# Synthesis of Polyfluoro Ketones for Selective Inhibition of Human Phospholipase $A_2$ Enzymes

Constantinos Baskakis,[†] Victoria Magrioti,[†] Naomi Cotton,[‡] Daren Stephens,[‡] Violetta Constantinou-Kokotou,[§] Edward A. Dennis,*[,‡] and George Kokotos*[,†]

*Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Panepistimiopolis, Athens 15771, Greece, Department of Chemistry and Biochemistry and Department of Pharmacology, School of Medicine, MC 0601, University of California, San Diego, La Jolla, California 92093-0601, Chemical Laboratories, Agricultural University of Athens, Athens 11855, Greece*

*Received May 29, 2008*

The development of selective inhibitors for individual $PLA_2$ enzymes is necessary in order to target $PLA_2$-specific signaling pathways, but it is challenging due to the observed promiscuity of known $PLA_2$ inhibitors. In the current work, we present the development and application of a variety of synthetic routes to produce pentafluoro, tetrafluoro, and trifluoro derivatives of activated carbonyl groups in order to screen for selective inhibitors and characterize the chemical properties that can lead to selective inhibition. Our results demonstrate that the pentafluoroethyl ketone functionality favors selective inhibition of the GVIA iPLA$_2$, a very important enzyme for which specific, potent, reversible inhibitors are needed. We find that 1,1,1,2,2-pentafluoro-7-phenyl-heptan-3-one (FKGK11) is a selective inhibitor of GVIA iPLA$_2$ ($X_I(50) = 0.0073$). Furthermore, we conclude that the introduction of an additional fluorine atom at the $\alpha'$ position of a trifluoromethyl ketone constitutes an important strategy for the development of new potent GVIA iPLA$_2$ inhibitors.

## Introduction

Phospholipase $A_2$ ($PLA_2$) enzymes catalyze the hydrolysis of the *sn*-2 ester bond of glycerophospholipids, producing free fatty acids and lysophospholipids.[1,2] Both products are precursor signaling molecules that are involved in a plethora of biological functions. The $PLA_2$ superfamily currently consists of 15 groups and many subgroups, of which a number of enzymes differ in primary sequence, structure and catalytic mechanism.[1] Among the various $PLA_2$ enzymes, Group IVA cPLA$_2$ (GIVA cPLA$_2$)[a] is considered the rate-limiting provider of arachidonic acid and lysophospholipids that can be converted into prostaglandins, leukotrienes, and PAF, respectively.[1−3] Another major intracellular $PLA_2$, the calcium-independent $PLA_2$ (GVIA iPLA$_2$) appears to be the primary phospholipase for basal metabolic functions within the cell.[1,2,4,5] Both intracellular enzymes share the same catalytic mechanism of utilizing a serine residue as the nucleophile. The $PLA_2$ superfamily also includes a type of small, secreted phospholipase (sPLA$_2$) that is characterized by a catalytic His/Asp dyad as well as a catalytic $Ca^{2+}$.[1,2,6] A well-studied example of this class is the human Group V secreted phospholipase $A_2$ (GV sPLA$_2$).[7] In many cases, the activity of sPLA$_2$ has been shown to be dependent on or linked to the activity of GIVA cPLA$_2$.[8−10]

Various classes of synthetic compounds have been studied as inhibitors of human GIVA cPLA$_2$, GVIA iPLA$_2$, and GV sPLA$_2$; and the results are summarized in recent review articles.[11,12] One of the most potent inhibitors of GIVA cPLA$_2$ is pyrrophenone (**1**, Figure 1).[13] Other recently reported inhibitors include 2-propanone derivatives combined with the indole ring (e.g., **2**, Figure 1)[14−16] and a series of indole derivatives[17−19] presented by Wyeth (for example compounds **3a** and **3b**, Figure 1), of which Efipladib (**3b**) is currently in phase I clinical trials.[19] Our laboratories have reported on the development of 2-oxoamide inhibitors of GIVA cPLA$_2$ (e.g., **4a**−**d**, Figure 1).[20−26]

Historically, the first potent inhibitor of GIVA cPLA$_2$ was a trifluoromethyl ketone analogue of arachidonic acid (AACOCF$_3$) in which the carboxyl group was replaced by COCF$_3$ (**5**, Figure 2).[27] This analogue was shown to be a slow- and tight-binding inhibitor of GIVA cPLA$_2$, and its mechanism of inhibition has been characterized via $^{19}$F NMR and $^{13}$C NMR.[28] Trifluoromethyl ketone analogues of $\gamma$-linolenic and linoleic acid as well as the analogue of palmitic acid (**6**, Figure 2) also inhibit GIVA cPLA$_2$.[29,30] Furthermore, a variety of trifluoromethyl ketones have been analyzed with phospholipid vesicle-, detergent-phospholipid mixed micelle-, and natural membrane-based assays.[31]

AACOCF$_3$ has been used as a tool to study the role of GIVA cPLA$_2$ inhibition in various animal models. Using this inhibitor, it was demonstrated that GIVA cPLA$_2$ plays an important role in the pathogenesis of experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis.[32] AACOCF$_3$ was also used to study possible contributions of central nervous $PLA_2$ enzymes to the development of allodynia after facial carrageenan injection in mice.[33] Intrathecal administration of AACOCF$_3$ prevented thermal hyperalgesia induced by intraplantar carrageenan as well as formalin-induced flinching in a dose-dependent manner.[34] Intrathecal injection of AACOCF$_3$, at antihyperalgesic doses, decreased the release of prostaglandin PGE-2 into spinal dialysate-evoked *N*-methyl-D-aspartate (NMDA).[34] Similarly, treatment of prion-infected cell lines indicated a pivotal role for $PLA_2$ enzymes in prion diseases.[35] Even so, the various in vivo activities of AACOCF$_3$

* To whom correspondence should be addressed. For G.K.: phone, (30210) 7274462; fax, (30210) 7274761; E-mail, gkokotos@chem.uoa.gr. For E.A.D.: phone, 858-534-3055; fax, 858-534-7390; E-mail, edennis@ucsd.edu.

[†] University of Athens.

[‡] University of California, San Diego.

[§] Agricultural University of Athens.

[a] Abbreviations: AACOCF$_3$, arachidonyl trifluoromethyl ketone; ATP, adenosine triphosphate; BEL, bromoenol lactone, DAST, diethylaminosulfur trifluoride; DIBALH, diisobutylaluminium hydride; DPPC, 1,2-dipalmitoylphosphotidylcholine; DTT, dithiothreitol; EAE, experimental autoimmune encephalomyelitis; EtOAc, ethyl acetate; GIVA cPLA$_2$, Group IVA cytosolic phospholipase $A_2$; GV sPLA$_2$, Group V secreted phospholipase $A_2$; GVIA iPLA$_2$, Group VIA calcium-independent phospholipase $A_2$; NMDA, *N*-methyl-D-aspartate; PAF, platelet activating factor; PAPC, 1-palmitoyl, 2-arachidonoyl phosphatidylcholine; PIP$_2$, phosphatidyl inositol (4,5)-bisphosphate; TBAF, tetra-*n*-butylammonium fluoride; TEMPO, 2,2,6,6-tetramethylpiperidine-1-yloxy free radical; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TLC, thin-layer chromatography; TMS, tetramethylsilane.

10.1021/jm800649q CCC: $40.75 
Published on Web 11/24/2008

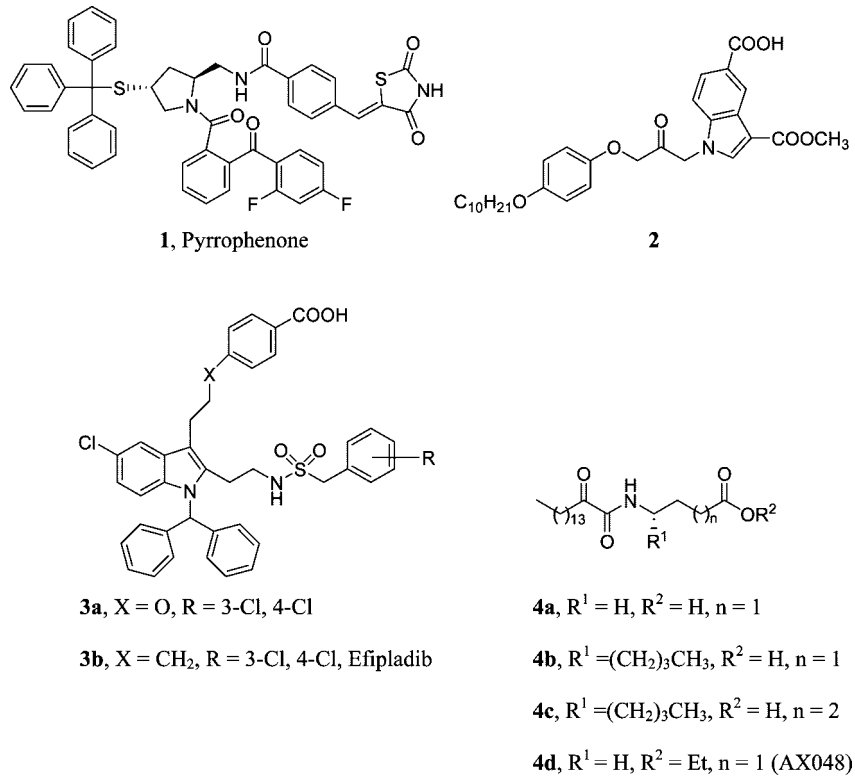



**Figure 1.** Some known inhibitors of GIVA $cPLA_2$.

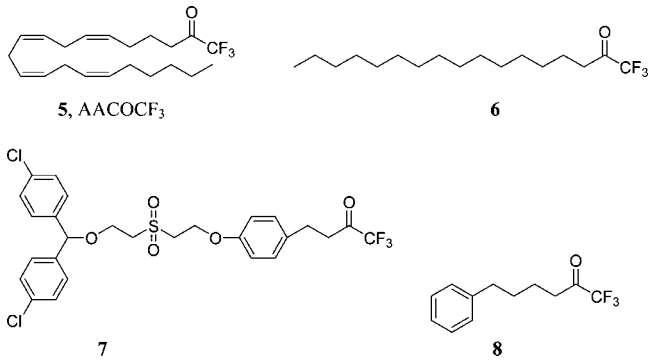



**Figure 2.** Trifluoromethyl ketone inhibitors of GIVA $cPLA_2$ and GVIA $iPLA_2$.

should be viewed with some caution because this inhibitor is not selective for GIVA $cPLA_2$ and has been reported to cause cell lysis.[36] Additional trifluoromethyl ketone derivatives are also observed to inhibit GIVA $cPLA_2$.[37−40] For example, BMS-229724[41] (**7**, Figure 2) was reported to be a tight-binding inhibitor of GIVA $cPLA_2$ possessing anti-inflammatory activity in skin inflammation models.[41]

