mixture is exactly what one could expected from the reaction of trimetaphosphites **5** with alcohols. The presence of these species can be explained by two subsequent nucleophilic attacks of alcohol on the same phosphorus center, which results in a ring opening, followed by the formation of phosphite triester **9b** and pyrophosphonate **7b**. The latter compound, upon reaction with ethanol, affords *H*-phosphonate diester **10b** and *H*-phosphonate monoester **1a**. In agreement with this, when excess of coupling agent was present in the reaction mixture, only **9b** and **10b** were formed. Analogous compounds were observed in the ^{31}P NMR spectra during the reaction of **5a** with 3′-*O*-benzoylthymidine and in the reaction of **5b** with ethanol and with a suitably protected thymidine.

In conclusion, these studies have established that activation of *H*-phosphonate monoesters by chlorophosphates **2** and **3**, or by arenesulfonyl derivatives **4**, results in the formation of trimetaphosphites of type **5**. Reactions of the latter compounds with hydroxyl-containing nucleophiles afforded phosphonate diesters **10** together with phosphite triesters **9** and the starting materials **1**. This explains the previously observed low yield of *H*-phosphonate diester formation when *H*-phosphonate monoesters were preactivated before the coupling reaction.[2] In addition, these results also shed some light on a possible mechanism of *H*-phosphonate diester formation. During the "regular" coupling reaction (activation of a *H*-phosphonate monoester in the presence of nucleosidic component), the formation of phosphite triesters as side products was never observed,[2,12] and also, these last species cannot be produced from *H*-phosphonate diesters.[2,8] Thus, trimetaphosphites **5** can be excluded as intermediates involved in the *H*-phosphonate diester formation during the regular coupling reaction. Instead, the most likely candidates seem to be pyrophosphonate **7** and/or mixed anhydrides **6** or **8**.

Experimental Section

Materials and Methods. Reactions were carried out in NMR tubes (at 25 °C), and spectra were recorded on a Jeol JNM GX 400 FT (161.7 MHz) or Varian Associates XL-100 FT (40.48) spectrometer. Chemical shifts are reported relative to 2% H_3PO_4 in D_2O (inner tube).

Pyridine was refluxed and distilled over P_2O_5, then refluxed and distilled over CaH_2, and stored over 3-Å molecular sieves. The same procedure was used for the preparation of anhydrous acetonitrile.

Diphenyl chlorophosphate, 2,4,6-triisopropylbenzenesulfonyl chloride, and diethyl phosphonate (Aldrich) were commercial grade.

5′-*O*-(4,4′-Dimethoxytrityl)thymidine 3′-hydrogen phosphonate (triethylammonium salt),[2] ethyl hydrogen phosphonate (triethylammonium salt),[11] [(2,4,6-triisopropylphenyl)sulfonyl]tetrazole,[7] and 3,3′-(chlorophosphinylidene)bis(2-oxo-1,3-oxazolidene)[5] were prepared according to published procedures. Phosphite triesters **9a** and **9b** were prepared in the reaction of 5′-*O*-(dimethoxytrityl)thymidine with PCl_3 (1.2 equiv) in pyridine, followed by addition of appropriate alcohols or nucleosides. In some cases procedures reported in ref 8 were used. Phosphonate diesters **10** were prepared as reported previously.[2,8]

Preparation of Trimetaphosphite 5a for the 2D ^{31}P–^{31}P Correlated NMR Spectra. Compound **1a** (0.2 mmol) was dissolved in dry acetonitrile (2.5 mL), and triethylamine (0.6 mmol) and diphenyl chlorophosphate (0.4 mmol) were added. After standing for a couple of hours, the precipitate was removed, and the clear solution was subjected to ^{31}P NMR analysis.

General Procedure for the Activation and Reactions of 5a and 5b. Compound **1a** or **1b** was rendered anhydrous by repeated evaporation of added pyridine, and finally the resulting oil was dissolved in pyridine (2.5 mL). An appropriate coupling agent (**2**, **3**, or **4**) (2 equiv or as stated in the text) was added and ^{31}P NMR spectra were recorded directly after mixing of the reagents.

