n*-propyl orthocarbonate: bp 132 °C. IR analysis (thin film, KBr): 1343 (m), 1243 (vs, br), 1204 (vs), 1140 (s), 1101 (s), 994 (s), 753 (m) cm^{-1}. MS analysis: *m/e* 567 ($M - C_3F_7O)^+$, 548 $(C_{10}F_{20}O_3)^+$, 401 $[CF(OC_3F_7)]^+$, 400 $(C_8F_{16})^+$, 382 $(C_7F_{14}O_2)^+$, 235 $(C_4F_9O)^+$, 213 $(C_4F_7O_2)^+$, 169 $(C_3F_7^+$, base peak), 119 $(C_2F_5)^+$, 100 $(C_2F_4)^+$, 69 $(CF_3)^+$, 47 $(CFO)^+$. ^{19}F NMR analysis: $\delta(CFCl_3)$ - 82.2 (CF_3), -85.5 (-OCF_2-), and -131.0 (-CF_2-). Anal. Calcd for $C_{13}F_{28}O_4$: C, 20.76; F, 70.73. Found: C, 20.51; F, 70.46.

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Registry No. $C(OCH_3)_4$, 1850-14-2; $C(OC_2H_5)_4$, 78-09-1; $C(OCF_3)_4$, 92639-87-7; $C(OC_2F_5)_4$, 118631-42-8; $C(OC_6H_7)_4$, 597-72-8; $C(OC_6F_7)_4$, 118631-43-9.

Reactions of Vinylogous Phosphonate Carbanions and Reformatsky Reagents with a Sterically Hindered Ketone and Enone

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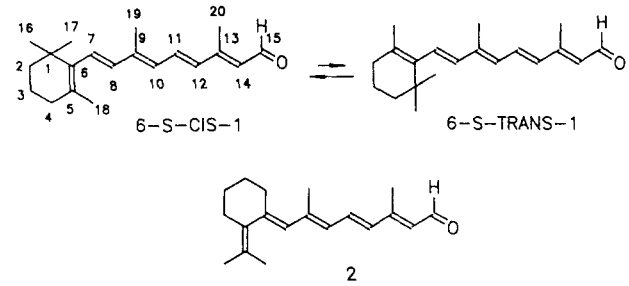
All *trans*-retinal (vitamin A aldehyde, 1) occurs in solution as a mixture of nearly planar 6-*s*-*trans* and distorted 6-*s*-*cis* conformations, with the latter predominating.[1,2] However, only one of these conformations is incorporated into retinal-protein complexes such as the visual pigment rhodopsin[3,4] and the highly studied analogue bacteriorhodopsin.[5-7] In order to further study the interactions of specific 6-s conformations of retinal with these proteins, we proposed the synthesis of a conformationally defined, distorted 6-*s*-*cis* analogue (2) of retinal. This analogue contains the same steric interaction that results in nonplanarity of the 6-*s*-*cis* conformation in retinal, namely that between the 18-methyl and 8-hydrogen.



We envisioned that the synthesis of 2 could be accomplished from the aldehyde derivative of 3 (Scheme I) by a Horner-Emmons condensation, which has been commonly employed in retinoid syntheses by others[8] as well as in our laboratory.[9] It was proposed that intermediate 3 could be prepared via an olefination of 2-isopropylidenecyclohexanone (5, Scheme I). However, our attempts to convert 5 to 3 by a Horner-Emmons condensation failed, and model reactions suggested that this was due to unfavorable steric and electronic effects. We then attempted a Reformatsky reaction, but the product obtained was the unprecedented (2*Z*,4*E*)-carboxylic acid 8 (Scheme I). We further investigated this Reformatsky reaction and here report a study of the reactions between two stereochemically defined vinylogous Reformatsky reagents and a sterically hindered ketone and enone. The results suggest that δ-lactone formation is required for the successful addition of vinylogous Reformatsky reagents to ketones in the presence of unfavorable steric and electronic effects and that vinylogous Reformatsky reagents likely stereomutate via s-cis, s-trans isomerization of the zinc dienolate during reversible addition to the ketone.

Results and Discussion

The first approach to unsaturated ester 3 involved a Horner-Emmons condensation between 4 and 5 (Scheme I), since we and others have previously employed this procedure in the preparation of retinoids from α,β-unsaturated ketones.[8,9] However, enone 5 was found to be unreactive under these conditions, which, as shown by the study summarized in Table I, is due to steric and electronic effects in both the ketone and phosphonate ester.

As shown in Scheme I, the next approach to 3 involved a Reformatsky reaction between 5 and vinylogous bromo ester 6 (as an isomeric mixture containing 65% *E* and 35% *Z* configurations). It was anticipated that this reaction would yield the normal hydroxy ester product 7 (Scheme I), but the only product isolated was the unprecedented carboxylic acid 8. The configuration of 8 was determined to be 2*Z*,4*E* by a study of the nuclear Overhauser effect (NOE) between the methyl protons and neighboring vinyl protons. Irradiation of the 3-methyl protons produced a large NOE to H-2 (27% enhancement), consistent with those reported for similar studies with crotonaldehyde and 9-*cis*- and 13-*cis*-retinal;[10,11] this established the 2*Z* configuration. The large NOE observed for H-4 (20% enhancement) when the H-9 methyl protons were irradiated likewise established the 4*E* configuration, while only small NOE values (4-6% enhancement) were observed when the H-8 methyl group was irradiated.

Except for the use of *tert*-butyl ester Reformatsky reagents,[12] Reformatsky reactions have not been reported

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