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Radical addition of R_FI to alkenylsuccinic anhydrides and *gem*-substituted alkenyl triesters Zinc and radical induced, or spontaneous radical cyclization, of the δ-iodoalkanoic esters to γ-lactones☆

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Abstract

Radical addition of R_FI to alkenylsuccinic anhydrides affords ω-(perfluoroalkyl)-δ-iodoalkyl-2-butane-1,4-dioc acid anhydrides, and these adducts are reductively dehalogenated and esterified by zinc and acid *in ethanol* without lactonization. However, the R_FI adducts react with KOH in ethanol to give the alkenyl half esters (but no γ-lactone), which convert to the γ-lactones by acid catalysis. When treated with water, ethanol, Zn and 48% HBr, the R_FI adduct from but-3-en-2-yl-succinic anhydride converts to the iodo half ester, $R_FCH_2CHICH(CH_3)CH(CO_2H)CH_2CO_2Et$, which undergoes Zn induced (S_Hi) conversion to γ-lactone. R_FI (AIBN) and the triester $CH_2{=}CHCH_2C(CO_2Et)_2CH_2CO_2Et$ yield $R_FCH_2CHICH_2C(CO_2Et)_2CH_2CO_2Et$ (95%). When heated to 140 °C, the adduct loses iodoethane.and cyclizes to diester γ-lactones (94%). With benzoyl peroxide, R_FI and the triester at 99 °C, spontaneous radical cyclization of the adduct to lactone occurs. Evidently, the *gem*-disubstituted triester readily forms a five-membered lactone as a consequence of steric compression in the open chain form.

Keywords: R_FI free radical addition reactions; R_F-substituted anhydrides; Perfluoroalkyl lactones; Acid catalyzed lactonization; Homolytic (S_Hi) lactonization; *gem*-Dialkyl induced lactonization; Peroxide induced lactonization

1. Introduction

The synthesis of fluorinated γ-lactones is of continuing interest, and Qing and Jiang review the extensive literature on this subject in connection with the synthesis of 3-trifluoromethyl-2-(5*H*)-furanones (γ-lactones) [1]. Though lactones as a class are widely distributed in nature, fluorine-containing lactones are seldom encountered [2,3].[1] A γ-lactone, ''atorvastatin,'' contains a *p*-fluorophenyl group and is highly effective in cholesterol-lowering therapy. The drug was first conceptualized as a pharmacore, and was synthesized by Roth as an inhibitor for (HMG CoA) reductase, a crucial enzyme in the cholesterol biosynthetic pathway in the liver [4]. Known as ''Liptor®'', it ''has become the world's fastest growing and top-selling pharmaceutical since its launch in 1997''.[2] Ismail, in his review, cites the effects caused by fluorine on the properties of drugs; ''the incorporation of fluorine in a drug allows simultaneous modulation of electronic, lipophilic and steric parameters, all of which can critically influence both the pharmacodynamic and pharmacokinetic properties of drugs [2,3]''. Ismail also reports that fluorine substitution in the A ring (a phenyl ring) of *homo*camptothecin greatly enhances its biological activity [2]. The parent compound contains a 7-membered lactone ring. Fluorine occupies a van der Waals radius (1.47 Å) positioned between oxygen (1.52 Å) and hydrogen (1.30 Å), allowing it to mimic a hydroxyl group, and to participate in hydrogen bonding interactions [2].[3]

☆ This work is done at Wheaton College during 1976–1984. A portion of the synthetic work is reported in a review [6]. The lactonization of iodo esters, and mechanistic implications, are presented at the International Symposium on Organic Free Radicals [10].

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[1] O'Hagan reports that only about a dozen natural products containing fluorine have been isolated [3].

[2] Roth invented the substance, [*R*-(*R**,*R**)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoic acid, lactone. The substance is named atorvastatin, and sold as ''Liptor®'' by Pfizer [4].

[3] The small elemental radius of fluorine is cited as an important requirement when these compounds bind within topoisomerase I, the intended drug target: [38] in this paper [2].

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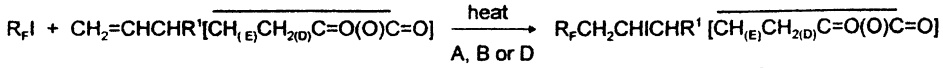
Table 1
Radical addition of perfluoroalkyl iodides (**1**) to prop-2-en-1-yl- and but-3-en-2-yl-succinic anhydrides (**2** and **3**); 3-(perfluoroalkyl)-2-iodoalkyl-2-butane-1,4-dioic acid anhydrides (**4a**,**b** and **5a**,**b**)[a]



Reactants									Products		
Entry	R_FI		Anhydride		Initiator[a]		Time (h)	Temperature (°C)	Code	Conversion (%)	Yield (%)
	R_F	mmol	Code	mmol	Code	mmol					
1[b]	*n*-C_6F_{13}	123	**2**	101	A	2.60	7.0	70–92	**4a**,**b**	99.6	99.6
2	*n*-C_8F_{17}	60.0	**2**	50.0	A	1.00	2.0	77–101	**4a**,**b**	99.6	99.6
3	*n*-C_8F_{17}	57.7	**2**	58.0	B	1.65	4.5	100–103	**4a**,**b**	96.7	96.7
4[c]	R_FI	117.8	**2**	100	D	4.10	1.75	133–147	**4a**,**b**	97.3	97.3
5	*n*-C_8F_{17}	60.0	**2**	50.9	D	2.00	1.5	131–150	**4a**,**b**	95.5	95.5
6	*n*-C_6F_{13}	72.2	**3**	50.0	A	2.22	6.0	72–84	**5a**,**b**	94.4	99.7

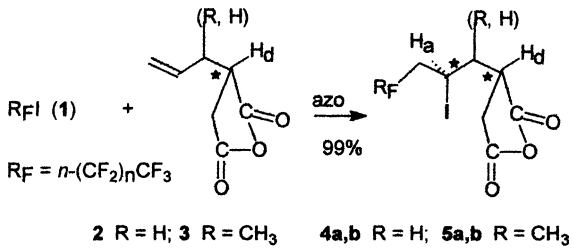
[a] The initiators used are A, AIBN; B, benzoyl peroxide; and D, *bis-tert*-butyl peroxide.
[b] For a typical procedure of an AIBN induced reaction, see Section 3.2.1.
[c] The R_FI (**1**) is a mixture of R_FI homologues (C6, C8 and C10), and the **4a**,**b** is a clear liquid. In another run, the initiator is AIBN (2 mol% on **2**) and the mol amounts of **1** and **2** are the same as in entry 2. The conversion to **4a**,**b**, C6, C8, and C10 homologues is 90% (IR, ^{1}H NMR), and the yield is 100%. Similar results are obtained with the use of BPO as initiator as in entry 3.

R_F-long chain, substituted lactones were encountered during the free radical addition of perfluoroalkyl iodide (**1**; R_FI) to certain unsaturated acids and esters [5,6]. The process has the characteristics of a radical reaction, and it is accelerated by heat or peroxide initiators [7–10]. The purpose of this paper is to explore further the effects of structure and reaction conditions on the lactonization of certain perfluoroalkyl substituted, iodoalkanoic esters and acids. Mechanistic implications for these reactions are discussed, and new perfluoroalkyl substituted γ-lactones are described in detail.

2. Results and discussion

2.1. Radical addition of R_FI to alkenylsuccinic anhydrides affords ω-(perfluoroalkyl)-δ-iodoalkyl-2-butane-1,4-dioc acid anhydrides and derivatives (Scheme 1)

The radical addition of R_FI (**1**, R_F = *n*-C_6F_{13} to *n*-$C_{10}F_{17}$) to 2-propenylsuccinic anhydride (**2**) (Scheme 1) affords



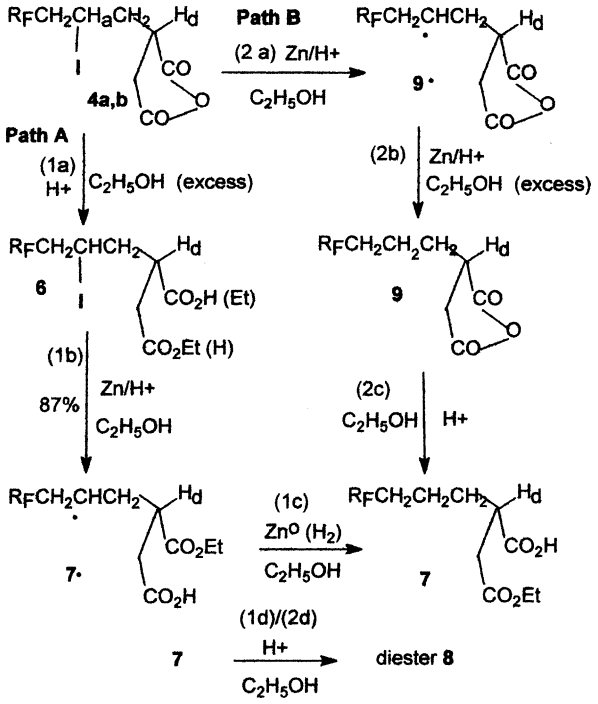
Scheme 1. Addition of R_FI to prop-2-en-yl-2-butane-1,4-dioic acid anhydride (**2**) and to but-2-en-1-yl-2-butane-1,4-dioic acid anhydride (**3**).

diastereomeric **4a**,**b** in 99% yield and conversion; and, similarly, but-3-en-2-yl-succinic anhydride (**3**) converts to diastereomers **5a**,**b** in 99% yield. Either azonitrile or peroxide initiators may be used at 70–140 °C *without evidence of lactonization* (Table 1, entries 1–6). Controlled addition and useful procedures are described in Section 3 [11]. Chemical reactions of adducts **4a**,**b**, and **5a**,**b** are described below.