To investigate the chemical reactivity of **5a** or **5b**, ethanol (1.5–20 equiv) or 3′-*O*-benzoylthymidine (1.1–5 equiv) in pyridine was added. For the identification of reaction products, appropriate compounds **9a–c** and/or **10a–c** (prepared in different ways) were added, and ^{31}P NMR spectra were recorded.

Acknowledgment. We are indebted to Prof. Bengt Lindberg for his interest and to the Swedish National Board for Technical Development and The Swedish Natural Science Research Council for financial support.

Registry No. **1a**, 50571-26-1; **1b**, 15845-66-6; **2**, 2524-64-3; **3**, 102054-53-5; **5a**, 105784-89-2; **5b**, 105784-90-5; **7b**, 105784-91-6; **9a**, 105784-92-7; **9b**, 105784-93-8; **10a**, 102987-86-0; **10b**, 105784-94-9; **10c**, 762-04-9; TPS-Cl, 6553-96-4; TPS-Te, 59128-88-0; 3′-*O*-benzoylthymidine, 17331-53-2.

(12) For the automated solid-phase synthesis, at least as now constituted, the possibility of phosphite triester formation, as a side reaction, should be kept in mind.

(13) **Abbreviations**: PV-Cl, pivaloyl chloride; DPCP, diphenyl chlorophosphate; OXP, 3,3′-(chlorophosphinylidene)bis(2-oxo-1,3-oxazolidene); TPS-Cl, 2,4,6-triisopropylbenzenesulfonyl chloride; TPS-Te, 2,4,6-triisopropylbenzenesulfonyl tetrazolide; DMT-T, 5′-*O*-(4,4′-dimethoxytrityl)thymidin-3′-yl.

(14) **Note added in proof**: Recently, a series of sterically hindered triaryl trimetaphosphites has been synthesized and isolated (Chaser, D. W.; Fackler, O. P.; Mazany, A. M.; Komoroski, R. A.; Kroenke, W. T. *J. Am. Chem. Soc.* **1986**, *108*, 5956). These compounds and the trialkyl trimetaphosphites **5** reported here give a similar pattern of ^{31}P NMR resonances.

Selective Metal-Catalyzed Autoxidation of 2-Arylpropionaldehydes. An Improved Synthesis of Ibuprofen

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The potential for increased useage of nonsteroidal anti-inflammatory agents such as ibuprofen (**1**) has prompted much interest in improved methods for the synthesis of 2-arylpropionic acids and of 2-(4-isobutylphenyl)propionic acid, in particular.[1] One synthesis of this material from the patent literature utilizes the glycidic ester route involving a stoichiometric oxidation of the aldehyde **2** as a final step.[2] The use of either $KMnO_4$ or Ag_2O was reported for this oxidation.[1d] Many other oxidants have been reported in the patent literature[3] with the most significant utilizing sodium hypochlorite[4] and hydrogen peroxide.[5] In only one instance has the use of O_2 and a metal catalyst been reported, but yields were unsatisfactory (68% selectivity to **1**).[6,7] While the literature

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(2) (a) Dytham, R. A. Brit. Pat. 1 160 725, 1967. (b) Dytham, R. A. Fr. Pat. 1 545 270, 1968.

(3) (a) Quadro, G., Swiss Pat. 605 545, 1978. (b) Arakawa, M., Jap. Kokai 7 797 930, 1977. (c) Omiya, T.; Sabakini, M., Jap. Kokai 7 665 730. (d) Kogure, K.; Nakagawa, K., Ger. Offen. 2 404 158, 1974.

(4) (a) Okazaki, T.; Sakamoto, T.; Nagayama, I.; Kutsuma, T. Jap. Kokai 7 818 534, 1978. (b) Bruzzi, G.; Javier, V., Ger. Offen. 2 724 702, 1977. (c) Jap. Kokai 78 149 962, 1978.