Trifluoromethyl ketone analogues of arachidonic and palmitic acids also inhibit GVIA $iPLA_2$.[42] Both compounds inhibited macrophage GVIA $iPLA_2$ in a concentration-dependent manner and, in contrast to GVIA $cPLA_2$, GIVA $iPLA_2$ showed a preference for the saturated fatty chain.[42] Inhibition studies of a variety of trifluoromethyl ketones as inhibitors of GVIA $iPLA_2$ in mixed-micelle assays found that one trifluoromethyl ketone (**8**, Figure 2) is a potent inhibitor of GVIA $iPLA_2$ presenting a $X_I(50)$ value of 0.0043, which is 10-fold more potent than the corresponding value against GIVA $cPLA_2$.[31]

Continuing our efforts to synthesize selective inhibitors for the various $PLA_2$ enzyme types, we designed a variety of polyfluoro ketone-based derivatives. In this work, we present

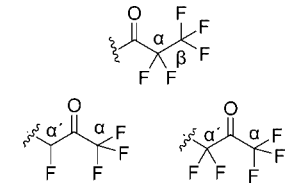


**Figure 3.** Polyfluoro ketone functionalities.

routes for the synthesis of polyfluoro ketones and demonstrate their inhibition of the three major human $PLA_2$ enzymes: GIVA $cPLA_2$, GVIA $iPLA_2$, and GV $sPLA_2$ but with vastly different specificities. Of particular note is the development of specific GVIA $iPLA_2$ inhibitors.

**Design and Synthesis of Polyfluoro Ketones.** We designed a variety of polyfluoro ketones, and examples of such activated carbonyl functionalities are depicted in Figure 3. The rationale behind our design of polyfluoro ketones was based on: (a) Increase of the carbonyl reactivity by introduction of additional fluorine atoms at the $\beta$- or $\alpha'$- positions. The inductive effect of additional fluorine atoms may increase carbonyl reactivity against nucleophiles, such as the active-site serine hydroxyl group in GIVA $cPLA_2$ and GVIA $iPLA_2$. (b) Increase of the inhibitor binding affinity to the target enzymes. Additional fluorine atoms at the $\beta$- or $\alpha'$- position may contribute to the development of additional interactions, further stabilizing the enzyme−inhibitor complex. Recently, it has become clear that fluorine can enhance binding efficacy and selectivity in pharmaceuticals due to a variety of multipolar C−F···H−N, C−F···C═O, and C−F···H−$C_\alpha$ interactions between a fluorinated ligand and protein binding-site.[43,44] Because the natural substrates of $PLA_2$ enzymes are long-chain phospholipids, we chose to attach the polyfluoro ketone functionality to a long aliphatic chain as well as to short or medium chains carrying a nonsubstituted or para-alkoxy (or aryloxy) substituted ring.

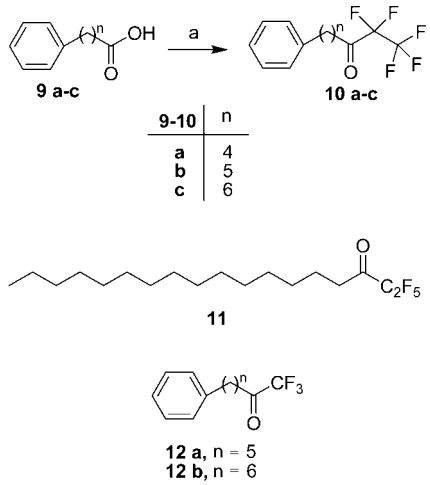



**Figure 4.** Reagents and conditions: (a) (i) $(COCl_2)_2$, $CH_2Cl_2$; (ii) $(CF_3CF_2CO)_2O$, pyridine, $CH_2Cl_2$.

Among the existing methods, the synthesis of trifluoromethyl ketones through conversion of carboxylic acids into chlorides followed by subsequent treatment with trifluoroacetic anhydride and pyridine[45] has found wide application. We observe that simple carboxylic acids, amino acids and peptides,[46] and even lipophilic glyceride analogues, as we have demonstrated for the synthesis of potent gastric lipases inhibitors,[47] are able to produce trifluoromethyl ketones in satisfactory yields. For the synthesis of pentafluoroethyl ketones, carboxylic acids **9a**−**c** were converted to chlorides by treatment with oxalyl chloride and then to the target compounds **10a**−**c** using pentafluoropropionic anhydride and pyridine (Figure 4). For comparison purposes, we prepared pentafluoroethyl ketone **11** corresponding to palmitic acid as well as trifluoromethyl ketones **12a**,**b** corresponding to pentafluoro derivatives **10b**,**c**.

The synthesis of various trifluoromethyl and pentafluoroethyl ketones is depicted in Figure 5. The hydroxymethyl group of compounds **13a**,**b** was oxidized to an aldehyde by the NaOCl/TEMPO method.[48] Wittig olefination of aldehydes **14a**,**b** and Wadsworth−Horner−Emmons reaction led to elongation of the chain by two or four carbon atoms, respectively. After hydrogenation and saponification, carboxylic acids **17a**,**b** and **18a**,**b** were converted to fluoroketones **19a**,**b**, **20a**,**b**, and **21** as described above. The trifluoromethyl ketone **23** was prepared from the known carboxylic acid **22** (Figure 6).

Tetrafluoro derivative **26** was synthesized as shown in Figure 7. The replacement of the hydroxyl group of methyl 2-hydroxyhexadecanoate (**24**) with fluorine was carried out by treatment with diethylaminosulfur trifluoride (DAST), a well-known fluorinating agent.[49] Treatment of methyl ester **25** by (trifluoromethyl)trimethylsilane in the presence of a catalytic amount of cesium fluoride, followed by hydrolysis of silyl ether intermediate,[50] led directly to tetrafluoro derivative **26**. It should be noted that a 2-fluorocarboxylic acid cannot transform into a trifluoromethyl ketone by conversion to chloride and treatment with anhydride and pyridine, probably because the intermediate ketene required for such a transformation[45] cannot be formed.

To synthesize pentafluoro derivative **30**, we explored two different routes (Figures 8 and 9). Reaction of diethyl oxalate with Grignard reagent[51] **27** led to 2-oxoester **28** (Figure 8). DAST is an efficient reagent for the conversion of 2-oxoesters to 2,2-difluoroesters;[52,53] therefore, 2-oxoester **28** was fluorinated by treatment with DAST and ethyl ester **29** was converted to trifluoromethyl ketone **30** as described above. Alternatively, compound **30** was prepared starting from aldehyde **31** (Figure 9). Formation of cyanohydrin **32** was followed by methanolysis and finally oxidation to produce 2-oxoester **34**. By similar procedures to those described above, the pentafluoro derivative **30** was prepared.

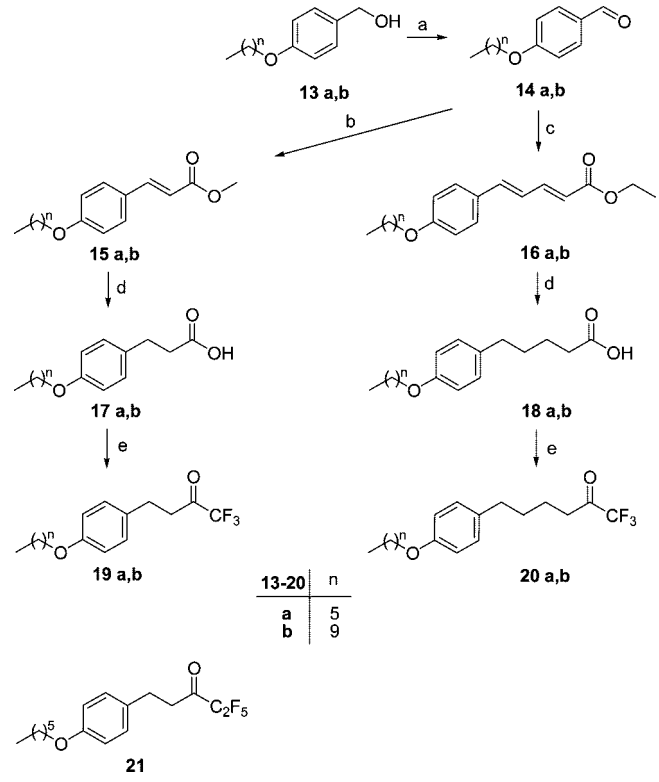



**Figure 5.** Reagents and conditions: (a) NaOCl, TEMPO, NaBr, $NaHCO_3$, toluene/EtOAc, $H_2O$; (b) $Ph_3P{=}CHCOOCH_3$, $CH_2Cl_2$; (c) $C_2H_5OOCH{=}CHCH_2P(=O)(OC_2H_5)_2$, LiOH, THF; (d) (i) $H_2$, 10% Pd, (ii) NaOH, $CH_3OH$, (e) (i) $(COCl_2)_2$, $CH_2Cl_2$, (ii) $(CF_3CO)_2O$, pyridine, $CH_2Cl_2$.

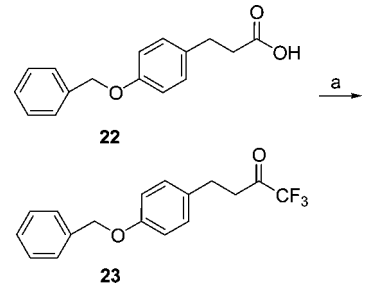



**Figure 6.** Reagents and conditions: (a) (i) $(COCl_2)_2$, $CH_2Cl_2$, (ii) $(CF_3CO)_2O$, pyridine, $CH_2Cl_2$.

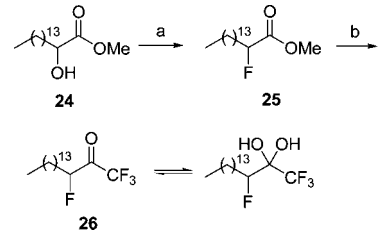



**Figure 7.** Reagents and conditions: (a) DAST, dry $CH_2Cl_2$; (b) (i) $(CH_3)_3SiCF_3$, CsF, $CH_3OCH_2CH_2OCH_3$, (ii) conc HCl.