2.1.1. The reductive dehalogenation and esterification of δ-iodoalkylanhydrides (*4a*,*b*) by zinc and acid in ethanol occurs without lactonization (Scheme 2)

Zinc and acid reduction of **4a**,**b** to iodine free, half ester **7** occurs rapidly [10]. As in previous work with R_F-substituted iodoalkanoic esters, lactonization does not occur [12].[4] Reaction of the iodoalkanoic ester **6** in Path A (step 1b) with Zn^0 (''activated'' by reaction with H^+) produces the 2-propyl radical (**7**•), which abstracts hydrogen and converts to half ester **7** [12,13].[5] In Path B, similar reduction of **4a**,**b** to radical (**9**•) is followed by H• abstraction to give 3-(perfluoroalkyl)propylsuccinic anhydride (**9**) (Scheme 2). Esterification of **9** gives half ester **7** and diester **8**. Reaction conditions may determine which path takes precedence.

[4] R_F-terminated α-aminoalkanoic acids, etc. [12]. Zinc and acid, in ethanol, reacting with 3-(perfluoropropyl)-2-iodo-butanoic acid gives ethyl 4-(perfluoropropyl)butanoate (67%); and, ethyl 3-(perfluoropropyl)-2-iodo-propylmalonate gives ethyl 3-(perfluoropropyl)propylmalonate (74%) [12].
[5] The radical (**7**•), in Scheme 4, step 1c, abstracts hydrogen (possibly, from hydrogen molecules adsorbed on the Zn(s) surface), and converts to half ester **7**. Cyclization during the zinc reduction of iodoalkenes is observed, suggesting free radical intermediates [13].



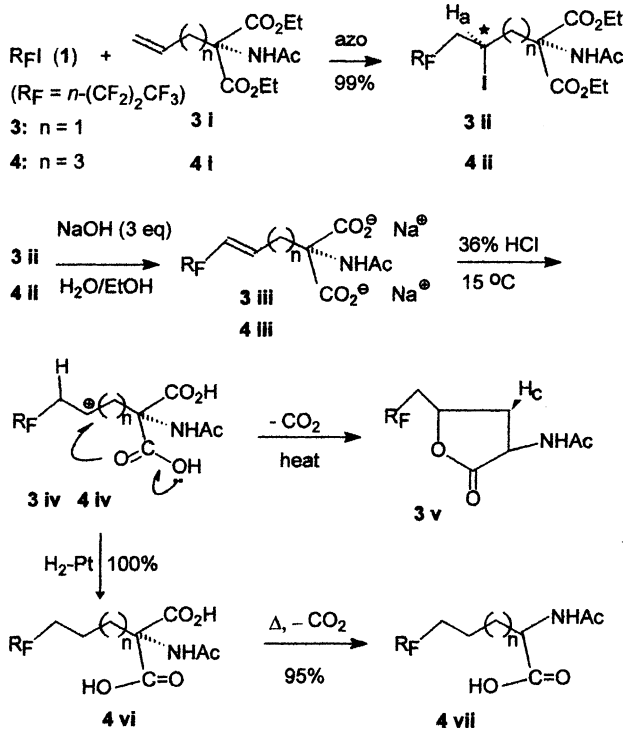
Scheme 2. Esterification of anhydride **4** to iodo ester **6**, and reduction to esters **7** and **8**. Reductive dehalogenation of **4** to anhydride **9** and esterification to esters **7** and **8**.

2.1.2. *Dehydroiodination of δ-iodoalkylanhydrides (**4a,b**) to half ester **10** and conversion to γ-lactones (**11a,b**) by acid catalyzed lactonization. The effect of a β-perfluoroalkyl (R_F) group on the rate and products of reaction*

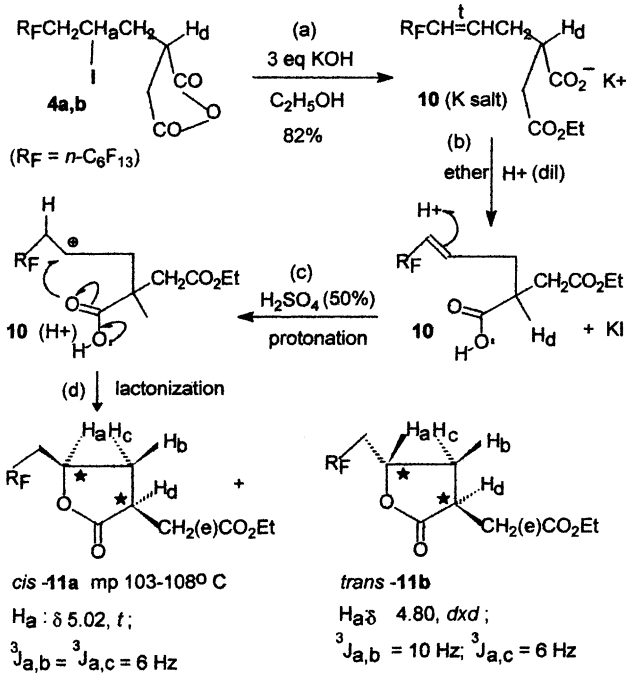
In previous work, which serves as a model for the present study, homologues of ethyl R_F-iodoalkyl-acetamidomalonates (**3ii** or **4ii**) react with strong base to eliminate HI and give R_F-alkenyl-acetamidomalonic acids, disodium salts (**3iii** or **4iii**), respectively, Scheme 3 [12]. Heat and acid cyclizes the free malonic acid (**3iv**), which decarboxylates to the γ-lactone (**3v**). By contrast, the homologue, **4iii** ($n = 3$) converts to free acid **4iv** (which can not lactonize), and hydrogen over Pt reduces **4iv** to the saturated dicarboxylic acid (**4vi**). When heated, **4vi** decarboxylates (as a malonic acid) to the 2-acetamido-6-(R_F)-hexanoic acid (95%) [12]. Strong base does not lactonize the 4-iodo ester (**3ii**) by an S_Ni process, as previously observed with 4-haloalkanoic acids or esters [14,15].[6] However, **3ii** and **4ii** are β-R_F-substituted iodoalkanes, for which the rate of E-2 reaction is three orders of magnitude greater than that of the hydrocarbon analogue, 2-iodooctane [16].[7]

[6] 4-Haloalkanoic acids and esters convert to γ-lactones by heating in boiling alcohol with sodium ethoxide, or by heating the dry sodium salt of the acid [14,15].

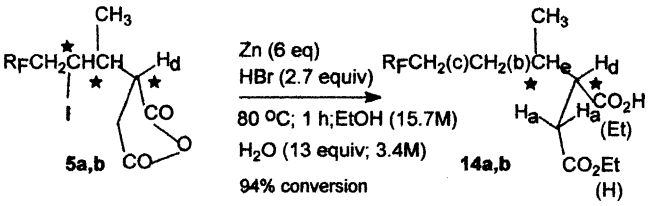
[7] Reaction of $R_FCH_2CHI(CH_2)_nCH_2$ ($n = 3$, 4, or 5) with NaOH at 30.0 °C, in 92.6% aqueous ethanol gives $k_2 = 3.3–4.1 \times 10^{-2}$ l/mol s (second order), and the sole product is $R_FCH{=}CH(CH_2)_nCH_2$ ($n = 3$, 4, or 5; E/Z = ca. 3). Similar reaction of 2-iodooctane with NaOH gives $k_2 = 7.9 \times 10^{-5}$ l/mol s (second order), and the products are 1-octene, 9.1%; 2-octanol, 3.9%; *E*-2-octene, 61%; and 25.9% recovery of 2-iodooctane [16].



Scheme 3. Base induced deiodination of 2-acetamido-3-(perfluropropyl)-2-iodoalkylmalonic esters to **3iii**, or **4iii**; acid induced lactonization of the unsaturated acid (**3iv**) to χ-lactone (**3v**). Hydrogenation of **4iv** to 2-acetamido-2-[5-(perfluoropropyl)-pentyl]-1,3-propanedioc acid, **4vi**; and decarboxylation of **4vi** to 2-acetamido-7-(perfluoropropyl)-heptanoic acid, **4vii**.



Scheme 4. Dehydroiodination of **4a,b** to 3-(perfluorohexyl)-*E*-2-propenylsuccinic acid salt **10**. Conversion of salt to free acid half ester **10**. Acid catalyzed lactonization of **10** to χ-lactone **11** (isomers).



Scheme 5. Reductive deiodination of anhydride **5a**,**b** to half ester **14a**,**b** in ethanol, with HBr and Zn.

By chemistry similar to that of Scheme 3, anhydrides **4a**,**b** are converted to γ-lactones (**11a**,**b**), Scheme 4. In step (a), **4a**,**b** reacts with KOH to give the 3-(perfluorohexyl)-*E*-2-propenylsuccinate half ester (**10**, K salt), but no γ-lactone (IR and NMR) [16]. Treated with 50% H_2SO_4 in steps (c) and (d), **10** converts to the γ-lactones (**11a**,**b**) [17].[8] When chromatographed on alumina, pure *cis*-**11** (37.6%) is isolated from the mixture (IR and ^{1}H NMR) [18,19]. The stereochemistry of these γ-lactones is elaborated further below [19].