(5) Kogure, K.; Sueda, N.; Himoto, S.; Yoshino, Y.; Nakagawa, K. Ger. Offen. 2 533 397, 1976.

(6) Miyatake, T.; Teruya, H. Jap. Kokai 72 39 050, 1972.

(7) In addition, a photochemical oxidation has been reported to proceed in 94% yield, see: Miura, S.; Kawashima, T.; Iizuka, Y.; Sawa, Y. Jap. Kokai 76 100 042, 1976.

0022-3263/87/1952-0287$01.50/0 © 1987 American Chemical Society

Table I. Effect of Reaction Variables on the Autoxidation of 2-(4-Isobutylphenyl)propionaldehyde[a]

catalyst	solvent	P_{O_2} (psi)	% convn	%1	%3	%4	%5
Co(II) stearate	CH_3CO_2H	120	20	6			
Mn(II) stearate	CH_3CO_2H	120	13	7			
Co(II) stearate	acetone	120	33	10	7	3	12
Mn(II) stearate	acetone	120	21	12	6	1	3
Mn(II) stearate	toluene	120	63	45	7	2	4
Mn(II) stearate	chlorobenzene	120	67	49	7	3	5
Mn(II) stearate	decane	120	83	72	9	1	1
Co(II) stearate	decane	120	96	61	15	5	15
Co(II) stearate	decane	120	82	68	9	1	4
Mn(II) stearate	decane	40	79	61	11	2	1
Mn(II) stearate	decane	200	85	82	9	1	2
Mn(II) stearate[b]	decane	120	89	58	19	6	4
Mn(II) stearate[c]	decane	120	88	85	7	2	1

[a] Reaction time = 2 h, [sub 2] = 0.4 M, [cat.] = 6.0×10^{-3} M, temp = 0 °C. [b] Same as (a) but temp = 25 °C. [c] [*m*-Chloroperoxybenzoic acid] = [cat.], added as initiator.

examples of the autoxidation of aldehyde 2 are surprisingly nonselective, we report here a catalytic method employing manganese catalysts that promote a very selective and rapid autoxidation of 2 to yield the acid ibuprofen (1) in high yields under mild conditions.

Experimental Section

Materials. Ibuprofen (1) and 2-(4-isobutylphenyl)propanal (2) were prepared by literature procedures.[1c,2] The 4-isobutylphenyl methyl ketone (3) was prepared by standard Friedel–Crafts methodology.[8]

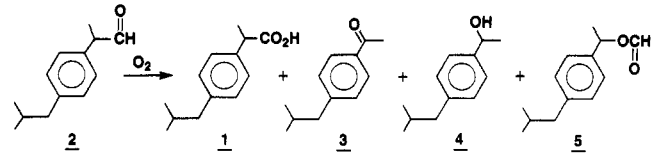
1-(4-Isobutylphenyl)ethanol.[9] Under N_2 atmosphere, a diethyl ether solution containing 5.3 g of 4-isobutylphenyl methyl ketone was added dropwise with stirring to a diethyl ether solution containing 3.25 g of $LiAlH_4$. After the addition, the mixture was refluxed for 1 h. The treatment of the reaction with H_2O (3.25 mL) and then base (3.25 mL, 15% NaOH) and H_2O (10 mL) gave a precipitate which was separated by filtration. The ether filtrate was dried over $MgSO_4$. Removal of the ether yielded crude alcohol in 50% yield. Distillation under vacuum at 111 °C (1 mmHg) gave pure (GC, ^1H NMR) product. ^1H NMR ($CDCl_3$, δ): 6.95 (AB quartet, 4 H), 4.5 (q, J = 7 Hz, 1 H), 2.3 (d, J = 7 Hz, 2 H), 1.8 (septuplet, J = 7 Hz, 1 H), 1.2 (d, J = 7 Hz, 3 H), and 0.85 (d, J = 7 Hz, 6 H).