To synthesize pentafluoro derivative **30**, we explored two different routes (Figures 8 and 9). Reaction of diethyl oxalate with Grignard reagent[51] **27** led to 2-oxoester **28** (Figure 8). DAST is an efficient reagent for the conversion of 2-oxoesters to 2,2-difluoroesters;[52,53] therefore, 2-oxoester **28** was fluorinated by treatment with DAST and ethyl ester **29** was converted to trifluoromethyl ketone **30** as described above. Alternatively, compound **30** was prepared starting from aldehyde **31** (Figure

Electrophilic ketones, like fluoroketones, may exist in equilibrium with their corresponding hydrates (gem diols) depending on the environment. On the basis of the $^1H$ NMR data, the trifluoromethyl ketones and the pentafluoroethyl ketones syn-

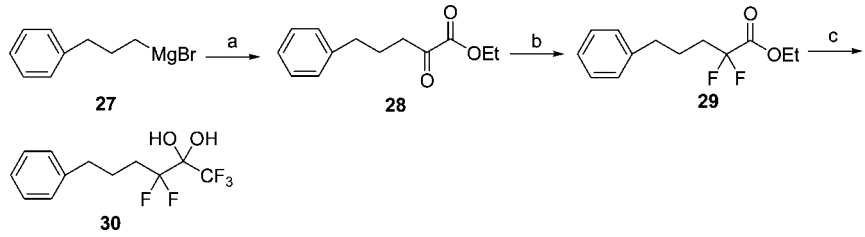



**Figure 8.** Reagents and conditions: (a) dry $Et_2O$, diethyl oxalate; (b) $Et_2NSF_3$; (c) (i) $(CH_3)_3SiCF_3$, CsF, $CH_3OCH_2CH_2OCH_3$, (ii) conc HCl.

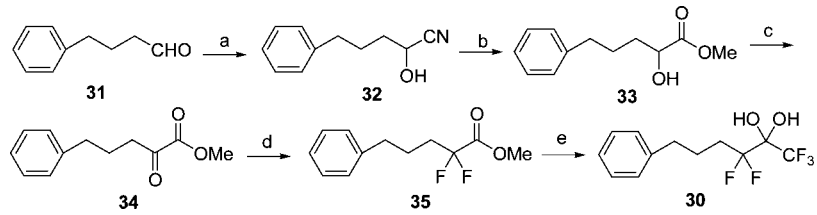



**Figure 9.** Reagents and conditions: (a) $NaHSO_3$, KCN, $CH_2Cl_2$; (b) HCl, MeOH; (c) Dess−Martin periodinane, $CH_2Cl_2$; (d) $Et_2NSF_3$, $CH_2Cl_2$; (e) (i) $(CH_3)_3SiCF_3$, CsF, $CH_3OCH_2CH_2OCH_3$, (ii) conc HCl.

thesized in this work were found to exist solely in their ketone forms in chloroform solution. However, tetrafluoro derivative **26** appears to be a mixture of ketone−hydrate form in a ratio 1:2, whereas pentafluoro derivative **30** is completely hydrated (see NMR data in Experimental Section). $^{19}F$ NMR spectroscopic data confirm the existence of the hydrated form in the cases of compounds **26** and **30**.

**In Vitro Inhibition of GIVA cPLA$_2$, GVIA iPLA$_2$ and GV sPLA$_2$.** All synthesized inhibitors were tested for inhibition of human GIVA cPLA$_2$, GVIA iPLA$_2$, and GV sPLA$_2$ using previously described mixed micelle-based assays.[20,21,24,25] The resulting degrees of inhibition are presented in Table 1 as either percent inhibition or $X_I(50)$ values. Initially, the percent of inhibition for each PLA$_2$ enzyme at 0.091 mol fraction of each inhibitor was determined and $X_I(50)$ values were estimated for compounds that displayed greater than 90% inhibition. The $X_I(50)$ is the mole fraction of the inhibitor in the total substrate interface required to inhibit the enzyme by 50%.

In accordance with the literature, the long-chain saturated palmitoyl trifluoromethyl ketone **6** inhibits both intracellular enzymes GIVA cPLA$_2$ and GVIA iPLA$_2$ at a similar level. In this work, we show that compound **6** is also a weak inhibitor of GV sPLA$_2$ (79% inhibition at 0.091 mol fraction). However, compound **8** is considered to be a selective inhibitor of GVIA iPLA$_2$ with an observed $X_I(50)$ 0.0096, while high mole fraction of the inhibitor causes only 38% inhibition of GIVA cPLA$_2$ and does not affect GV sPLA$_2$.

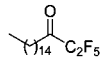
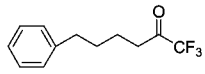
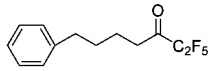
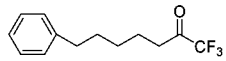
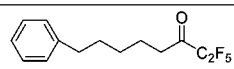
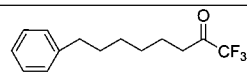
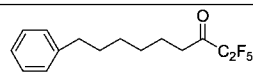
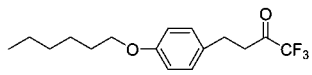
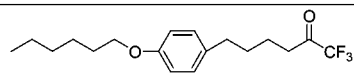
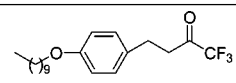
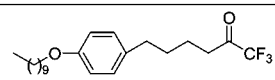
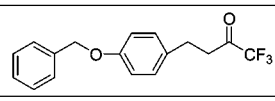
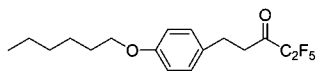
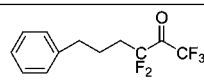
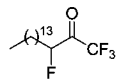
The introduction of a pentafluoroethyl ketone functionality led to adverse effects depending on the nature of the chain. 1,1,1,2,2-Pentafluoro-7-phenyl-heptan-3-one (**10a**, FKGK11) presents slightly higher inhibitory activity on GVIA iPLA$_2$ ($X_I(50)$ 0.0073) than the corresponding trifluoromethyl derivative **8**. The dose−response curve for the inhibition of GVIA iPLA$_2$ by pentafluoroethyl ketone **10a** is shown in Figure 10. In addition, it demonstrates selective inhibition for GVIA iPLA$_2$ because high mole fractions (0.091) do not affect GIVA cPLA$_2$ and caused slight inhibition (28%) of GV sPLA$_2$. Interestingly, the long-chain saturated pentafluoroethyl ketone **11** abolished the inhibitory potency and selectivity, demonstrating only 50% inhibition of GVIA iPLA$_2$ and 43% inhibition of GV sPLA$_2$ at 0.091 mol fraction.

In pentafluoroethyl derivatives, increasing the chain length (from four to five or six carbon atoms) between the activated carbonyl group and the aromatic ring resulted in decreased selectivity for GVIA iPLA$_2$. Derivatives **10b** and **10c** (five and six carbon atoms, respectively) inhibit GVIA iPLA$_2$ at a similar level as inhibitor **10a** ($X_I(50)$ 0.0065). However, both **10b** and **10c** are weak inhibitors of GIVA cPLA$_2$ (56% and 65%, respectively) and GV sPLA$_2$ (46% and 75%, respectively). For the trifluoromethyl ketone derivatives **12a** and **12b**, the inhibitory activity increased as the chain length increased between the carbonyl group and the aromatic ring. Both **12a** and **12b** are more potent inhibitors of GVIA iPLA$_2$ ($X_I(50)$ 0.0025 and $X_I(50)$ 0.0018, respectively) than compound **8**; however, these compounds also weakly inhibit GIVA cPLA$_2$ (62% and 68%, respectively) and GV sPLA$_2$ (48% and 53%, respectively) at 0.091 mol fraction. These results demonstrate that an increase of carbon atoms between the activated carbonyl group and the aromatic ring leads to a loss in selectivity.

Trifluoromethyl ketones **19a**, **19b**, **20a**, and **20b** containing a medium (hexyloxy) or a long (decyloxy) chain substituent at the *para* position of the aromatic ring inhibit both GIVA cPLA$_2$ and GVIA iPLA$_2$. The dose−response curves for the inhibition of GVIA iPLA$_2$ and GIVA cPLA$_2$ by 1,1,1-trifluoro-6-(4-hexyloxy-phenyl)-hexan-2-one (**20a**, FKGK2) are shown in Figure 11. Comparison of **19a** with **20a** and **19b** with **20b** shows that the increase of the chain length between the carbonyl group, and the aromatic ring from two to four carbon atoms results in increased inhibitory potency for both GIVA cPLA$_2$ and GVIA iPLA$_2$. All of these compounds (**19a**, **19b**, **20a**, and **20b**) also inhibit GV sPLA$_2$. Thus, trifluoromethyl ketones containing an alkoxy group at the *para* position of the aromatic group can be considered to be pan inhibitors of the all three enzymes: GIVA cPLA$_2$, GVIA iPLA$_2$, and GV sPLA$_2$. In particular, compound **20a** is an inhibitor suitable for applications involving the inhibition of both intracellular and extracellular PLA$_2$ enzymes. The replacement of the hexyloxy by a benzyloxy group led to derivative **23**, which weakly inhibited all the three PLA$_2$ enzymes. Comparison of inhibitors **8**, **20a**, **20b**, and **23** demonstrates that the introduction of an alkoxy or a benzyloxy group in the aromatic ring destroys the selectivity for GVIA iPLA$_2$.