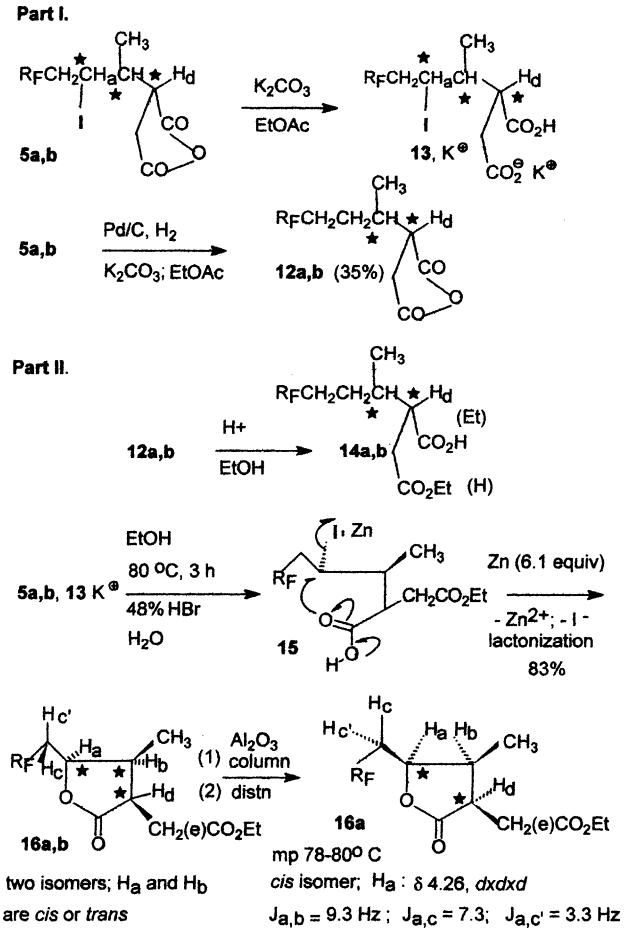
2.1.3. Reductive dehalogenation of anhydrides *5a,b* with HBr and Zn in ethanol, and esterification to half ester *14*

In Scheme 5, the diastereomeric **5a**,**b** undergo zinc reduction in ethanol, water, and 48% HBr, to provide the half esters **14a**,**b** (94%). There is no γ-lactone (IR, NMR) [18,19]. The reaction mixture is less polar than that in Section 2.1.4, and this apparently increases the rate of reduction, relative to the rate of lactonization.

2.1.4. Part I. Catalytic reduction of anhydrides *5a,b* to anhydride *12*, and partial conversion to the K salt of diacid *13*. Part II. Simultaneous esterification and zinc-induced lactonization reactions (Scheme 6)

A straightforward catalytic reduction of the iodoalkyl anhydride **5a**,**b**, with hydrogen over Pd/C in *anhydrous* ethyl acetate solution (K_2CO_3 acid acceptor) in a Parr hydrogenation apparatus, gives the iodine free anhydride **12** in *only* ca. 35% conversion. The absorption of hydrogen ceases because of the unexpected foaming of the slurry into the H_2 line. At the same time, **5a**,**b** converts *in part* to the insoluble iodo succinic acid, K salt (**13**).

In Part II of Scheme 6, the mixture of **5a**,**b** and its products is treated with granular zinc, HBr in water and ethanol, in order to complete the reduction as in Section 2.1.3. Vigorous gas evolution and exothermic reaction ensues, and surprisingly, a substantial conversion to lactones **16a**,**b** occurs. It is speculated that esterification of **5a**,**b** and **13** to half ester **15** occurs first. Then, **15** undergoes S_Hi concerted displacement of iodine by its carbonyl oxygen, simultaneously with the abstraction of the iodine atom by zinc. Thus, iodo ester **15** is



Scheme 6. Reactions of anhydride **5**: catalytic reduction to **12**; salt formation with K_2CO_3; esterification of **5**, **12** and **13** to half esters **14** and **15**; Zn induced lactonization of **15** to lactones **16a**,**b**.

converted to the γ-lactones (**16a**,**b**) by a free radical process [10,13]. In the work up, the reaction mixture of **14**, **15** and **16a**,**b** is made basic with $NaHCO_3/Na_2CO_3$ to remove the half ester **14**. The neutral layer of **16a**,**b** (83.6%) is fractionally distilled, and *cis*-isomer **16a** (IR and ^{1}H NMR) crystallizes from the pot residue [18,19].

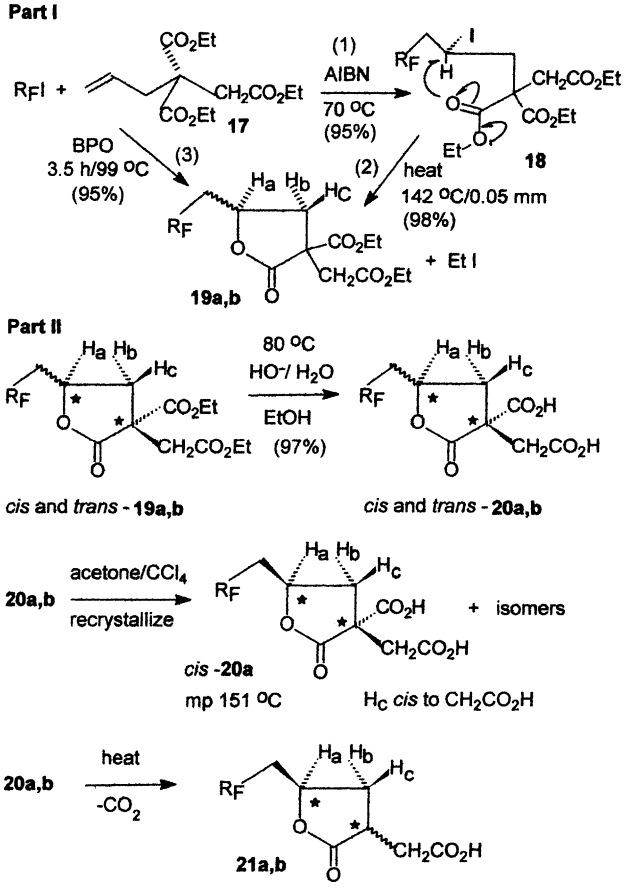
2.2. R_FI, in a radical reactions, adds to propenyl triester, $CH_2{=}CHCH_2C(CO_2Et)_2CH_2CO_2Et$ (*17*)

2.2.1. Heating the adduct, $R_FCH_2CHICH_2C(CO_2Et)_2CH_2CO_2Et$ (*18*) gives γ-lactones (*19a,b*) and iodoethane

Triester **17** is readily prepared in two steps from diethyl malonate [20–22].[9] Free radical addition of **1** (n-$C_8F_{17}I$) to **17** (AIBN) at 70 °C, yields **18** (95%), Scheme 7, Part I

[8] 2-, 3- or 4-Pentenoic acids, when boiled with 50% H_2SO_4, give γ-lactones (97–100%) and little or no δ-lactone, with a total conversion (yield) of 17–40% lactone [17].

[9] Ethyl 3,3-(*bis*-ethoxycarbonyl)-hex-5-enoate (**17**) is prepared from ethyl 2-propenylmalonate and $ClCH_2CO_2H_5$ [20]. Ethyl ethoxycarbonyl-butane-1,4-dioate (**22**) is prepared from ethyl malonate and ethyl chloroacetate [21]; and, **17** is prepared in 95% yield and conversion from alkylation of **22** with allyl bromide [10,22].



Scheme 7. Lactone formation during free radical addition of R_FI to 2-alkenyl-2-carboethoxysuccinate esters. Part II: Hydrolysis of **19a**,**b** to dicarboxylic acid mixture **20a**,**b**; isolation of *cis* isomer **20a**. Decarboxylation of **20a** to **21a**.

(Eq. (1)) [6,10]. Heating the highly substituted iodoalkyl triester **18** to 140 °C at 0.05 mm (Eq. (2)), causes the evolution of iodoethane and cyclization to isomeric γ-lactones (**19a**,**b**). Analogous reaction of **1** (n-$C_8F_{17}I$) and **17** is induced by benzoyl peroxide (2 mol%) at 99 °C. The reaction mixture turns dark with iodine and HI, iodoethane refluxes, and impure γ-lactones (**19a**,**b**) are obtained (ca. 95% conversion; 1:1). The ^{1}H NMR cleanly differentiates the *cis*- and *trans*-isomers. This aggressive behavior of peroxide is a significant feature of reactions involving R_FI and alkenes [6,10,23–26]. Benzoyl peroxide induces side reactions with **1**; specifically, ($R_F^{\bullet}$) abstracts allylic hydrogen atoms from **17**, and a side product probably $H(CF_2)_7CF_3$ is isolated [6,23–26]. Evidently, the *gem*-disubstituted triester **18** readily cyclizes into a five-membered lactone ring as a consequence of steric compression in the open chain form (“*gem*-dialkyl” effect; Thorpe–Ingold effect) [5,6,10,12,27–30].

2.2.2. γ-Lactone diacids (*20a,b*), and isolation of pure cis-*20a*, with the larger groups cis to each other (Scheme 7, Part II)

Basic hydrolysis (NaOH, or KOH) of lactone diesters **19a**,**b** provides isomeric *cis*- and *trans*-diacids **20a**,**b** (97%), which decarboxylate when heated (i.e. as a malonic acid). The ^{1}H NMR assignment of *cis*-**20a** is based on the field effects in the NMR (Section 3).