Methods. A capillary GC analytical procedure was developed and used dodecane as the internal standard. The analysis of the reaction mixtures was performed by silylating the samples with Regisil-RC-3 [bis(trimethylsilyl)trifluoroacetamide + 10% trimethylchlorosilane with 0.1 mL of sample to 0.5 mL of RC-3]. The samples were then heated for 20 min at 100 °C. Compounds 1 and 4 were analyzed as their trimethylsilyl derivatives, whereas 2, 3, and 5 were analyzed directly. A Varian 3700 gas chromatograph equipped with a 10 m × 0.5 mm "530" FSOT methylsilicone capillary column was used with the following conditions: column temperatures, start at 80 °C hold for 4 min and programmed at 10°/min to 280 °C; injection temperature, 250 °C, and detector temperature of 250 °C.

Typical Oxidation Procedure. A Fisher Porter bottle equipped with a micro gas mixing pump (Cole Parmer), a thermocouple enclosed in a glass liner, one $^1/_8$ in. Teflon tube for gas mixing, and one $^1/_8$ in. Teflon tube for removing samples was used for the oxidation. In a typical run the bottle was charged with 0.12 mmol of catalyst, 1.7 mL (1.6 g × 94.2% purity) of 2-(4-isobutylphenyl)propionaldehyde, 2.3 mL (1.7 g) of dodecane as internal standard, and 16 mL (11.3 g) of decane. The bottle was immersed in a cooling bath, purged three times with 60 psig O_2, and then raised to the desired pressure of O_2. As oxygen was consumed, additional O_2 was added to maintain a constant pressure. In some reactions samples were removed with time. When reactions contained solids, samples were not removed. At the end of the reaction period the gas was vented and 5 mL of methylene chloride was added to dissolve the solids. Samples were then analyzed as described in the analytical procedure.

(8) Amin, S.; Walker, J. U.S. Pat. 4 142 054, 1979.
(9) Takeda, M.; Uchide, M.; Iwane, H. U.S. Pat. 4 329 507, 1982.

Scheme I



Results

Our initial attempts to autoxidize aldehyde 2 to the desired acid 1 using common autoxidation catalysts and reaction conditions (25 °C and 60–100 psi O_2, acetic acid solvent) gave very poor selectivities (Table I). In our initial studies several variables were shown to be important. For example, improved selectivities were only observed at lower temperatures and in less polar solvents (e.g., decane or toluene). Oxygen pressure also was significant. While the reactions appeared to be zero order in oxygen (rates were the same over the pressure range 20–200 psi O_2), the selectivities to acid were improved at higher O_2 pressures. In general, little selectivity improvement was observed by employing O_2 pressures greater than 120 psi. The ketone 3 and alcohol 4 were two of the major side products produced in these autoxidations, especially at lower O_2 pressures. Another major byproduct was identified by GC–mass spectral analysis and independent synthesis as the formate 5 (Scheme I).

As can be seen in Table I (and in the supplementary material table), the production of the undesired formate 5 is in most cases a major problem in the autoxidation of the 2-arylpropionaldehyde 2. Only with manganese is this undesired side reaction suppressed. The use of more soluble salts of manganese (stearate, acetylacetonate) in our reaction system also not only gave better reproducibility (rates and products) but minimized the formate production.

Simple soluble salts of the metals commonly known to catalyze the autoxidation of aldehydes were screened (supplementary material). In general, cobalt-catalyzed autoxidations proceeded with the fastest rates, although manganese-catalyzed autoxidations proceeded at rates nearly as fast. All of the other metals (Ni(II), Cr(III), Cu(II), Fe(II, III) gave markedly slower catalytic rates with poor selectivities to the desired acid 1. Only the manganese systems afforded both good rates and selectivities (as high as 88%) to the product acid 1. Cobalt catalysis suffers from the formation of the formate byproduct 5, which in some cases is as much as 25% of the converted product.