Comparison of pentafluoroethyl ketone **21** with the corresponding trifluoromethyl ketone **19a** reinforces our observation that pentafluoroethyl ketone functionality favors the inhibition of GVIA iPLA$_2$ ($X_I(50)$ 0.0075). However, the presence of a

**Table 1.** Inhibition of $PLA_2$ by Fluoroketones[a]

| No | Structure | GIVA cPLA2 | | GVIA iPLA2 | | GV sPLA2 | |
|---|---|---|---|---|---|---|---|
| | | % Inhibition | $X_I(50)$ | % Inhibition | $X_I(50)$ | % Inhibition | $X_I(50)$ |
| **6** |  | 96 ± 2 | 0.0223 ± 0.0023 | 92 ± 3 | 0.0195 ± 0.0053 | 79 ± 9 | |
| **11** |  | N.D. | | 50 ± 13 | | 43 ± 8 | |
| **8** |  | 38 ± 2 | | 96 ± 3 | 0.0096 ± 0.0008 | N.D. | |
| **10a** |  | N.D. | | 98 ± 16 | 0.0073 ± 0.0007 | 28 ± 1 | |
| **12a** |  | 62 ± 5 | | 96 ± 6 | 0.0025 ± 0.0003 | 48 ± 6 | |
| **10b** |  | 56 ± 4 | | 98 ± 5 | 0.0065 ± 0.001 | 46 ± 8 | |
| **12b** |  | 68 ± 6 | | 99 ± 10 | 0.0018 ± 0.0005 | 53 ± 14 | |
| **10c** |  | 65 ± 12 | | 98 ± 4 | 0.0065 ± 0.0008 | 75 ± 10 | |
| **19a** |  | 91 ± 2 | 0.0199 ± 0.0025 | 85 ± 4 | 0.0328 ± 0.0035 | 82 ± 8 | |
| **20a** |  | 92 ± 3 | 0.0098 ± 0.0006 | 91 ± 4 | 0.0169 ± 0.0021 | 86 ± 2 | |
| **19b** |  | 96 ± 2 | 0.0156 ± 0.0019 | 94 ± 8 | 0.0208 ± 0.0032 | 80 ± 6 | |
| **20b** |  | 95 ± 2 | 0.0116 ± 0.0012 | 94 ± 8 | 0.0166 ± 0.0022 | 84 ± 7 | |
| **23** |  | 88 ± 1 | | 71 ± 14 | | 49 ± 12 | |
| **21** |  | 73 ± 4 | | 95 ± 5 | 0.0075 ± 0.0011 | 86 ± 4 | |
| **30** |  | 27 ± 3 | | 49 ± 12 | | 59 ± 12 | |
| **26** |  | 94 ± 2 | 0.0167 ± 0.0018 | 93 ± 4 | 0.0011 ± 0.0002 | 86 ± 10 | 0.0236 ± 0.004 |

[a] Average percent inhibition and standard error ($n = 3$) reported for each compound at 0.091 mole fraction. $X_I(50)$ values determined for inhibitors with greater than 90% inhibition. N.D. signifies compounds with less than 25% inhibition (or no detectable inhibition).

hexyloxy substituent leads to loss of selectivity for GVIA $iPLA_2$ because compound **21** weakly inhibits GIVA $cPLA_2$ (73%) and GV $sPLA_2$ (86%) at 0.091 inhibitor mole fraction.

Comparison of compound **26** with **6** shows that the introduction of an additional fluorine atom at the α′ position in a long chain saturated derivative results in a derivative with slightly better activity for GIVA $cPLA_2$ ($X_I(50)$ 0.0167) than the parent trifluoromethyl ketone **6** ($X_I(50)$ 0.0223). More importantly, tetrafluoro derivative **26** is approximately 20-fold more potent inhibitor of GVIA $iPLA_2$ ($X_I(50)$ 0.0011) than the trifluoro derivative **6** ($X_I(50)$ 0.0195). To our knowledge, compound **26** is the most potent inhibitor of GVIA $iPLA_2$ reported, indicating that introduction of an additional fluorine atom at the α′ position constitutes an important strategy for the development of new potent GVIA $iPLA_2$ inhibitors. However, the tetrafluoro derivative **26** also inhibits GIVA and GV $PLA_2$. Interestingly, the introduction of two fluorine atoms at the α′ position in an aromatic ring containing derivative destroyed the inhibitory potency and the selectivity for GVIA $iPLA_2$. For example, at 0.091 mol fraction, derivative **30** is a weak inhibitor of GVIA $iPLA_2$ (49%), GV $sPLA_2$ (59%), and presents no significant inhibition of GIVA $cPLA_2$ (27%).

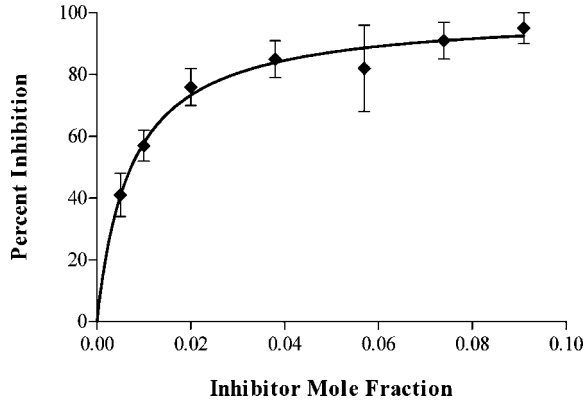



**Figure 10.** Inhibition curve for pentafluoro ketone **10a** in a mixed-micelle assay with human GVIA iPLA$_2$. Nonlinear regression (hyperbolic) estimated a $X_I(50)$ value of 0.0073 ± 0.0007. Compound **10a** inhibited GIVA cPLA$_2$ less than 25% and GV sPLA$_2$ approximately 28% at 0.091 mol fraction.

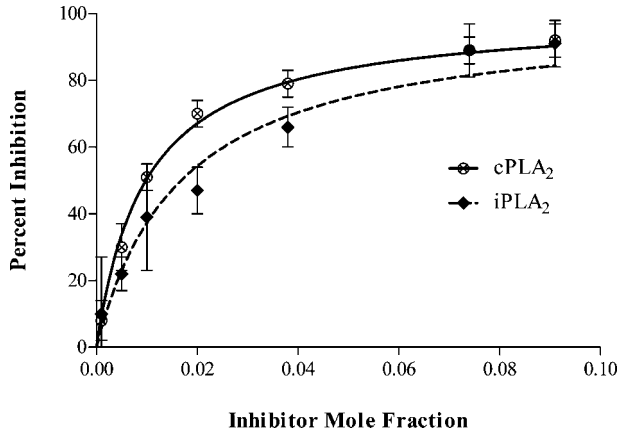
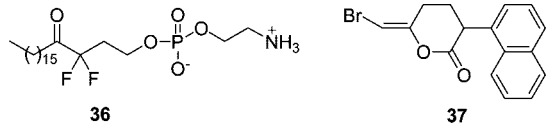



**Figure 11.** Inhibition curves for trifluoromethyl ketone **20a** in a mixed-micelle assay with human GVIA cPLA$_2$ and GIVA iPLA$_2$. Nonlinear regressions (hyperbolic) estimated $X_I(50)$ values of 0.0169 ± 0.0021 and 0.0098 ± 0.0006 for GIVA cPLA$_2$ and GVIA iPLA$_2$, respectively. Compound **20a** inhibited GV sPLA$_2$ approximately 86% at 0.091 mol fraction.




**36** **37**

**Figure 12.** Structures of difluoro ketone inhibitor **36** of cobra venom PLA$_2$ and BEL inhibitor **37**.

Our data indicate the importance of screening selective inhibitors against multiple enzyme classes within the PLA$_2$ superfamily. As mentioned above, our work shows that the known inhibitor palmitoyl trifluoromethyl ketone **6**, reported to strictly inhibit intracellular GVIA iPLA$_2$ and GIVA cPLA$_2$, also weakly inhibits GV sPLA$_2$. Similarly, some of our synthesized trifluoromethyl, pentafluoroethyl and tetrafluoro derivatives (for example, compounds **20a**, **21**, **26**) were found to inhibit GV sPLA$_2$. Futhermore, Gelb et al. demonstrated that difluoro ketones similar to **36** (Figure 12) inhibit cobra venom PLA$_2$.[54] Therefore activated ketones, such as polyfluoro ketones, are likely to inhibit serine enzymes, GIVA cPLA$_2$ and GVIA iPLA$_2$, as well as histidine enzymes like secreted PLA$_2$.

Bromoenol lactone (BEL) **37** (Figure 12) is considered to be a selective and irreversible GVIA iPLA$_2$ and has been widely applied to study potential biological roles for GVIA iPLA$_2$.[55,56] However, Turk et al. have recently reported that BEL inactivates GVIA iPLA$_2$ by generating a diffusible bromomethyl keto acid that alkylates cysteine thiols, rather than creating an acyl−enzyme intermediate with the active-site serine.[57] Therefore, it is likely that BEL affects multiple enzymes and should be used with appropriate caution when studying potential roles of GVIA iPLA$_2$.[57] These observations lead us to design selective inhibitors of GVIA iPLA$_2$ such as the pentafluoroethyl ketone **10a**.

In conclusion, we developed and applied a variety of synthetic routes to produce various pentafluoro, tetrafluoro, and trifluoro derivatives containing activated carbonyl groups. We studied their in vitro activity on the three major human PLA$_2$ enzyme classes and demonstrated that the pentafluoroethyl ketone functionality favors GVIA iPLA$_2$ inhibition. Furthermore, 1,1,1,2,2-pentafluoro-7-phenyl-heptan-3-one (**10a**) was shown to be a selective inhibitor of GVIA iPLA$_2$. Additionally, introduction of an additional fluorine atom at the α′ position of a trifluoromethyl ketone constitutes an important strategy for the development of new potent GVIA iPLA$_2$ inhibitors. The tetrafluoro derivative of palmitic acid **26** is observed to be the most potent inhibitor of GVIA iPLA$_2$ to date; however, it also inhibits GIVA cPLA$_2$ and GV sPLA$_2$. Polyfluoro ketones displaying an array of selectivities for the major PLA$_2$ enzyme classes will prove to be valuable tools for the in vivo characterization of the roles of PLA$_2$ enzymes. Furthermore, we found that these compounds do not show cytotoxicity toward cells in culture and we are currently utilizing these polyfluoro ketone derivatives for the comparison of intracellular versus extracellular PLA$_2$ enzyme roles in animal models of neurological disorders such as multiple sclerosis, spinal cord injury, and peripheral nerve injury.[58]

## Experimental Section

**Synthesis of Fluoroketone Inhibitors.** Melting points were determined on a Buchi 530 apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained on a Varian Mercury spectrometer ($^1$H NMR recorded at 200 MHz, $^{13}$C NMR recorded at 50 MHz, $^{19}$F NMR recorded at 188 MHz) and are referenced in ppm relative to TMS for $^1$NMR and $^{13}$C NMR and relative to TFA as an internal standard for $^{19}$F NMR. Thin layer chromatography (TLC) plates (silica gel 60 $F_{254}$) and silica gel 60 (230−400 mesh) for flash column chromatography were purchased from Merck. Visualization of spots was effected with UV light and/or phosphomolybdic acid, in EtOH stain. Tetrahydrofuran (THF), toluene, and $Et_2O$ were dried by standard procedures and stored over molecular sieves or Na. All other solvents and chemicals were reagent grade and used without further purification. All the products gave satisfactory elemental analysis results.