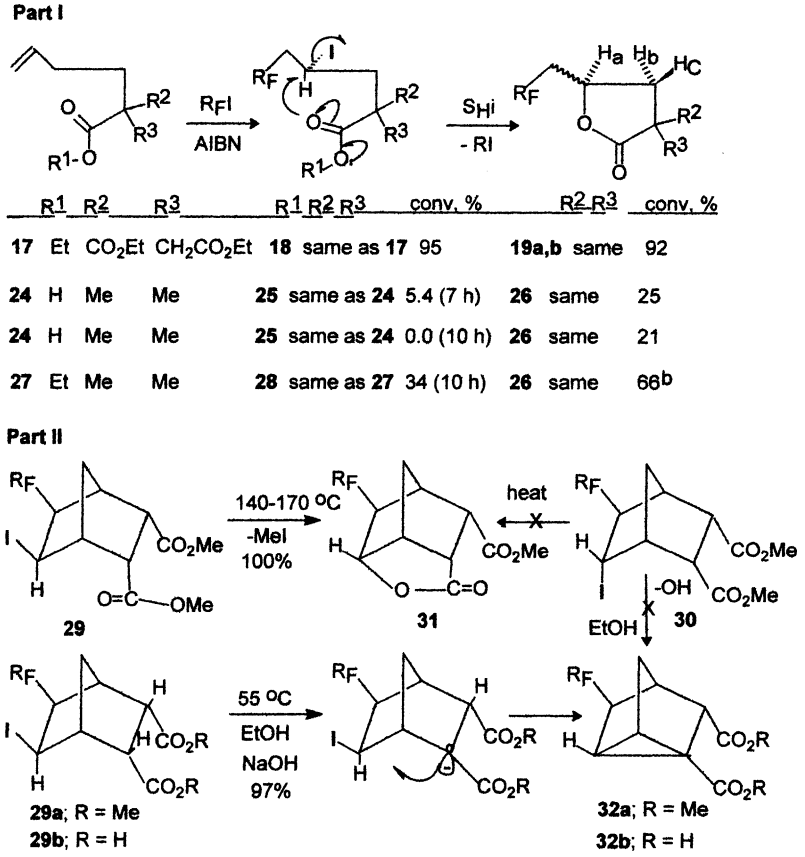
2.2.3. Literature precedents for homolytic cyclization of δ-iodoalkanoate esters to γ-lactones (Scheme 8)

(1) In the reaction of **1** (C6) with 2,2-dimethyl-4-pentenoic acid (**24**) at 75 °C, as AIBN is added, an exotherm to 85 °C occurs, the color of HI/I_2 appears, and further reaction is inhibited [5,6,10]. All of **24** is gone.[10] By contrast, **1** reacts with ethyl 2,2-dimethyl-4-pentenoate (**27**) at 67 °C for 10 h (AIBN), to give ca. 80% conversion to lactone **26** (66%) and adduct **28** (34%; ethyl ester). In this respect, esters **18** and **27** are similar. The proposed two-step mechanism (Scheme 8) envisions the shifting of an unpaired electron from the ether oxygen to the carbonyl oxygen of **17** (or **27**), and an unpaired electron from the carbonyl oxygen of **18** (or **28**) to the anti-bonding orbital of the C–I bond, with the expulsion of I^-. The coplanarity of the necessary bonds is readily assumed, as discerned from models, and the radical nature of lactone formation is proved for some similar reactions by Nikishin et al. [8,9].

(2) A study of iodonorbornane esters (**29** and **30**) sheds new light on this situation, Scheme 8, Part II [6,7,10,31]. Heat causes homolytic cyclization of the *exo*-6-iodo ester (**29**), with inversion of the carbon atom no. 6. Iodomethane is displaced while the γ-lactone (**31**) (100%) is being formed [7,31]. There is strong stereospecificity in the transition state for lactonization. In a mixture of *exo*-**29** and *endo*-6-iodo ester (**30**), *only the exo isomer reacts* and **30** is recovered unchanged. The attack of an unpaired electron of the C=O in **29** on the antibonding orbital of HC-I causes inversion of C6, and this S_Hi reaction is thus similar to the S_N2 reaction. For steric reasons, the antibonding orbital of CH-I in 6-*endo*-**30** is not accessible to the unpaired electron. Further, the process does not involve the formation of a free carbon radical. If it did, both the *exo*- and the *endo*-6-iodo isomers should react.

(3) This remarkable stereospecificity for lactone formation is seen in the base induced conversion of the *exo*-iodo-**29** to the three-membered ring nortricyclene (**32**), Scheme 8, Part II [7,10,31]. Under mild conditions, a base (–OH, –OMe, or even an amine) gives S_Ni displacement of iodine in *exo*-iodo-**29**. The base abstracts an *exo*-hydrogen atom of CH(2), and the carbanion thus formed displaces an iodine ion from HC(6)-I, with inversion, leading to **32** [7,31]. In *aqueous base*, of course, the diester **32a**, first formed, hydrolyzes to the diacid **32b**.

[10] Acid catalyzed lactonization of **24**, induced by the strong acid HI (formed during the reaction) reduces the concentration of **24**; further, HI and I_2 are both strong inhibitors of free radical chain reactions [23]. The conversion to γ-lactone $CH_3[CHCH_2C(CH_3)_2C{=}O(O)]$ increases from 21 to 70% during 3–10 h reaction time.



Scheme 8. Part I. Homolytic lactonization of iodoalkanoic acids and esters: self lactone of **24** (70%); total conversion of 80% to **26** and **28** (distilled). Part II. Lactone **31** from *exo*-5-R_F *exo*-6-iodo-2,3-norbornane diester **29**. Nortricyclene **32** from diester **29**; neither product from *endo*-6-iodo diester **30**.

This is important, because the carbanion at C(2) dominates the reaction, and the *carboxylate ion* attached to C(2) does not bring about S_Ni displacement of iodine in *exo*-iodo-diacid (**29b**).[11]

3. Experimental

3.1. General experimental procedures

3.1.1. A typical procedure for the addition of perfluoroalkyl iodides to an alkenylsuccinic anhydride, or an alkenyltriester compound

See Section 3.2.1 for the preparation of 3-(perfluorohexyl)-2-iodopropyl-2-butane-1,4-dioic anhydride (**4a**,**b**).

3.1.2. Sources of materials

Perfluoroalkyl iodides, **1** (R_F = *n*-C_6F_{13} and *n*-C_8F_{17}; and R_F = C6, C8 and C10 chains in equimolar mixture) are a gift from Ciba-Geigy Corp., Ardsley, NY. The alkenylsuccinic anhydrides **2** and **3** are a gift from the Humphrey Chemical Co., New Haven, CT, and are distilled before use. The elemental analysis and ^{1}H NMR are satisfactory. Ethyl 3,3-(*bis*-ethoxycarbonyl)-hex-5-enoate (**17**) is prepared by alkylation of ethyl (2-ethoxycarbonyl)-1,3-propanedioate (**22**) with allyl bromide, in 95% yield and conversion (Section 3.5.2) [20–22]. Alkylation of ethyl 2-propenyl-1,3-propanedioate (**23**) with ethyl chloroacetate by a literature method gives **17** in 60.8% conversion [10,20]. The **22** is prepared from ethyl propane-1,3-dioate (2 eq.) and ethyl chloroaetate in 82% conversion, in a modified literature method [10,21,22].

3.1.3. Physical methods

Samples for ^{1}H NMR are dissolved in $DCCl_3$, and are run at 100 MHz unless otherwise indicated. ^{13}C NMR (at 80 MHz) and elemental analyses are done through the courtesy of the Analytical Research Division of Ciba-Geigy Corp., Ardsley, NY. The purities and structures of all the compounds prepared are ascertained by GC (when appropriate), IR, ^{1}H NMR; and by elemental analyses. Pure liquids are obtained by distillation in an 18 in., stainless steel spinning band column (A; Nester-Faust) or a 3 ft, platinum mesh spinning band column (B; Nester-Faust).

[11] The *endo*-6-iodo norbornane anhydride (**33**) is hydrolyzed in aqueous NaOH solution at 70 °C. The sodium salt is acidified to the diacid **34** (99% yield). The iodine atom is unaffected. For this to happen, intramolecular substitution by the carbanion (or the carboxylate ion) at *endo*-C(6)-I, could not have occurred [6,7,10,31].

3.2. Radical addition of perfluoroalkyl iodides (**1**) to prop-2-en-1-yl-2-butane-1,4-dioic acid anhydride (**2**), and to but-3-en-2-yl-2-butane-1,4-dioic acid anhydride (**3**); preparation of 3-(perfluoroalkyl)-2-iodoalkyl-2-butane-1, 4-dioic acid anhydride (**4a**,**b** and **5a**,**b**) (Scheme 1)

3.2.1. 3-(Perfluorohexyl)-2-iodopropyl-2-butane-1,4-dioic acid anhydride (**4**) (Table 1, entry 1)

The reactants (**1**, *n*-$C_6F_{13}I$ and AIBN) are stirred under nitrogen in a 100 ml flask immersed in a heated, stirred bath. Anhydride **2** (14 ml) is added drop wise at 63–70 °C during 15 min, and forms a cloudy mixture. After 25 min, and 11 ml of **2** are added, temperature rises to 82 °C, and continues to 132 °C in 2 min, as the flask is removed from the bath. The clear mixture is cooled to 82 °C, the remaining **2** is added drop wise, and the flask is heated at 82 °C for 1.5 h. A 3.0 g sample shows unreacted **2**; thus, AIBN (0.61 mmol) and **1** (11.0 mmol) are added, and after 5 h at 70–92 °C, the flask is set up for distillation (water pump). Unreacted **1** (8.33 g, 18.7 mmol, 100% of theory) is recovered. The solid **4a**,**b** (diastereomers) remains (56.0 g; 99.6% conversion and yield) mp 83–88 °C. Re-crystallization from CCl_4/$HCCl_3$, yields pure **4a**,**b**, mp (sinter 84 °C) 85–88 °C. ^{1}H NMR: δ 2.06–2.6, broad m, 2H, CHICH_2; δ 4.20 and 4.80, 1H total, 1:1, complex m, CHI (diastereomers). Anal. Calcd. for $C_{13}H_8F_{13}IO_3$: C, 26.6; H, 1.38; F, 42.1; I, 21.7. Found: C, 27.0; H, 1.27; F, 41.6; I, 21.0.

3.2.2. 3-(Perfluorooctyl)-2-iodopropyl-2-butane-1,4-dioic acid anhydride (**4a**,**b**) (Table 1, entry 2)

At 72 °C (bath), the reaction occurs exothermally, and it is cooled as necessary. After heating for 2 h, the mixture of **4a**,**b** is cooled and solidifies (39.9 g, 100% recovery; mp (sinter 96 °C) 114–117 °C; IR: **2**). Solid **4a**,**b** is slurried with ligroine (30 ml; bp 60–70 °C) and acetic anhydride (1.0 ml; to prevent hydrolysis), and filtered. The **4a**,**b** is dried; corrected weight 34.2 g (99.7% yield and conversion). ^{1}H NMR: δ 4.28 and 4.61, 1:1 multiplets of CHI. Re-crystallization of 1.3 g gives 0.586 g of pure **4a**,**b**, 1:1 diastereomers, mp 115–116 °C. Anal. Calcd. for $C_{15}H_8F_{17}IO_3$: C, 26.3; H, 1.18; F, 47.1; I, 18.5. Found: C, 26.3; H, 1.08; F, 46.5; I, 18.3.