In general, use of any soluble manganese(II or III) or cobalt(II or III) catalyst under typical conditions (decane, ≤0 °C, 120 psi O_2) gave variable and long initiation periods (up to 1 h). These initiation periods could be eliminated

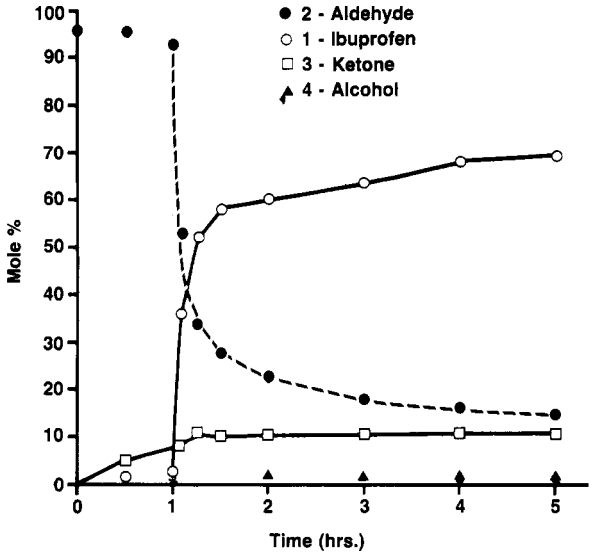
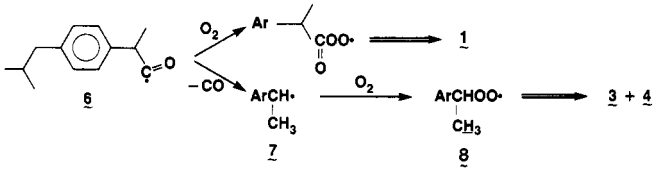


Figure 1. Reaction profile of the autoxidation of **2** at 0 °C in decane under 120 psig O_2 pressure using manganese(II) stearate as catalyst. The dotted line represents a generated best fit with aldehyde order = 3 and oxygen order = 0.

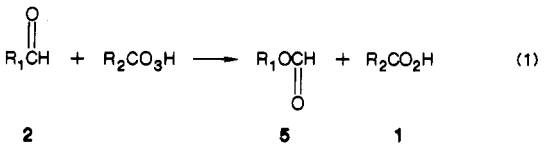
Scheme II



by addition in catalytic amounts ([In.] = [cat.]) of a peracid initiator such as *m*-chloroperoxybenzoic acid with a slight increase in selectivity. A second unusual feature of these autoxidations is shown in the reaction profile in Figure 1. Once initiated, the reaction proceeds very rapidly to about 80% completion and then dramatically slows down. Added substrate **2** causes an immediate resumption of the reaction with an identical rate, but better overall selectivities are obtained in the recycle runs. Thus, once the catalyst has been generated, selectivities approaching 90% are achieved.

Discussion

The autoxidation of the 2-arylpropionaldehyde **2** to the desired acid **1** turned out to be a surprisingly difficult reaction to catalyze selectively. As described here, manganese catalysts appear to give the highest selectivities with good rates—virtually eliminating the undesired formate **5**. Unfortunately, another side-reaction producing ketone **3** and alcohol **4** could not be completely suppressed. Those products likely reflect the competing rates of reaction between O_2 with the intermediate acyl radical **6** and the loss of CO from **6** to yield the stable secondary benzylic radical species **7** (Scheme II). The reaction of **7** with O_2 would yield a benzylic hydroperoxide **8** whose decomposition would lead to the observed ketone and alcohol byproducts **3** and **4**, respectively. Such products have been observed in other α-branched aldehyde autoxidation systems and are linked to decarbonylation.[10] Presumably the higher selectivities observed at increased oxygen pressures are due to more efficient trapping of **6** by molecular oxygen. The production of the formate byproduct **5** was unexpected and a major problem in all the systems except for manganese. The origin of **5** is probably a result of a Baeyer–Villiger reaction[11] of the intermediate peracid with the aldehyde **2** (eq 1, $R_1 = R_2$ = 1-(4-isobutylphenyl)ethyl).