**General Procedure for the Synthesis of Pentafluoroethyl Ketones.** Oxalyl chloride (0.38 g, 3 mmol) and *N*,*N*-dimethylformamide (40 μL) were added to a solution of carboxylic acid (1 mmol) in dry dichloromethane (40 mL). After 3 h stirring at room temperature, the solvent and excess reagent were evaporated under reduced pressure and the residue was dissolved in dry dichloromethane (10 mL). Pyridine (0.64 mL, 8 mmol) and pentafluoropropionic anhydride (0.85 mL, 6 mmol) were added dropwise to this solution at 0 °C consecutively. After stirring at 0 °C for 30 min and at room temperature for 1.5 h, the reaction mixture was cooled again at 0 °C and water (2 mL) was added dropwise. After stirring for 30 min at 0 °C and another 30 min at room temperature, the reaction mixture was diluted with dichloromethane (10 mL). The organic phase was then washed with brine and dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure, and the residual oil was purified by flash column chromatography [EtOAc-petroleum ether (bp 40−60 °C) 1/9].

**1,1,1,2,2-Pentafluoro-7-phenyl-heptan-3-one (10a).** Yield 53%; yellowish oil. $^1$H NMR ($CDCl_3$): δ 7.31−7.17 (5H, m, Ph), 2.80

(2H, t, $J = 6.2$ Hz, $CH_2$), 2.66 (2H, t, $J = 6.6$ Hz, $CH_2$), 1.73−1.67 (4H, m, 2 × $CH_2$). $^{13}$C NMR: $\delta$ 194.2 (t, $J_{C-C-F} = 26$ Hz, CO), 141.6 (Ph), 128.4 (Ph), 128.3 (Ph), 125.9 (Ph), 117.8 (qt, $J_{C-F3} = 287$ Hz, $J_{C-CF2} = 34$ Hz, $CF_3$), 106.8 (tq, $J_{C-F2} = 267$ Hz, $J_{C-CF3} = 38$ Hz, $CF_2$), 37.1 ($CH_2$), 35.5 ($CH_2$), 30.3 ($CH_2$), 21.9 ($CH_2$). $^{19}$F NMR: $\delta$ −4.1 ($CF_3$), −45.5 ($CF_2$). MS (ESI) *m/z* (%): 279 ($M^-$, 100). Anal. ($C_{13}H_{13}F_5O$) C, H.

**1,1,1,2,2-Pentafluoro-8-phenyl-octan-3-one (10b).** Yield 75%; yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.35−7.21 (5H, m, Ph), 2.79 (2H, t, $J = 6.8$ Hz, $CH_2$), 2.68 (2H, t, $J = 7.4$ Hz, $CH_2$), 1.80−1.68 (4H, m, 2 × $CH_2$), 1.48−1.40 (2H, m, $CH_2$). $^{13}$C NMR: $\delta$ 194.3 (t, $J_{C-C-F} = 26$ Hz, CO), 142.2 (Ph), 128.3 (Ph), 128.2 (Ph), 125.7 (Ph), 117.8 (qt, $J_{C-F3} = 285$ Hz, $J_{C-CF2} = 34$ Hz, $CF_3$), 106.9 (tq, $J_{C-F2} = 265$ Hz, $J = 37$ Hz, $CF_2$), 37.2 ($CH_2$), 35.6 ($CH_2$), 31.0 ($CH_2$), 28.2 ($CH_2$), 22.1 ($CH_2$). $^{19}$F NMR: $\delta$ −4.2 ($CF_3$), −45.6 ($CF_2$). MS (ESI) *m/z* (%): 293 ($M^-$, 100). Anal. ($C_{14}H_{15}F_5O$) C, H.

**1,1,1,2,2-Pentafluoro-9-phenyl-nonan-3-one (10c).** Yield 60%; yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.31−7.18 (5H, m, Ph), 2.76 (2H, t, $J = 6.8$ Hz, $CH_2$), 2.64 (2H, t, $J = 8.0$ Hz, $CH_2$), 1.72−1.58 (4H, m, 2 × $CH_2$), 1.44−1.34 (4H, m, 2 × $CH_2$). $^{13}$C NMR: $\delta$ 194.4 (t, $J_{C-C-F} = 26$ Hz, CO), 142.5 (Ph), 128.4(Ph), 128.3 (Ph), 125.7 (Ph), 117.8 (qt, $J_{C-F3} = 285$ Hz, $J_{C-CF2} = 34$ Hz, $CF_3$), 106.9 (tq, $J_{C-F2} = 265$ Hz, $J_{C-CF3} = 37$ Hz, $CF_2$), 37.3 ($CH_2$), 35.8 ($CH_2$), 31.1 ($CH_2$), 28.8 ($CH_2$), 28.5 ($CH_2$), 22.2 ($CH_2$). $^{19}$F NMR: $\delta$ −4.2 ($CF_3$), −45.6 ($CF_2$); MS (ESI) *m/z* (%): 307 ($M^-$, 100). Anal. ($C_{15}H_{17}F_5O$) C, H.

**1,1,1,2,2-Pentafluoro-octadecan-3-one (11).** Yield 24%; colorless oil. $^1$H NMR ($CDCl_3$): $\delta$ 2.75 (2H, t, $J = 7.4$ Hz, $CH_2$), 1.67 (2H, t, $J = 7.0$ Hz, $CH_2$), 1.38−1.20 (24H, m, 12 × $CH_2$), 0.88 (3H, t, $J = 7.0$ Hz, $CH_3$). $^{13}$C NMR: $\delta$ 194.5 (t, $J_{C-CF2} = 26$ Hz, CO), 117.8 ppm (qt, $J_{C-F3} = 285$ Hz, $J_{C-CF2} = 34$ Hz, $CF_3$), 106.9 ppm (tq, $J_{C-F2} = 265$ Hz, $J_{C-CF3} = 38$ Hz, $CF_2$), 37.4 ($CH_2$), 31.9 ($CH_2$), 30.3 ($CH_2$), 29.7 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.2 ($CH_2$), 28.7 ($CH_2$), 22.7 ($CH_2$), 22.3 ($CH_2$), 14.1 ($CH_3$). $^{19}$F NMR: $\delta$ −4.2 ($CF_3$), −45.6 ($CF_2$). MS (ESI) *m/z* (%): 357 ($M^-$, 93). Anal. ($C_{18}H_{31}F_5O$) C, H.

**1,1,1,2,2-Pentafluoro-5-(4-hexyloxy-phenyl)-pentan-3-one (21).** Yield 76%; yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.10 (2H, d, $J = 8.6$ Hz, Ph), 6.85 (2H, d, $J = 8.6$ Hz, Ph), 3.94 (2H, t, $J = 6.6$ Hz, $CH_2O$), 3.02 (2H, t, $J = 7.0$ Hz, $CH_2$), 2.96 (2H, t, $J = 7.0$ Hz, $CH_2$), 1.86−1.73 (2H, m, $CH_2$), 1.60−1.25 (6H, m, 3 × $CH_2$), 0.93 (3H, t, $J = 6.4$ Hz, $CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ 193.5 (t, $J_{C-C-F} = 26$ Hz, CO), 157.9 (Ph), 130.9 (Ph), 129.2 (Ph), 117.8 (qt, $J_{C-F3} = 286$ Hz, $J_{C-CF2} = 34$ Hz, $CF_3$), 114.7 (Ph), 106.8 (tq, $J_{C-F2} = 265$ Hz, $J_{C-CF3} = 38$ Hz, $CF_2$), 68.0 ($CH_2O$), 39.4 ($CH_2$), 31.6 ($CH_2$), 29.3 ($CH_2$), 27.5 ($CH_2$), 25.7 ($CH_2$), 22.6 ($CH_2$), 13.9 ($CH_3$). $^{19}$F NMR: $\delta$ −4.2 ($CF_3$), −45.6 ($CF_2$). MS (ESI) *m/z* (%): 351 ($M^-$, 100). Anal. ($C_{17}H_{21}F_5O_2$) C, H.

**Synthesis of Trifluoromethyl Ketones.** The synthesis of trifluoromethyl ketones was carried out following the procedure described above for pentafluoromethyl ketones, except that trifluoroacetic anhydride was used instead of pentafluoropropionic anhydride. The products were purified by flash column chromatography [EtOAc-petroleum ether (bp 40−60 °C) 3/7].

**1,1,1-Trifluoro-7-phenylheptan-2-one (12a).**[59] Yield 45%; yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.34−7.19 (5H, m, Ph), 2.76−2.62 (4H, m, 2 × $CH_2$), 1.77−1.66 (4H, m, 2 × $CH_2$), 1.46−1.39 (2H, m, $CH_2$). $^{13}$C NMR: $\delta$ 191.8 (q, $J_{C-C-F} = 35$ Hz, $COCF_3$), 142.2 (Ph), 128.3 (Ph), 128.2 (Ph), 125.7 (Ph), 115.5 (q, $J_{C-F} = 290$ Hz, $CF_3$), 36.2 ($CH_2$), 35.7 ($CH_2$), 30.9 ($CH_2$), 28.2 ($CH_2$), 22.2 ($CH_2$). $^{19}$F NMR: $\delta$ −1.5 ($CF_3$). MS (ESI) *m/z* (%): 243 ($M^-$, 100).