3.2.3. Benzoyl peroxide induced reaction, thiol **1**=C8 (**4a**,**b**) (Table 1, entry 3)

Thiol **1** and half of B is stirred at 100 °C, while **2** is added drop wise (half h), followed by B remaining. Exothermic reaction occurs and the mixture is cooled as necessary. After 0.75 h at 100 °C, the mixture is cooled to 89 °C and turns solid. Unreacted **1** is stripped to leave **4a**,**b**, 38.6 g, 96.7% yield and conversion. ^{1}H NMR: a mixture of diasteromers of **4a**,**b**; unreacted **2** is absent.

3.2.4. bis-tert-Butyl peroxide; thiol **1**=C6, C8, C10, equimolar; average C8 and **2** (Table 1, entry 4)

Thiol **1** (C6, C8, C10, equimolar; average C8) and half of D is stirred at 125 °C, while **2** is added drop wise (half h), followed by D remaining. Exothermic reaction occurs and the mixture is cooled as necessary (turns red in color). After 1.5 h, the excess **1** is stripped (water pump), and excessive foaming occurs. This leaves solid **4a**,**b** (C6, C8, C10 homologues), 68.3 g, 99.9% yield and conversion. Re-crystallized from CCl_4, mp: sinter 89 °C, mp 91–95–109 °C (clear). Anal. Calcd. for $C_{15}H_8F_{17}IO_3$ (**4a**,**b**; average C8): C, 26.3; H, 1.18; F, 47.1; I, 18.5. Found: C, 25.9; H, 1.21; F, 46.1; I, 18.6.

3.2.5. R_FI (C6) adds to anhydride **3** (AIBN); 4-(perfluorohexyl)-3-iodo-2-butyl-2-butane-1,4-dioic anhydride (**5a**,**b**) (Table 1, entry 6)

The conditions of Section 3.2.1 are employed. At the water pump, excess **1** (11.0 g; 24.7 mmol) distills, and **5a**,**b** remains as a viscous oil, 28.3 g (94.4% conversion and 99.4% yield). ^{1}H NMR: δ 1.05, 1.08, and 1.15, complex m, total 3H, CH_3 (diastereomers); δ 4.37–4.5, complex m, 1H, CHI (diastereomers). Anal. Calcd. for $C_{14}H_{10}F_{13}IO_3$: C, 28.0; H,1.68, F, 39.7; I, 21.2. Found: C, 28.6; H, 1.78; F, 39.7; I, 20.7.

3.3. Reactions of 3-(perfluorohexyl)2-iodo-propyl-2-butane-1,4-dioic acid anhydride (**4a**,**b**)

3.3.1. The reductive dehalogenation of anhydride **4a**,**b** by zinc and acid to ethyl 3-(perfluorohexyl)propyl-2-butane-1-oic acid-4-oate (half ester **7**); and diester **8** (Scheme 2)

A mixture of **4a**,**b** ($R_F = C_6F_{13}$; 23.3 g, 50.0 mmol), zinc (30–40 mesh, 19.5 g, 298 mmol, added in two portions) and ethanol (118 g, 2.6 mol, 150 ml; moles EtOH/**4a**, **4b** = 52) is stirred by a magnet bar at 73–76 °C, as HCl (g, anhydrous) is bubbled below the surface of the liquid by means of a glass tube. A gas bubbler device filled with oil is used to monitor the flow of HCl. After 5 min, the flow of HCl is stopped, and in 10 min, it is turned on again, briefly. As the solution becomes colorless, the surface of the zinc is covered with gas bubbles, and the mixture is foamy with evolved gases (H_2, HCl). The heat is removed during this rapid, exothermic reaction at 76 °C. After 1.5 h, the colorless mixture is cooled, and the liquid is decanted into 100 ml of water. The aqueous layer is extracted twice with benzene, with CCl_4 (each, 25 ml), and the solvent is added to the heavy oil layer, 25.76 g (100% conversion as **7**); ^{1}H NMR: chiefly **7**; some **8** and **9**). The solution is dried ($MgSO_4$), and distilled in column A at the water pump, to give three fractions: (1) bp 109–154 °C/14 mm, total, 2.11 g; fraction (2), bp 131–148 °C/14 mm, 1.09 g; NMR: a mixture of **2** and **8**, 44/56, from integration of signals δ 1.26 and 4.18 (CH_3CH_2O); and δ 5.10 and 5.70 (CH_2=CH in **2**); and, fraction (3), bp 148–154 °C/14 mm, 0.85 g; n_D^{25} 1.3726; IR, νC=O 1780 cm^{-1}, strong, COOH, and 1735, strong, COOEt [18]. ^{1}H NMR: a mixture of **7** and **8**. The residue (weight 22.0 g) (86.9% as **7**) is mostly **7** (80%) and **8** (20%) by integration. Some **9** is indicated by IR: νOH in bonded COOH, 3200–3000 cm^{-1}; 1860, 1800, anhydride, as in succinic anhydride; 1780, strong, COOH, monomer; 1735, very strong, COOEt.

^{1}H NMR: δ 1.3, t, $J = 7$ Hz, CH_3CH_2; δ 1.8, m, CH_2; δ 2.0–3.5, multiplets, R_FCH_2, CH_2, CH; δ 4.22, q × q, 2H, $CO_2CH_2CH_3$; 5.5, m, 1H, COOH, exchangeable. The sample (IR, NMR and elemental analysis) is primarily **7**, with some **8** and **9**. No CHI, nor CH=CH is present.

Anal. Calcd. for $C_{15}H_{15}F_{13}O_4$: C, 35.5; H, 3.0; F, 48.6. Found: C, 36.6; H, 3.0; F, 48.0.

3.3.2. Dehydrohalogenation of *4a,b* by KOH in aqueous ethanol to potassium 2-[3(perfluorohexyl)-2-E-propenyl]butane-1,4-dioc acid (*10*, K salt), and ethyl 2-[3-(perfluorohexyl)-E-2-propenyl]-1-oic acid-4-oate (*10*, half ester) (Scheme 4)

To a stirred solution of KOH (5.1 g, 0.0909 mol) in water (20 ml, 1.11 mol) and ethanol (90 ml, 1.53 mol), at 25 °C, is added anhydride **4a**,**b** (18.0 g, 0.0307 mol; mols EtOH:**4a**,**b** = 50; KOH:**4a**,**b** = 3; H_2O:**4a**,**b** = 30), and stirring continued for 6.5 h. The clear solution of **10** (K salts) and KI foams, and is weakly basic; it is evaporated slowly in a beaker to a soft solid, wt 17.1 g (**10**, 82% as K salt). The surface tension in water at 0.1 wt.% is 15.7 dyn/cm at 25 °C. A 1.0 g portion of the K salts is shaken while adding 2 M HCl to a pH 3, extracted into ether, the solution dried and passed down alumina. Fractions are eluted with CH_2Cl_2, acetone and then CH_3OH, and evaporated to white solid (**10**; half ester). IR: *v*OH, bonded COOH; *v*C=O, 1760, ester; 1710, COOH, dimer; *v*C=C, 1650 (R_FCH=CH, *trans*), 1640, 1615 [10,16,18]. ^{1}H NMR (100 MHz): δ 1.28, q, t, 3H, OCH_2CH_3; δ 4.22, q, 2H, OCH_2CH_3; δ 5.72, dxt, 1H, CH_a; $^3J_{a,b} = 16$ Hz, $J_{a,CF_2} = 12$ Hz; in the segment, CF_2CH_a=$CH_bCH_{2(c)}$, the high $^3J_{a,b} = 16$ Hz indicates a *trans* isomer; δ 6.34, dxt, CH_b; $^3J_{b,CH_2} = 7$ Hz; δ 10.7, m, broad, exchangeable, COOH.

Anal. Calcd. for $C_{15}H_{13}F_{13}O_4$: C, 35.7; H, 2.6; F, 49.0. Found: C, 35.6; H, 2.6; F, 48.1.

3.3.3. Conversion of half ester *10* to cis and trans-γ-lactone (*11*) by acid induced lactonization (Scheme 4, Eqs. (c) and (d))

The remaining **10** (16.0 g, 0.025 mol of **10** K salt; and KI, ca 0.025 mol) is stirred into H_2SO_4 (9.0 ml, 50% aq. solution; 0.046 mol; H_2SO_4:**10** = 1.8 mol) to give a dark, gummy liquid. Water (20 ml) is added and stirred (magnet bar) for 1/2 h. The gummy liquid mixture of acids and **11** is washed twice by decantation with ice/water. The strongly acidic wash liquid is extracted with ether, then with CH_2Cl_2, and evaporated to give 0.1 g of solid. The combined organic layer is extracted with $NaHSO_3$ solution (now colorless), dried and evaporated to an orange, viscous gum, 7.0 g (63% recovery as **10** or **11**). The mixture is re-dissolved in CH_2Cl_2, passed down an alumina column (5 in. × 1/2 in.), and washed successively with 100 ml each of ether, acetone and CH_3OH, while taking 30 ml eluates. The three combined solvent fractions are examined by IR, NMR and elemental analysis. Combined fraction (1) (2.00 g) contains **10**, chiefly. IR: *v*C=C, 1650; *v*C=O, 1700–1750 cm^{-1} (COOH, COOEt); ^{1}H NMR: same as above for **10**; CHF anal, same as for **10**. Fraction (2) (2.83 g) a mixture of **10** (mostly) and **11**. IR: *v*C=O, 1765, γ-lactone, 1700–1750 cm^{-1}, COOH, COOEt. ^{1}H NMR: in addition to the signals of **10** (including 10.0, bonded OH) as in (1), signals for **11** are present as in (3). Fraction (3) (1.51 g) is *cis*- and *trans*-**11**. Total recovery of products, 4.74 g, 37.6% of theory. One eluate fraction of (3) is evaporated separately to white solid, mp 103–108 °C. This is pure *cis*-**11**; IR: 1765 cm^{-1}; ^{1}H NMR of *cis*-**11** (see Scheme 4 for structure; cf. Scheme 7, **20a**): δ 5.02, t, H_a; $J_{a,b} = 6$ Hz = $J_{a,c}$ = ca. 6 Hz. The coincidence of coupling constants suggests that the bulky substituents of *cis*-**11** twist away from each and distort the bond angles in such a way as to minimize the shielding difference in H_b and H_c. ^{1}H NMR of *trans*-**11**: δ 4.80, d × d, H_a; $J_{a,b} = 10$ Hz and $J_{a,c} = 6$ Hz; the bulky substituents are *trans* (cf. Scheme 7, **21a**,**b**). Weak signals for the (di)ethyl ester are present, but no exchangeable H is seen in the NMR.