The obvious question arises as to how only manganese catalysts are able to suppress this reaction. It is known from studies of acetaldehyde and benzaldehyde[10c] autoxidations that cobalt catalysts favor the production of peracid while in the manganese-catalyzed systems the peracid production is low. This is likely due to the fact that manganese efficiently catalyzes the decomposition of peracids[10a,12] owing to the accessibility of the +4 oxidation state. Thus, in the manganese-catalyzed reactions, the intermediate peracid is catalytically reduced to the acid product **1** before an undesireable Baeyer–Villiger reaction can occur to yield formate **1**.

The autoxidation of aldehydes to carboxylic acids catalyzed by transition metals is generally thought to proceed by a radical chain process involving the following essential initiation and propagation steps (eq 2–7):[10b]

$$RCHO + M^{(n+1)+} \rightarrow RCO\cdot + M^{n+} + H^+ \quad (2)$$

$$RCO\cdot + O_2 \rightarrow RCOOO\cdot \quad (3)$$

$$RCOOO\cdot + RCHO \rightarrow RCOOH + RCOO\cdot \quad (4)$$

$$RCOOO\cdot + RCHO \rightarrow RCOOH + RCO\cdot \quad (5)$$

$$RCOOOH + M^{n+} \rightarrow RCOO\cdot + M^{(n+1)+} + OH^- \quad (6)$$

$$RCOOOH + RCHO \rightarrow 2RCOOH \quad (7)$$

Several aspects of our studies of the autoxidation of 2-arylpropionaldehydes suggest that this scheme (eq 2–7) is operative in the manganese-catalyzed autoxidations in nonpolar solvents and at low temperatures. As noted the autoxidation possesses an initiation period followed by a "burst" reaction leading to 80–90% consumption of aldehyde. This behavior is consistent with a chain reaction. The subsequent very slow observed rates were shown not to be a result of catalyst poisoning, but addition of fresh aldehyde reveals that this phenomenon is simply a kinetic consequence of a high reaction order in aldehyde concentration. In fact, computer-generated "best" fits to our reaction rate profiles are only obtained when the order in aldehyde concentration is ≥ 3 and oxygen is zero order (Figure 1). Such a surprisingly large order in aldehyde concentration is consistent with the apparent rates for initiation (eq 1) and propagation (eq 3 and 4) being similar. Such behavior is not unknown in metal-catalyzed autoxidations of aldehydes and is apparently operative in this system.

Acknowledgment. We thank Dr. D. Willis and Mr. J. Scanlon for their assistance and Dr. Eric Sall for helpful discussions.

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Registry No. 1, 15687-27-1; 2, 51407-46-6; 3, 38861-78-8; 4, 40150-92-3; 5, 105899-75-0; Co(II) stearate, 1002-88-6; Mn(II) stearate, 3353-05-7.

Supplementary Material Available: Table documenting the effect of different metals and their complexes on the autoxidation of 2 (1 page). Ordering information is given on any current masthead page.

Facile Synthesis of Ethyl 3,3-Difluoroacrylate from Dibromodifluoromethane and Diels-Alder Cycloaddition with Furan[1]

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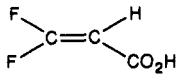
Esters of acrylic acid have received continuous interest as reagents in organic synthesis. On the contrary, their β-fluorinated analogues were somewhat deserted,[2] albeit they potentially allow the direct introduction of one or several fluorine atoms into a molecule. Thus, for an attempted route to 6,6-difluoroshikimic acid, we needed esters of 3,3-difluoroacrylic acid (1). Previously, such