**1,1,1-Trifluoro-8-phenyloctan-2-one (12b).**[59] Yield 42%; yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.28−7.17 (5H, m, Ph), 2.72−2.60 (4H, m, 2 × $CH_2$), 1.70−1.61 (4H, m, 2 × $CH_2$), 1.42−1.24 (4H, m, 2 × $CH_2$). $^{13}$C NMR: $\delta$ 191.4 (q, $J_{C-C-F} = 35$ Hz, $COCF_3$), 142.5 (Ph), 128.3 (Ph), 128.2 (Ph), 125.7 (Ph), 115.6 (q, $J_{C-F} = 291$ Hz, $CF_3$), 36.3 ($CH_2$), 35.8 ($CH_2$), 31.1 ($CH_2$), 28.7 ($CH_2$), 28.6 ($CH_2$), 22.3 ($CH_2$). $^{19}$F NMR: $\delta$ −1.5 ($CF_3$). MS (ESI) *m/z* (%): 257 ($M^-$, 100).

**1,1,1-Trifluoro-4-(4-hexyloxy-phenyl)-butan-2-one (19a).** Yield 53%; yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.10 (2H, d, $J = 8.6$ Hz, Ph), 6.84 (2H, d, $J = 8.6$ Hz, Ph), 3.93 (2H, t, $J = 6.2$ Hz, $CH_2O$), 3.10−2.92 (4H, m, 2 × $CH_2$), 1.82−1.62 (2H, m, $CH_2$), 1.55−1.22 (6H, m, 3 × $CH_2$), 0.91 (3H, t, $J = 6.6$ Hz, $CH_3$). $^{13}$C NMR: $\delta$ 190.7 (q, $J_{C-C-F} = 35$ Hz, $COCF_3$), 157.9 (Ph), 131.0 (Ph), 129.2 (Ph), 115.5 (q, $J_{C-F} = 292$ Hz, $CF_3$), 114.7 (Ph), 68.0 ($OCH_2$), 38.3 ($CH_2$), 31.6 ($CH_2$), 29.2 ($CH_2$), 27.5 ($CH_2$), 25.7 ($CH_2$), 22.6 ($CH_2$), 13.9 ($CH_3$). $^{19}$F NMR: $\delta$ −1.5 ($CF_3$). MS (ESI) *m/z* (%): 301 ($M^-$, 100). Anal. ($C_{16}H_{21}F_3O_2$) C, H.

**4-(4-Decyloxy-phenyl)-1,1,1-trifluoro-butan-2-one (19b).** Yield 46%; yellowish oil; $^1$H NMR ($CDCl_3$): $\delta$ 7.12 (2H, d, $J = 8.6$ Hz, Ph), 6.85 (2H, d, $J = 8.6$ Hz, Ph), 3.95 (2H, t, $J = 6.6$ Hz, $CH_2O$), 3.05−2.85 (4H, m, 2 × $CH_2$), 1.81−1.62 (2H, m, $CH_2$), 1.56−1.22 (14H, m, 7 × $CH_2$), 0.92 (3H, t, $J = 6.8$ Hz, $CH_3$). $^{13}$C NMR: $\delta$ 190.5 (q, $J_{C-C-F} = 35$ Hz, $COCF_3$), 157.9 (Ph), 131.0 (Ph), 129.2 (Ph), 115.5 (q, $J_{C-F} = 292$ Hz, $CF_3$), 114.6 (Ph), 68.0 ($CH_2O$), 38.3 ($CH_2$), 31.8 ($CH_2$), 29.6 ($CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$), 27.4 ($CH_2$), 26.0 ($CH_2$), 22.7 ($CH_2$), 14.0 ($CH_3$). $^{19}$F NMR: $\delta$ −1.5 ($CF_3$). MS (FAB) *m/z* (%): 358 ($M^+$, 85). Anal. ($C_{20}H_{29}F_3O_2$) C, H.

**1,1,1-Trifluoro-6-(4-hexyloxy-phenyl)-hexan-2-one (20a).** Yield 45%; yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.09 (2H, d, $J = 8.0$ Hz, Ph), 6.85 (2H, d, $J = 8.0$ Hz, Ph), 3.95 (2H, t, $J = 6.6$ Hz, $CH_2O$), 2.74 (2H, t, $J = 6.6$ Hz, $CH_2$), 2.60 (2H, t, $J = 6.2$ Hz, $CH_2$), 1.82−1.62 (6H, m, 3 × $CH_2$), 1.46−1.25 (6H, m, 3 × $CH_2$), 0.94 (3H, t, $J = 6.8$ Hz, $CH_3$). $^{13}$C NMR: $\delta$ 191.4 (q, $J_{C-C-F} = 34$ Hz, $COCF_3$), 157.9 (Ph), 133.4 (Ph), 129.1 (Ph), 115.4 (q, $J_{C-F} = 290$ Hz, $CF_3$), 114.4 (Ph), 67.9 ($CH_2O$), 36.1 ($CH_2$), 34.5 ($CH_2$), 31.6 ($CH_2$), 30.6 ($CH_2$), 29.3 ($CH_2$), 25.7 ($CH_2$), 22.6 ($CH_2$), 21.8 ($CH_2$), 13.9 ($CH_3$). $^{19}$F NMR: $\delta$ −1.6 ($CF_3$). MS (FAB) *m/z* (%): 330 ($M^+$, 23). Anal. ($C_{18}H_{25}F_3O_2$) C, H.

**6-(4-Decyloxy-phenyl)-1,1,1-trifluoro-hexan-2-one (20b).** Yield 46%; yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.08 (2H, d, $J = 8.6$ Hz, Ph), 6.84 (2H, d, $J = 8.6$ Hz, Ph), 3.94 (2H, t, $J = 6.6$ Hz, $CH_2O$), 2.73 (2H, t, $J = 6.6$ Hz, $CH_2$), 2.59 (2H, t, $J = 7.0$ Hz, $CH_2$), 1.82−1.62 (6H, m, 3 × $CH_2$), 1.45−1.22 (14H, m, 7 × $CH_2$), 0.90 (3H, t, $J = 6.8$ Hz, $CH_3$). $^{13}$C NMR: $\delta$ 191.6 (q, $J_{C-C-F} = 35$ Hz, $COCF_3$), 157.7 (Ph), 133.7 (Ph), 129.4 (Ph), 115.8 (q, $J_{C-F} = 292$ Hz, $CF_3$), 114.6 (Ph), 68.2 ($CH_2O$), 36.4 ($CH_2$), 34.8 ($CH_2$), 32.1 ($CH_2$), 30.9 ($CH_2$), 29.8 ($CH_2$), 29.7 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 26.6 ($CH_2$), 26.3 ($CH_2$), 22.9 ($CH_2$), 22.1 ($CH_2$), 14.32 ($CH_3$). $^{19}$F NMR: $\delta$ −1.5 ($CF_3$). MS (FAB) *m/z* (%): 386 ($M^+$, 100). Anal. ($C_{22}H_{33}F_3O_2$) C, H.

**4-(4-Benzyloxy-phenyl)-1,1,1-trifluoro-butan-2-one (23).** Yield 43%; yellowish solid; mp 71−72 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.46−7.35 (5H, m, Ph), 7.15 (2H, d, $J = 8.4$ Hz, Ph), 6.95 (2H, d, $J = 8.4$ Hz, Ph), 5.07 (2H, s, $PhCH_2$), 3.12−2.85 (4H, m, 2 × $CH_2$). $^{13}$C NMR: $\delta$ 190.7 (q, $J_{C-C-F} = 35$ Hz, $COCF_3$), 157.4 (Ph), 136.9 (Ph), 131.5 (Ph), 129.2 (Ph), 128.5 (Ph), 127.9 (Ph), 127.4 (Ph), 115.4 (q, $J_{C-F} = 290$ Hz, $CF_3$), 114.9 (Ph), 70.0 ($CH_2O$), 38.3 ($CH_2$), 27.4 ($CH_2$). $^{19}$F NMR: $\delta$ −1.4 ($CF_3$). MS (ESI) *m/z* (%): 307 ($M^-$, 100). Anal. ($C_{17}H_{15}F_3O_2$) C, H.

Intermediate compounds **14a**,**b** and **22** were prepared by known methods, and their spectroscopic data were in accordance with those in the literature.[60,61]

**Horner−Wadsworth−Emmons Olefination.** A suspension of aldehyde **14a** or **14b** (1 mmol), triethyl 4-phosphonocrotonate (0.37 g, 1.5 mmol), lithium hydroxide (0.036 g, 1.5 mmol), and molecular sieves (beads, 4−8 mesh, 1.5 g/mmol aldehyde) in dry tetrahydrofuran (10 mL) was refluxed under argon for 24 h. The reaction mixture was then cooled to room temperature, filtered through a thin pad of celite and the solvent evaporated under reduced pressure. The residual oil was purified by chromatography on silica gel eluting with ether−petroleum ether (bp 40−60 °C) 1/9.

**Ethyl (2*E*,4*E*)-5-(4-Hexyloxy-phenyl)-penta-2,4-dienoate (16a).** Yield 71%; white solid; mp 68−69 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.48−7.20 (3H, m, CH, Ph), 6.90−6.75 (3H, m, CH, Ph), 6.71 (1H, d, $J = 15.4$ Hz, CH), 5.94 (1H, d, $J = 15.4$ Hz, CHCOO), 4.23 (2H, q, $J = 7.4$ Hz, $OCH_2CH_3$), 3.97 (2H, t, $J = 6.2$ Hz, $CH_2O$), 1.85−1.62 (2H, m, $CH_2CH_2O$), 1.45−1.02 (9H, m, 3 × $CH_2$, $CH_3$), 0.92 (3H, t, $J = 6.8$ Hz, $CH_3$). $^{13}$C NMR: $\delta$ 167.2

(COO), 160.0 (Ph), 145.0 (CH), 140.2 (CH), 131.9 (Ph), 128.6 (Ph), 123.9 (CH), 119.9 (CH), 114.7 (Ph), 68.0 ($CH_2O$), 60.2 ($OCH_2CH_3$), 31.6 ($CH_2$), 29.1 ($CH_2$), 25.7 ($CH_2$), 22.6 ($CH_2$), 14.3 ($CH_3$), 14.0 ($CH_3$). Anal. ($C_{19}H_{26}O_3$) C, H.