Anal. Calcd. for $C_{15}H_{13}F_{13}O_4$ (**11**): C, 35.7; H, 2.6; F, 49.0. Found (fraction 1): C, 34.7; H, 2.5; F, 49.4. Found (fraction 3): C, 33.0; H, 2.3; F, 49.0.

3.3.4. Reductive deiodination of anhydride *5a,b* to ethyl 4-(perfluorohexyl)-2-butyl-2-butane-1-oate-4-oic acid (half ester *14a,b*) (Scheme 5)

Anhydride **5a**,**b** (*n*-C_6F_{13}; 20.0 g, 0.0333 mol, 0.266 M), ethanol (100 ml; 78.5 g, 1.96 mol, 15.7 M), HBr (10.0 ml, 48 wt.%, 14.9 g total weight; thus, HBr, 7.15 g, 0.0884 mol, 0.71 M; HBr:**5a**,**b** = 2.65 mol), water (in HBr solution; 7.75 g, 0.430 mol, 0.344 M; water:**5** = 12.9 mol), and zinc (20–40 mesh, 6.5 g, 0.10 mol) is stirred at 78 °C. The solution becomes colorless in five min, zinc (6.5 g; total 0.2 mol; Zn:**5a**,**b** = 6.0 mol) is added after 10 min, and stirring continued for 1 h. When decanted into 100 ml of water, an oil (19.4 g, 0.0341 mol as **1a**,**b**, impure) separates. The aqueous layer is extracted with ether and benzene (together), combined with the oil and shaken with sodium bisulfite solution. The colorless solution is dried, and the solvent distilled (column A) to 104 °C (T_{pot}); the viscous gum, weight 18.3 g, is further pumped down to 80 °C/10 mm for 1/2 h to give **14a**,**b** (16.24 g, 93.9% conversion; sample 1). IR and NMR are consistent with impure **14a**,**b** (COOH and COOEt position isomers), and there is no CH=CH, and no γ-lactone. ^{1}H NMR (see Scheme 5 for notation): δ 1.00, 3 H, d × d, CH_3CH_e, diastereoisomers; 1.26, t, 3 H, OCH_2CH_3; 2.44–3.26, complex m, 8H, CH_2(a), CH_2(b); CH_2(c), H(e), H(d); 4.16, q, 2 H, OCH_2CH_3; 9.44, broad, exchangeable, CO_2H. The spectrum is consistent with a 1:1 mixture of two diastereomers of **14a**,**b**.

Anal. Calcd. for $C_{16}H_{17}F_{13}O_3$ (**14a**,**b**): C, 36.9; H, 3.3; F, 47.5; I, 0.0. Found: C, 35.1; H, 3.2; F, 45.5; I, 1.22. Anal. Calcd. for $C_{14}H_{10}F_{13}IO_3$ (**5**): C, 28.0; H, 1.7; F, 39.7, I, 21.2.

The elemental anal shows ca. 5.7 wt.% of unreacted **5** (or equivalent) is present. In order to react with and remove **5**, NaOH (0.030 mol) in water (25 ml) is added to a portion (81.5%) of the material, and the mixture heated to 80 °C for

2 h to form a thick paste. This is dissolved in 50 ml of water, made acid with 6N HCl (17 ml; 0.1 mol), and extracted with ether (twice), benzene, and $NaHSO_3$ solution, to remove the iodine (dark red color; some of the half ester **14** may have reacted and dissolved in the basic solution, and lost). The dry extract is again distilled and pumped down to 90 °C/10 mm for 1 h. The viscous gum remaining (**14a**,**b**, 11.63 g; 88.8% recovery) contains ca. 20% of the *diacid* formed during the hydrolysis reaction, Calculated from the integrals in the NMR (82.5% yield and conversion).

Anal Calcd. for $C_{16}H_{17}F_{13}O_3$ (**14a**,**b**): C, 36.9; H, 3.3; F, 47.5. Found: C, 36.7; H, 3.3; F, 47.0.

*3.3.5. Catalytic deiodination of anhydride **5a**,**b** over Pd/C and H_2 to 4-(perfluorohexyl)-2-butyl-2-butane-1,4-dioic acid anhydride (**12**); reaction of **5a**,**b** with K_2CO_3 to give ethyl 4-(perfluorohexyl)-2-butyl-2-butane-1,4-dioic acid, K salt (**13**) (Scheme 6, Part I)*

Anhydride **5a**,**b** (*n*-C_6F_{13}; 27.1 g, 0.0383 mol; contains **3**, 1.04 g; 6.83 mmol), K_2CO_3 (6.91 g, 0.0500 mol), ethyl acetate (anhydrous, 100 ml) and 5% Pd/C (5.00 g) are charged to a Parr hydrogenator bottle, evacuated and filled three times with H_2 to 50 psi. When shaken, the black slurry begins to foam in 15 min, and plugs the valve and the vent. Shaking is continued for 2.5 h (no *apparent loss in pressure*), the bottle stopper is loosened, and a burst of H_2 and slurry vents into the surroundings. The remainder is rinsed from the bottle onto a Buchner funnel with ethyl acetate (50 ml). The black filter cake on the Buchner funnel is rinsed with portions of water (total 100 ml), and dried, wt 6.37 g (1.4 g excess). The filtrate of K salts foams and forms a gel when cooled. The water is evapd and leaves a white solid (KI; **13**, K salt), 13.6 g (ca. 13.6 mmol of **13** or KI; from total mmol of **5** + **12**). The original (ethyl acetate) clear liquid filtrate is evaporated for 1 h in a rotary evaporator to 40 °C/20 mm. The viscous oil, weight 17.0 g, is a mixture of **5** (ca. 62%; 10.5 g, 17.5 mmol, 45.7% recovery on **5**), ethyl acetate (15 mol%), and anhydride **12** (ca. 23 mol%; 3.4 g, 7.2 mmol, 18.7% conversion on **5**), from iodine anal and NMR. IR (smear on KBr): *v*OH, 3200 cm^{-1}, weak, bonded OH of COOH; *v*C=O, 1860, 1790, very strong, **12** anhydride; 1735, **5**, COOEt. ^1H NMR: δ 4.37, 5.22, d × d, CHI of **5a**,**b** (diastereomers); integrates to ca. 60% of the total integral; ethyl acetate is ca. 15 mol% of the total. The iodine analysis is 13.2/21.2 = 62.2% of **5a**,**b** remaining in the sample.

Anal. Calcd. for $C_{14}H_{11}F_{13}O_3$ (**12**): C, 35.5; H, 2.3; F, 52.1; I, 0.0. Anal. Calcd. for $C_{14}H_{10}F_{13}IO_3$ (**5a**,**b**): C, 28.0; H, 1.7; F, 39.7, I, 21.2. Found: C, 33.1; H, 2.5; F, 39.9; I, 13.2.

*3.3.6. Esterification of anhydride **12** to half ester **14**; and, of anhydride **5a**,**b** and K salt **13** to half ester, **15**; zinc induced lactonization of **15** to 2-ethoxycarbonyl-3-methyl-4-(perfluorohexyl)methyl-4-hydroxybutanoic acid γ-lactone (**16a**,**b**) (Scheme 6, Part II)*