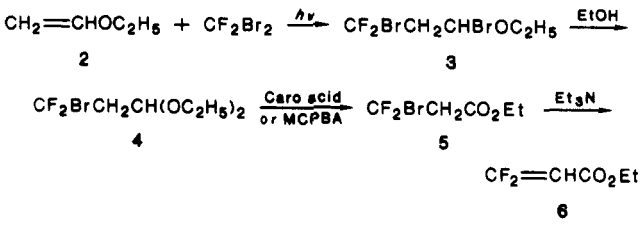


1

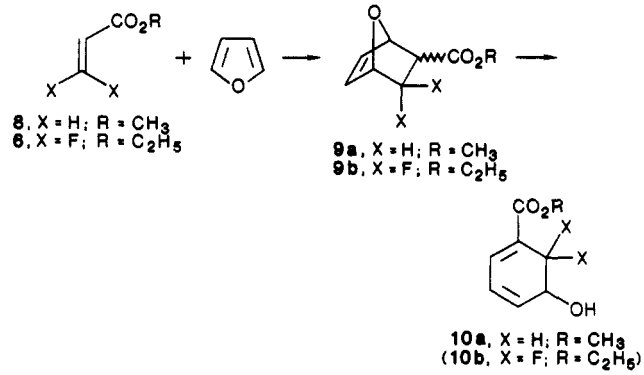
esters were prepared by multistep synthesis from not easily available materials by tedious or not clear procedures.[3-6] Recently, an elegant but delicate one-pot synthesis of the acid 1 was described starting from 1,1-difluoroethylene via (2,2-difluorovinyl)lithium.[7] Nevertheless, the authors did not describe the esters. We developped an easy synthesis of ethyl 3,3-difluoroacrylate (6) in 36% overall yield, starting from ethyl vinyl ether 2 and dibromodifluoromethane.

In the first step, the two reagents were condensed under ultraviolet irradiation; then the resulting α-bromo ether 3 was treated with ethanol to give the bromodifluoroacetal 4,[8] following Tarrant's procedure[9] (see Scheme I). The next step was the direct oxidation of the acetal 4 to the ethyl ester 5 either with Caro acid[10] or *m*-chloroperoxybenzoic acid[11,12] in comparable yields. Attempted oxidations by ozone[13] gave only complex mixtures of fluorinated compounds.

Scheme I



Scheme II



Rapid dehydrobromination of the ester 5 was carried out with triethylamine in dichloromethane at 0 °C to give ethyl 3,3-difluoroacrylate (6) in 74% yield. For this step, the temperature must be carefully controlled and the reaction quenched as soon as the addition of the amine is finished, in order to avoid the formation of ethyl 3,3,3-trifluoropropanoate. We had previously shown that dehydrochlorination of cyclohexyl 3-chloro-3,3-difluoropropanoate, prepared by Bayer-Villiger oxidation of the corresponding ketone, led to an unresolvable mixture of the expected acrylate and cyclohexyl 3,3,3-trifluoropropanoate[2] due to fluoride ion random. Obviously, replacing chlorine by the better leaving group bromine enhances the selectivity of the reaction.

In a recent work, it was shown that the [4 + 2] cycloaddition reaction between furan and acrylic monomers, to give the 7-oxabicyclo[2.2.1]heptyl system, was greatly accelerated by the addition of zinc iodide[14] or boron trifluoride etherate.[15] As a route to (±)-shikimic acid and to its epimers[16] the Diels-Alder adduct **9a** obtained from furan and methyl acrylate (8) led, upon the base induced cleavage of the oxygen bridge, to the cyclohexadienol **10a**[14,16] (see Scheme II).

With the aim of preparing the difluorocyclohexadienol **10b**, we reacted first furan with ethyl 3,3-difluoroacrylate (6) in the presence of zinc iodide (boron trifluoride etherate or aluminum chloride[17] were ineffective). Although ex-

(1) Presented in part at the 4th European Symposium on Organic Chemistry, Aix-en-Provence, France, Sept 1985.
(2) Molines, H.; Wakselman, C. *J. Fluorine Chem.* **1984**, *25*, 447.
(3) Dickey, J. B.; McNally, J. G. U.S. Pat. 2571687; *Chem. Abstr.* **1952**, *46*, 4279b.
(4) Paleta, O.; Svoboda, J.; Dedek, V. *J. Fluorine Chem.* **1983**, *23*, 171.
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(8) We failed to hydrolize 4 to the corresponding aldehyde, a precursor of 3,3-difluoroacrolein. The diethyl acetal 7 was obtained in 85% yield by treating 4 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature. We failed also to hydrolize 7.

CF_2=CHCH$(OEt)_2$
7

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