**Ethyl (2*E*,4*E*)-5-(4-Decyloxy-phenyl)-penta-2,4-dienoate (16b).** Yield 65%; white solid; mp 80−81 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.45−7.38 (3H, m, CH, Ph), 6.88−6.80 (3H, m, CH, Ph), 6.78 (1H, d, $J$ = 12 Hz, CH), 5.94 (1H, d, $J$ = 15.4 Hz, CHCOO), 4.23 (2H, q, $J$ = 7.4 Hz, $OCH_2CH_3$), 3.97 (2H, t, $J$ = 6.6 Hz, $CH_2O$), 1.81−1.75 (2H, m, $CH_2CH_2O$), 1.50−1.14 (17H, m, 7 × $CH_2$, $CH_3$), 0.89 (3H, t, $J$ = 6.8 Hz, $CH_3$). $^{13}$C NMR: $\delta$ 167.3 (COO), 160.0 (Ph), 145.1 (CH), 140.2 (CH), 131.9 (Ph), 128.6 (Ph), 124.0 (CH), 119.9 (CH), 114.8 (Ph), 68.1 ($CH_2O$), 60.2 ($OCH_2CH_3$) 31.9 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$), 26.0 ($CH_2$), 22.7 ($CH_2$), 14.3 ($CH_3$), 14.1 ($CH_3$). Anal. ($C_{23}H_{34}O_3$) C, H.

**Wittig Olefination.** A solution of aldehyde **14a** or **14b** (1 mmol) and methyl (triphenylphosphanylidene)acetate (0.334 g, 1 mmol) in dry dichloromethane (3 mL) was refluxed under argon for 24 h. The reaction mixture was then cooled to room temperature and the solvent evaporated under reduced pressure. The residual oil was purified by flash column chromatography on silica gel eluting with EtOAc−petroleum ether (bp 40−60 °C) 1/9.

**Methyl (*E*)-3-(4-Hexyloxy-phenyl)-acrylate (15a).** Yield 93%; white solid; mp 84−85 °C. H NMR ($CDCl_3$): $\delta$ 7.63 (1H, d, $J$ = 15.8 Hz, $CH$ = CHCO), 7.43 (2H, d, $J$ = 8.8 Hz, Ph), 6.87 (2H, d, $J$ = 8.8 Hz, Ph), 6.28 (1H, d, $J$ = 15.8 Hz, CHCOO), 3.95 (2H, t, $J$ = 6.4 Hz, $CH_2O$), 3.77 (3H, s, $OCH_3$), 1.76 (2H, m, $CH_2CH_2O$), 1.46−1.21 (6H, m, 3 × $CH_2$), 0.89 (3H, t, $J$ = 6.8 Hz, $CH_3$). $^{13}$C NMR: $\delta$ 167.7 (COO), 161.0 (Ph), 144.6 (CH), 129.6 (Ph), 126.8 (Ph), 115.0 (CH), 114.7 (Ph), 68.1 ($CH_2O$), 51.5 ($OCH_3$), 31.5 ($CH_2$), 29.0 ($CH_2$), 25.6 ($CH_2$), 22.5 ($CH_2$), 13.9 ($CH_3$). Anal. ($C_{16}H_{22}O_3$) C, H.

**Methyl (*E*)-3-(4-Decyloxy-phenyl)-acrylate (15b).** Yield 92%; white solid; mp 75−76 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.63 (1H, d, $J$ = 15.8 Hz, $CH$ = CHCOO), 7.37 (2H, d, $J$ = 8.8 Hz, Ph), 6.85 (2H, d, $J$ = 8.8 Hz, Ph), 6.23 (1H, d, $J$ = 15.8 Hz, CHCOO), 3.87 (2H, t, $J$ = 6.6 Hz, $CH_2O$), 3.71 (3H, s, $OCH_3$), 1.78−1.62 (2H, m, $CH_2CH_2O$), 1.40−1.22 (14H, m, 7 × $CH_2$), 0.84 (3H, t, $J$ = 7 Hz, $CH_3$). $^{13}$C NMR: $\delta$ 167.4 (COO), 160.8 (Ph), 144.3 (CH), 129.4 (Ph), 126.6 (Ph), 114.8 (CH), 114.5 (Ph), 67.8 ($CH_2O$), 51.2 ($OCH_3$), 31.7 ($CH_2$), 29.4 ($CH_2$), 29.2 ($CH_2$), 29.1 ($CH_2$), 29.0 ($CH_2$), 25.8 ($CH_2$), 22.5 ($CH_2$), 13.9 ($CH_3$). Anal. ($C_{20}H_{30}O_3$) C, H.

**Hydrogenation and Saponification of Unsaturated Esters.** A mixture of the unsaturated ester (0.7 mmol) in dry 1,4-dioxane (7 mL) and 10% palladium on activated carbon (0.07 g) was hydrogenated for 12 h under atmospheric conditions. After filtration through a pad of celite, the solvent was removed in vacuo to give the saturated compound.

The solution of the saturated ester in methanol (1.4 mL) was treated with sodium hydroxide 1N (1 mL, 1 mmol). The mixture was stirred at room temperature for 12 h, acidified with 1N HCl and extracted with EtOAc (3 × 10 mL). The solvent was removed in vacum to afford the saturated acid as a white solid.

**3-(4-Hexyloxy-phenyl)-propanoic acid (17a).** Yield 90%; white solid; mp 70−72 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.14 (2H, d, $J$ = 8.2 Hz, Ph), 6.86 (2H, d, $J$ = 8.2 Hz, Ph), 3.96 (2H, t, $J$ = 6.6 Hz, $CH_2O$), 2.93 (2H, t, $J$ = 7.6 Hz, $CH_2$), 2.67 (2H, t, $J$ = 7.6 Hz, $CH_2$), 1.76−1.60 (2H, m, $CH_2$), 1.41−1.30 (6H, m, 3 × $CH_2$), 0.92 (3H, t, $J$ = 6.7 Hz, $CH_3$). $^{13}$C NMR: $\delta$ 179.0 (COO), 157.6 (Ph), 132.0 (Ph), 129.1 (Ph), 114.5(Ph), 67.9 ($CH_2O$), 35.9 ($CH_2$), 31.5 ($CH_2$), 29.7 ($CH_2$), 29.2 ($CH_2$), 25.7 ($CH_2$), 22.5 ($CH_2$), 14.0 ($CH_3$). Anal. ($C_{15}H_{22}O_3$) C, H.

**3-(4-Decyloxy-phenyl)-propanoic acid (17b).** Yield 96%; white solid; mp 74−76 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.14 (2H, d, $J$ = 8.2 Hz, Ph), 6.86 (2H, d, $J$ = 8.2 Hz, Ph), 3.95 (2H, t, $J$ = 6.5 Hz, $CH_2O$), 2.93 (2H, t, $J$ = 7.7 Hz, $CH_2CH_2COO$), 2.67 (2H, t, $J$ = 7.7 Hz, $CH_2COO$), 1.85−1.68 (2H, m, $CH_2CH_2O$), 1.50−1.21 (14H, br s, 7 × $CH_2$), 0.92 (3H, t, $J$ = 6.2 Hz, $CH_3$). $^{13}$C NMR: $\delta$ 179.3 (COO), 157.6 (Ph), 132.0 (Ph), 129.1 (Ph), 114.5 (Ph), 67.9 ($CH_2O$), 35.9 ($CH_2$), 31.9 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 26.0 ($CH_2$), 22.6 ($CH_2$), 14.1 ($CH_3$). Anal. ($C_{19}H_{30}O_3$) C, H.

**5-(4-Hexyloxy-phenyl)-pentanoic acid (18a).** Yield 96%; white solid; mp 90−91 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.03 (2H, d, $J$ = 8.4 Hz, Ph), 6.77 (2H, d, $J$ = 8.4 Hz, Ph), 3.88 (2H, t, $J$ = 6.2 Hz, $CH_2O$), 2.52 (2H, t, $J$ = 6.8 Hz, $CH_2$), 2.32 (2H, t, $J$ = 6.7 Hz, $CH_2COO$), 1.80−1.60 (6H, m, 3 × $CH_2$), 1.60−1.21 (6H, m, 3 × $CH_2$), 0.89 (3H, t, $J$ = 6.7 Hz, $CH_3$). $^{13}$C NMR: $\delta$ 180.1 (COO), 157.3 (Ph), 133.9 (Ph), 129.2 (Ph), 114.4 (Ph), 68.0 ($CH_2O$), 34.6 ($CH_2$), 33.9 ($CH_2$), 31.6 ($CH_2$), 31.0 ($CH_2$), 29.3 ($CH_2$), 25.7 ($CH_2$), 24.2 ($CH_2$), 22.6 ($CH_2$), 14.0 ($CH_3$). Anal. ($C_{17}H_{26}O_3$) C, H.

**5-(4-Decyloxy-phenyl)-pentanoic acid (18b).** Yield 94%; white solid; mp 101−102 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.08 (2H, d, $J$ = 8.4 Hz, Ph), 6.82 (2H, d, $J$ = 8.4 Hz, Ph), 3.93 (2H, t, $J$ = 6.2 Hz, $CH_2O$), 2.57 (2H, t, $J$ = 6.8 Hz, $PhCH_2$), 2.37 (2H, t, $J$ = 7 Hz, $CH_2COOH$), 1.80−1.60 (6H, m, 3 × $CH_2$), 1.51−1.22 (14H, m, 7 × $CH_2$), 0.89 (3H, t, $J$ = 6.6 Hz, $CH_3$). $^{13}$C NMR: $\delta$ 179.5 (COO), 157.2 (Ph), 133.8 (Ph), 129.1 (Ph), 114.3 (Ph), 67.9 ($CH_2O$), 34.5 ($CH_2$), 33.8 ($CH_2$), 31.8 ($CH_2$), 30.9 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$), 26.0 ($CH_2$), 24.2 ($CH_2$), 22.6 ($CH_2$), 14.0 ($CH_3$). Anal. ($C_{21}H_{34}O_3$) C, H.