The reactants (above experiment, assuming that all of **5a**,**b** and/or its products are recovered) comprise: **5a**,**b** (17.5 mmol, 0.11 M), **12** (8.3 mmol, 0.054 M), and **13**, K salt (13.6 mmol, 0.88 M dissolved in water, 20 ml). The mixture is added, while stirring (magnet bar), to ethanol (100 ml, 1.96 mol, 60 eq., 12.6 M) and water (20 ml). Water is added to give a homogenous liquid (total water 2.2 mol, 91 eq., 14 M). The liquid volume is 155 ml. While stirring, HBr (48 wt.%, 20 ml, 29.8 g; actual HBr, 14.3 g, 0.177 mol, 1.14 M; HBr/**5a**,**b** + **13** = 5.45 mol) and zinc (6.5 g, 0.10 mol) are added, and the mixture is heated. At 62 °C, it becomes colorless, and gas evolves. In 10 min, additional zinc (6.5 g, 0.10 mol; 0.20 mol total; Zn/**5a**,**b** + **13** = 6.15 mol) is added, and the colorless solution is stirred at 80 °C for 3 h. The solution is decanted from Zn into 100 ml of water, and γ-lactone (**16**), 17.6 g (0.034 mol, 88% recovery) is extracted with benzene (70 ml), but does not dissolve. Ether (30 ml) is added, and the clear layer is washed with sodium bisulfite solution to remove the iodine (red color), and dried ($MgSO_4$). Solvents are distilled (column A) to 102 °C (pot temperature) to leave half ester **14** and γ-lactone (**16a**,**b**) isomers, as a colorless oil. IR: *v*OH, 3500–3000 cm^{-1}, heavy, bonded OH of COOH, **14**; *v*C=O, very strong, 1780, γ-lactone; 1735, COOEt, **16a**,**b**. The mixture is re-dissolved in benzene and ether, extracted with $NaHCO_3$/Na_2CO_3 solution (to pH 8) to remove **14**, and distilled (column A) at the water pump. Fractions: (1), bp 138–150 °C/9.5 mm, 0.64 g; (2), bp 170–179 °C/11.0 mm, 6.86 g, and (3), bp 174 °C/11 mm, 5.24 g; (4) hold up, 1.18 g, white solid (total 14.0 g). The yield of **16a**,**b** (0.0270 mol) is 87% based on the **5a**,***b*** + **13** (0.0311 mol) used in the zinc reduction. IR (1)–(3): *v*C=O, very strong, 1780 cm^{-1}, γ-lactone; 1735, COOEt; but no bonded OH of CO_2H. ^1H NMR (see Scheme 6 for notation): Fractions (2) and (3) are a **16a**,**b** isomer mixture, not pure. Fraction (4) is re-crystallized from ligroine/ethanol to give pure *cis*-isomer **16a**, 0.16 g, mp 78–80 °C. IR (**16a**): *v*OH, none; *v*C=O, 1770 cm^{-1}, very strong; 1735, same, ester. ^1H NMR (**16a**; see Scheme 6 for notation): δ 1.19, d, 3H, CH_3 *cis* to R_FCH_2; 1.28, t, 3 H, CH_3CH_2O; 2.0–2.9, complex, 6H, CH_2(c), CH_2(e), H_d, H_b; 4.19, q, 2H, CH_3CH_2O; 4.26, d × d × d, H_a; $^3J_{HaHb}$ = 9.3 Hz, $^3J_{HaHc}$ = 7.2 Hz; $^3J_{HaHc}$ = 3.3 Hz. The NMR spectrum is consistent with a single isomer **16a**; both the clean signals observed in the methyl region, and the simple clarity of the signal for H_a when the R_FCH_2 signal is irradiated, indicate a single isomer. The observed $^3J_{a,b}$ of 9.3 Hz suggests that H_a and H_b are *cis* to one another.

Anal. Calcd. for $C_{16}H_{15}F_{13}O_4$ (**16a**): C, 37.1; H, 2.92; F, 47.7. Found: C, 37.1; H, 3.0; F, 46.5.

*3.4. Free radical addition of 1-iodoperfluorooctane (**1**) to ethyl 3,3-bis-carboethoxy-hex-5-enoate (**17**); ethyl [5-iodo-6-(perfluorooctyl)-3,3-bis-carboethoxy]hexanoate (**18**) (Scheme 7, Part I, Eq. (1))*

1-Iodoperfluorooctane (**1**, 81.9 g, 40.8 ml, 150 mmol; passed down Al_2O_3), **17** (27.4 g, 95.8 mmol; re-distilled)

and AIBN (0.328 g, 2.00 mmol) are charged to a Fischer–Porter pressure tube, cooled to −78 °C, evacuated and filled with nitrogen three times, and heated in an oil bath at 70.0 °C for 23 h, while stirring by a magnet bar. The colorless, clear liquid changes to a yellow color when opened to the atmosphere (109.1 g, 100 wt.% recovery). Distillation at the water pump gives **1**, bp 72–67 °C/32 mm (T_{pot} up to 100 °C) 32.3 g, 59.1 mmol, (94.9% conversion of **1** to **18**); −78 °C trap, 2.0 g (EtI, ?); pot liquid (**18**), weight 74.8 g, 93.8% conversion. ^{1}H NMR: mixture of **17** (trace) and **18**; no γ-lactone (**19a**,**b**).

3.4.1. Adduct *18* is heated to give iodoethane and cis- and trans-4-(perfluorooctyl)methyl-2-carboethoxymethyl-2-carboxy-4-hydroxysuccinic acid lactone (*19a,b*) (Scheme 7, Part I, Eq. (2))

The impure **18** (74.8 g, 0.0893 mol) is heated in an oil bath to T_v 82 °C/0.05–0.65 mm; T_{pot} = 142–146 °C (ca. 1 h). Iodoethane (total, 10.5 g, 67.3 mmol; 70.2% of theory) collects in the dry ice trap. MS: m/e = 156 (mol ion), 141 (–CH_3), 127 (–I), 126, 29 (CH_3CH_2) and 27 (CH_3C). The residual oil **19a**,**b** solidifies on cooling and is collected on a Buchner funnel, weight 59.50 g (0.0880 mol, 98.5% of theory as γ-lactone **19a**,**b**), mp 59–65 °C. IR (KBr): νCH_2=CH (trace), 3090, 1640 and 990 cm^{-1}; νC=O (vs) 1780 cm^{-1}, γ-lactone, **19**; νC=O (vs) 1740 cm^{-1}, ester. ^{1}H NMR: **19a**,**b**; from the areas of δ 2.22 (H_c) and 4.98 (H_a), isomer **19a**:**19b** = 60/40. A 1 g portion of impure **19a**,**b** is re-crystallized from ligroine (bp 60–70 °C; 20 ml). Solid **19a**,**b** is collected: (1) weight 0.614 g, mp (sinter 55 °C) 56–59 °C; (2) 0.225 g, mp (sinter 59 °C) 60–65 °C; (3) 0.0672 g, mp 59–62 °C. IR (Nujol mull): νC=O (vs), 1780, 1735 cm^{-1}, equal intensity. ^{1}H NMR (sample (1); see Scheme 7 for structures; cf. Scheme 4, **11a**; and Scheme 6, **16a**): δ 1.28, 1.30, t × t, 1:1 area, six protons, two CH_3CH_2O; δ 2.22, H_c, d × d, $^3J_{Hc,HA}$ = 9 Hz; $^2J_{Hc,HB}$ = 14 Hz; δ 2.22–3.36, complex m, H_b, R_FCH_2, CH_2(e)COOEt; δ 4.28, qxq, 4 H, 2 × CH_3CH_2O; δ 5.08, m, 1H, H_a diastereomers. The NMR data are consistent with 1:1 isomers **19a**,**b**, and either γ-lactone or δ-lactone structure. However, IR clearly identifies **19a**,**b** as a γ-lactone.

Anal. Calcd. for $C_{22}H_{22}F_{17}IO_6$ (**18**): C, 31.7; H, 2.67; F, 38.8; I, 15.2. Anal. Calcd. for $C_{20}H_{17}F_{17}O_6$ (**19a**,**b**): C, 35.5; H, 2.58; F, 47.8. Found (impure **19a**,**b**): C, 36.4; H, 2.68; F, 42.6; I, 1.91. I: 1.91:15.2 = 12.6 wt.% of **18**. Found (**19a**,**b**, re-crystallized (1)): C, 35.2; H, 2.48; F, 47.6.

3.4.2. Benzoyl peroxide induced radical addition of R_FI (*1*) to *17*, and lactonization of adduct *18* to γ-lactone (*19a,b*) (Scheme 7, Part I, Eq. (3))

As in Part I, Step (1), **1** (*n*-C_8F_{17}; 81.9 g, 0.150 mol), **17** (28.1 g, 98.2 mmol) and benzoyl peroxide (0.484 g, 2.00 mmol) (sealed pressure tube) is stirred and heated at 99.0 °C in an oil bath for 3.5 h. Within 25 min, the mixture turns red, and in 1 h, dark purple in color (I_2). Iodoethane refluxes. The tube is cooled and the product (EtI, **1** and **19a**,**b**, 109.2 g; 98.6% recovery) is set up for distillation at the water pump. Very dark vapors (I_2, HI) distill with **1**, bp 62–59 °C/21–16 mm, T_{pot}, up to 108 °C, 18.4 g (0.0338 mol as **1**). Hence, 0.116 mol (77.5% of theory of **1**) is consumed, remains in **19a**,**b**, or is lost. The **19a**,**b** pot residue, and rinse of tube and flask (evaporated, 2.15 g), total weight (1), 77.3 g, 0.0956 mol (94.7% of theory as **19a**,**b**). IR and ^{1}H NMR: **19a**,**b**, 1:1. The cold trap (−78 °C) contains two layers; the smaller lower layer is solid at −78 °C (total weight, 13.0 g; 0.0833 mol, 84.9% as EtI). Impure **19a**,**b** (70.0 g) is re-crystallized from ligroine (200 ml); (1) 44.3 g, mp 61–3 °C. ^{1}H NMR: **19a**,**b** 1:1.

Anal. Calcd. for $C_{20}H_{17}F_{17}O_6$ (**19a**,**b**): C, 35.5; H, 2.58 F, 47.8; I, 0.0. Anal. Calcd. for $C_{22}H_{22}F_{17}IO_6$ (**18**): C, 31.7; H, 2.67; F, 38.8; I, 15.2. Anal. Calcd. for $C_8F_{17}I$ (**1**): C, 17.6; F, 59.1; I, 23.3. Found (impure **19a**,**b**): C, 33. 1; H, 2.42; F, 47.0, I, 2.45. I: 2.45:15.2 = 16.1 wt.% of **18**, if present; I: 2.45:23.3 = 10.5% of **1**, if present.

The trap liquid (12.6 g) is re-distilled in column A; (1), bp 63–66 °C, 3.4 g; two immiscible liquids, and (2), bp 66 °C (73 °C pot temp), 5.88 g, also two liquids; lit: iodoethane, bp 69–73 °C, mp −108 °C [32,33]. MS, iodoethane, chiefly. Water is not present (negative test). The lower layer may be 1-*H*-perfluorooctane; lit: (perfluorooctane): bp 103 °C, mp −25 °C [34]. The oil residue, 3.4 g (**1**).

3.4.3. Ethyl 5-iodo-6-perfluorooctyl-3,3-bis-carboethoxyhexanoate (*18*) and conversion to γ-lactone (*19a,b*) (Scheme 7, Part I)

The experiment (Part I, Step 1) is repeated. Recovered, re-distilled **1** (41.0 g, 75.0 mmol), **17** (14.3 g, 50.0 mmol) and AIBN (0.164 g, 1.00 mmol) are heated, while stirring, in an oil bath at 70.0 °C for 17 h. IR: **18**, no γ-lactone at 1780 cm^{-1}, and unreacted **17**. Distillation gives **1**, bp 31–37 °C/0.01 mm, T_{pot} 39–55 °C (29.4 g, 54.0 mmol; hence, 21 mmol (42%) of **17** is consumed, and/or converted to **18**. The residual oil (**17**, **18**; 26.3 g). A 4.56 g portion of the residual oil (0.173 fraction; ca. 3.60 mmol of **17** and 4.24 mmol of **18**) is heated for a half hr at 116–143 °C/26 mm and distilled. This affords **17**, bp 105–108 °C/0.15–0.10 mm, 1.03 g, 3.60 mmol, n_D^{26} 1.4330; and solid residue **19a**,**b**, 2.67 g, 3.95 mmol (93.7% yield); mp (sinter 49 °C) 53–59 °C. The cold trap contains iodoethane (0.439 g, 2.81 mmol, 78% conversion).

3.5. Hydrolysis of *19a,b* by NaOH to cis- and trans-2-carboxymethyl-2-carboxy-4-hydroxy-4-(perfluorooctyl)methyl-butanoic acid γ-lactone (*20a,b*) (Scheme 7, Part II)

A solution of NaOH (2.00 g, 50.0 mmol) in water (12 ml) and ethanol (28 ml) is added to **19a**,**b** (90% pure, 8.18 g, ca. 9.00 mmol), while stirring at 50 °C. The pasty mass is kept at 70 °C for 5.5 h, and allowed to stand at 35 °C for 18 h. Water (20 ml) is added, and after 5 h, the solution is poured

into dilute HCl (10 ml of 6N HCl in 100 ml of water), while stirring vigorously at 27 °C. The strongly acidic, soft gel of **20a**,**b** filters very slowly on a Buchner funnel; the soft solid **20a**,**b** is dried in air, and over P_2O_5 in a vacuum desiccator, weight 6.88 g (100% recovery), mp 143 °C (dec). The impure **20a**,**b** dissolves in hot acetone (50 ml), treated with carbon powder, and evapd to 25 ml; $CC1_4$ (25 ml) is added and then cooled. Crystalline **20a**,**b** is collected, rinsed with solvent and dried, first at 25 °C in air, and at 60 °C/16 h to give (1) wt 3.50 g, mp (sinter 136 °C) 136.5 °C (dec). IR: same as **20a**,**b** below, except *v*C=O: 1770 cm^{-1}, 1765 (COOH, monomer), 1730 and 1700 (COOH, dimer), δCH, 1320 only. ^{1}H NMR (see Scheme 7, Part II): **20a**,**b**, richest in **20a**, and a little of another substance. The mother liquor gives (2) **20a**,**b** and an unknown, probably **21**, weight 1.106 g, mp (sinter 139 °C) mp 147 °C (dec, ca. 1/2); then mp 176 °C (no dec); (3), **20a**,**b**, weight 0.692 g, mp (sinter 133 °C) 141–42 °C (dec). Total **20a**,**b** (and unknown) is 5.30 g, 8.54 mmol, 94.9% yield. The samples of **20a**,**b** decarboxylate to **21a**,**b** when heated; in no. 2, the higher mp substance does not decarboxylate, and thus may be **21**.

*3.5.1. Hydrolysis of **19a**,**b** by KOH in water (no ethanol) at 75–80 °C; isolation of pure isomer **20a**, ^{1}H NMR results (Scheme 7, Part II)*

As in 3.5.0, **19a**,**b** (8.32 g, 11.1 mm; ca. 90% pure) is added, while stirring at 35 °C, to KOH (3.09 g, 55.0 mmol, 2.8 M) in 12 ml of water (no alcohol); the mixture clears at 75 °C, and is stirred for 7 h at 75–80 °C. It is poured slowly into dilute HCl (12 ml 6N HCl and 80 ml of water). The solid **20a**,**b** is collected and dried as above; **20a**,**b** (1) wt, 6.96 g (10.1 mmol, 100%), mp 145–146 °C (dec), unchanged in a sealed tube. IR (Nujol mull): *v*C=O, 1770; 1730 (COOH, dimer) only. ^{1}H NMR (**20a**,**b**; no. 1; cf. Scheme 4, **11a**,**b** and Scheme 6, **19a**,**b**): δ 1.20, t, CH_3CH_2O, a small amount of **19a**,**b**; 2.24, d × d, H_c in **20a**; $^3J(H_cH_a) = 9$ Hz, $^2J(H_aH_b) = 14$ Hz; **20a**:**20b** = 70/30; 2.46–3.27, broad complex m, H_b, R_FCH_2, H_c in **20b**; 2.96, s, 2 H, CH_2COOH; 4.14, complex m, CH_3CH_2O, a small amount from **19a**,**b**; 4.98, broad m, H_a; 9.90, very broad m, exchangeable, 2H, COOH. The signal at δ 2.24 (d × d) for H_c in **20a** integrates to less than one proton relative to the H_a signal at δ 4.98. Alkyl groups are known to produce an upfield shift on *cis*-protons in five-membered rings [19]. *cis*-C=O functionalities also produce upfield shifts, but the examples cited indicate the effect of an alkyl group is larger [19]. The large ^3J value indicates that the δ 2.24 signal must have a proton *cis* to the proton giving rise to the signal (i.e. as in **20a** in Scheme 7). A 5.00 g portion of **20a**,**b** (no. 1) is re-crystallized from hot 1:1 acetone/CCl_4 as above to give sample **20a** (2), weight, 1.24 g, mp 150 °C (dec); recheck, mp 151–152 °C (dec); NMR shows it is a single substance. The mother liquor concentration is adjusted in hot acetone solution by adding a little CCl_4 to incipient cloudiness, then cooled; **20a**,**b** (3) weight, 2.07 g, mp (sinter 142 °C) 145–147 °C (dec). Similarly, **20a**,**b** (4) wt, 0.581 g, mp (sinter 140 °C) 144–145 °C (dec); and (5), 0.301 g, soft solid. Total recovery of **20a**,**b** is 97.7% of theory based on original **19a**,**b**. IR, KCl disc; **20a** (2): bonded *v*OH, 3200–2800 cm^{-1}; *v*C=O, 1770, 1730; δ CH 1420, 1380,1370, 1330, and 1325; *v*CF, 1250–1180; and bands at 965, 900, 740, 710, 705, 650, 600, 555, 540, and 440. ^{1}H NMR [100.1 MHz, DMSO-d^6 solution; **20a**, (2)]: The δ 2.20 and 4.96 regions integrate 1:1, and thus, it is a single isomer. Specifically, it is **20a** with the d × d upfield from the rest of the aliphatic moiety. For assignments see **20a**,**b** (1) above.

Anal. Calcd. for $C_{16}H_9F_{17}O_6$: C, 31.0; H, 1.46; F, 52.1. Found (**20a**,**b**; no. 1 of Section 3.5): C, 31.2; H, 1.29; F, 52.8, 52.9. Found (**20a**,**b**; 70/30 of 3.5.1): C, 30.0; H, 1.41; F, 49.7. Found [**20a** (2) of 3.5.1]: C, 30.9; H, 1.43; F, 51.6.

*3.5.2. Alkylation of ethyl (2-ethoxycarbonyl)-1,3-propanedioate (**22**) by 2-propenyl bromide to give ethyl 3,3-(bis-ethoxycarbonyl)-hex-5-enoate; $CH_2{=}CHCH_2C(CO_2Et)_2CH_2CO_2Et$ (**17**)*

Sodium (4.6 g, 0.20 mol, cut under toluene) is added to ethanol (100 ml, distilled into the reactor from sodium ethoxide solution) while stirring under a nitrogen atmosphere, and at a rate to maintain reflux. After all had reacted and dissolved, ethyl 1-ethoxycarbonylsuccinate, (**22**, 49.3 g, 0.200 mol; prepared above) is added dropwise during 25 min at 50–52 °C. A suspension of the enolate salt is formed. Allyl bromide (24.2 g, 0.200 mol) is added during 12 min at 40–78 °C. A precipitate of sodium bromide appears and heat is evolved. The temperature is kept at 82 °C (reflux) for 1 h, and the reaction mixture becomes neutral. Ethanol is removed (rotary-evaporator) at the water pump, heating to 40 °C. Water (50 ml) is added and the product is extracted into benzene (two times 25 ml). The oil layer is shaken with water (15 ml) and dried over magnesium sulfate. Distillation in column B affords **17**: (1) bp 100–110 °C/0.35 mm, 2.78 g, n_D^{25} 1.4390 (90% pure); (2) bp 114–115 °C/0.43 mm, n_D^{25} 1.4405, 49.1 g (100% pure), total yield (95%); and (3) residue, 0.70 g. IR: *v*C=O 1735 cm^{-1}, ester; *v*C=C 1645 cm^{-1}. NMR (**17**): δ 1.28, 2t, 9H, $2CH_3CH_2O$, and one $CH_2CO_2CH_2CH_3$; δ 2.78, d, 2H, $CH_2{=}CHCH_2$; δ 2.93, s, 2H, $CH_2CO_2CH_2CH_3$; δ 4.12, 4.20, 2q, 4H, $(CH_3CH_2O)_2C$–; δ 5.08, d, fine splitting, 2H, H_bH_c of $H_bH_cC{=}CH_aCH_2$; δ 5.70, complex m, H_a of $H_bH_cC{=}CH_aCH_2$. Double irradiation is used to show coupling between sets of protons.

Anal. Calcd. for $C_{14}H_{22}O_6$: C, 58.7; H, 7.75. Found: C, 59.0; H, 8.05.

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