**Methyl 2-Fluoro-hexadecanoate (25).** Compound **24** (1 mmol) was added to a solution of DAST (0.14 mL, 1 mmol) in dry dichloromethane (0.2 mL) at −78 °C. After stirring for 2 h at −78 °C and another 3 h at room temperature, the reaction mixture quenched with saturated aqueous $NaHCO_3$ (2.5 mL). The organic phase was then washed with brine and dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure, and the residual oil was purified by flash column chromatography on silica gel eluting with EtOAc−petroleum ether (bp 40−60 °C) 3/7. Yield 64%; yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 4.86 (1H, dt, $J_{H-F}$ = 49.2 Hz, $J_{H-H}$ = 6.6 Hz, CH), 3.74 (3H, s, $OCH_3$), 2.00−1.72 (2H, m, $CH_2$), 1.45−1.10 (24H, br, 12 × $CH_2$), 0.83 (3H, t, $J$ = 6.2 Hz, $CH_3$). $^{13}$C NMR: $\delta$ 170.4 (d, $J_{C-C-F}$ = 24 Hz, COO), 88.9 (d, $J_{C-F}$ = 183 Hz, CF), 52.0 ($OCH_3$), 32.3 (d, $J_{C-C-F}$ = 21, $CH_2$), 31.9 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$), 29.0 ($CH_2$), 24.6 ($CH_2$), 24.4 ($CH_2$), 24.3 ($CH_2$), 22.7 ($CH_2$), 14.0 ($CH_3$). $^{19}$F NMR: $\delta$ −120.8 (m, CF). Anal. ($C_{17}H_{33}FO_2$) C, H.

**1,1,1,3-Tetrafluoro-heptadecan-2-one (in Equilibrium with 1,1,1,3-Tetrafluoro-heptadecane-2,2-diol) (26).** A solution of compound **25** (173 mg, 0.6 mmol) and trifluoromethyltrimethylsilane (170 $\mu$L, 1.15 mmol) in ethylene glycol dimethyl ether (0.55 mL) at 0 °C was treated with cesium fluoride (3 mg). After stirring for 30 min at 0 °C and another 18 h at 25 °C the reaction mixture was treated with concentrated HCl (1 mL). After stirring for another 18 h at 25 °C, the reaction mixture was diluted with EtOAc (10 mL). The organic phase was then washed with brine and dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure, and the residual oil was purified by flash column chromatography on silica gel eluting with EtOAc−petroleum ether (bp 40−60 °C) 3/7. Yield 58%; white solid; mp 34−35 °C. $^1$H NMR ($CDCl_3$): $\delta$ 5.23 (1/3H, dt, $J_{H-F}$ = 48.2 Hz, $J_{H-H}$ = 6.2 Hz, CH), 4.65 (2/3H, dt, $J_{H-F}$ = 49.4 Hz, $J_{H-H}$ = 6.6 Hz, CH), 3.74 (2/3H, s, OH), 3.49 (2/3H, s, OH), 2.08−1.27 (26H, m, 13 × $CH_2$), 0.89 (3H, t, $J$ = 7 Hz, $CH_3$). $^{13}$C NMR: $\delta$ 122.6 (q, $J_{C-F3}$ = 286 Hz, $CF_3$), 115.4 (q, $J_{C-F3}$ = 290 Hz, $CF_3$), 92.9 [$C(OH)_2$], 92.4 (d, $J_{C-F}$ = 186 Hz, CF), 32.1 ($CH_2$), 31.6 (d, $J_{C-C-F}$ = 20 Hz, $CH_2$), 29.9 ($CH_2$), 29.8 ($CH_2$), 29.7 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.1 ($CH_2$), 28.5 ($CH_2$), 28.1 ($CH_2$), 22.7 ($CH_2$), 22.3 ($CH_2$), 14.3 ($CH_3$). $^{19}$F NMR: $\delta$ 1.6 ($CF_3$), −5.3 ($CF_3$), −121.7 (CF). MS (ESI) *m*/*z* (%): 343 ($M^-$, 100).

**Ethyl 2,2-Difluoro-5-phenyl-pentanoate (29).** To a stirring mixture of magnesium (350 mg, 14.6 mmol) and iodine in dry THF (10 mL), (3-bromo-propyl)-benzene (2.87 g, 14.4 mmol) was added dropwise under $N_2$ atmosphere. Once the Grignard reagent was formed, the resulting mixture was added dropwise to a cooled (−78 °C) solution of diethyl oxalate (1.6 mL, 11.8 mmol) in dry ether (17.3 mL). The reaction mixture was stirred at −78 °C for 45 min and then was quenched with 1N HCl. The aqueous layer was extracted with ether (3 × 25 mL) and the combined organic layers

were washed with brine, dried ($Na_2SO_4$) and the solvent was evaporated in vacuo. After flash column chromatography, a mixture of methyl 2-*oxo*-5-phenyl-pentanoate (**28**) with diethyl oxalate was obtained and treated with DAST (1 equib) at room temperature. After stirring for 4 h at 45 °C, the reaction mixture was quenched with ice−water. The reaction mixture was diluted with dichlolomethane, and the organic phase was then washed with brine and dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure, and the residual oil was purified by flash column chromatography on silica gel eluting with EtOAc−petroleum ether (bp 40−60 °C) 1/9. Yield 69%; yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.38−7.12 (5H, m, Ph), 4.30 (2H, q, $J$ = 6.8 Hz, $OCH_2$), 2.68 (2H, t, $J$ = 7.4 Hz, $PhCH_2$), 2.21−1.93 (2H, m, $CH_2CF_2$), 1.90−1.75 (2H, m, $CH_2$), 1.34 (3H, t, $J$ =6.8 Hz, $CH_3$). $^{13}$C NMR: $\delta$ 164.2 (t, $J_{C-C-F}$ = 24 Hz, COO), 140.9 (Ph), 128.4 (Ph), 128.3 (Ph), 126.1 (Ph), 116.2 (t, $J_{C-F}$ = 248 Hz, $CF_2$), 62.7 ($OCH_2$), 34.9 ($CH_2$), 33.8 (t, $J_{C-C-F}$ = 23 Hz, $CH_2CF_2$), 23.0 (t, $J_{C-C-C-F}$ = 4 Hz, $CH_2CH_2CF_2$), 13.8 ($CH_3$). $^{19}$F NMR: $\delta$ 28.0 (t, $J$ = 17 Hz, $CF_2$). Anal. ($C_{13}H_{16}F_2O_2$) C, H.

**1,1,1,3,3-Pentafluoro-6-phenyl-hexane-2,2-diol (30).** It was prepared following the method used for the synthesis of compound **26**. Yield 35%; yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.41−7.18 (5H, m, Ph), 3.93 (2H, br, 2 × OH), 2.69 (2H, t, $J$ = 7.6 Hz, $PhCH_2$), 2.22−1.88 (4H, m, 2 × $CH_2$). $^{13}$C NMR: $\delta$ 141.3 (Ph), 128.4 (Ph), 126.3 (Ph), 126.1 (Ph), 121.5 (q, $J$ = 286 Hz, $CF_3$), 120.7 (t, $J$ = 249 Hz, $CF_2$), 92.3 [$C(OH)_2$], 35.2 ($CH_2$), 30.8 (t, $J_{C-C-F2}$ = 23 Hz, $CH_2CF_2$), 22.5 (t, $J_{C-C-C-F2}$ = 2.4 Hz, $CH_2CH_2CF_2$). $^{19}$F NMR: $\delta$ −3.2 ($CF_3$), −36.4 ($CF_2$). MS (ESI) *m*/*z* (%): 283 ($M^-$, 65), 213 (100). Anal. ($C_{12}H_{13}F_5O_2$) C, H.

**2-Hydroxy-5-phenyl-pentanenitrile (32).**[62] A solution of 4-phenylbutanal **31** (0.56 g, 3.78 mmol) and $NaHSO_3$ (0.59 g in 1 mL $H_2O$) in dichloromethane was stirred for 30 min at room temperature. After the formation of the white salt, the organic solvent was evaporated and water (3.8 mL) was added. The mixture cooled to 0 °C and an aqueous solution of KCN (0.368 g, 567 mmol in 1 mL $H_2O$) was added dropwise. The reaction mixture was stirred for another 18 h at room temperature and then $CH_2Cl_2$ (10 mL) and water (10 mL) were added. The organic phase was washed with brine and dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure and the residual oil was purified by flash column chromatography on silica gel eluting with EtOAc−petroleum ether (bp 40−60 °C) 2/8 to give 0.653 g (99%) of the title compound as a clear oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.32−7.15 (5H, m, Ph), 4.40 (1H, t, $J$ = 8.8 Hz, CH), 2.63 (2H, t, $J$ = 6.6 Hz, $CH_2$), 1.90−1.70 (4H, m, 2 × $CH_2$). $^{13}$C NMR: 141.5 (Ph), 128.7 (Ph), 128.6 (Ph), 126.3 (Ph), 120.4 (CN), 61.2 (CH), 35.3 ($CH_2$), 34.7 ($CH_2$), 26.4 ($CH_2$). Anal. ($C_{11}H_{13}NO$) C, H.

**Methyl 2-Hydroxy-5-phenyl-pentanoate (33).**[63] Compound **32** (0.63 g, 3.59 mmol) was treated with HCl (0.6 mL·6N) in MeOH for 18 h at room temperature. The organic solvent was evaporated and an aqueous solution of $K_2CO_3$ was added to neutralize the pH of the mixture. After extraction with EtOAc (3 × 15 mL), the combined organic phases were washed with brine and dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure, and the residual oil was purified by flash column chromatography on silica gel eluting with EtOAc−petroleum ether (bp 40−60 °C) 3/7 to give 0.56 g (79%) of the title compound as a clear oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.30−7.12 (5H, m, Ph), 4.22 (1H, t, $J$ = 4.0 Hz, CH), 3.74 (3H, s, $OCH_3$), 3.18 (1H, s, OH), 2.66 (2H, t, $J$ = 6.6 Hz, $CH_2$), 1.85−1.62 (4H, m, 2 × $CH_2$). $^{13}$C NMR: 175.4 (COO), 141.6 (Ph), 128.1 (Ph), 128.0 (Ph), 125.5 (Ph), 70.1 (CHOH), 52.1 ($OCH_3$), 35.2 ($CH_2$), 33.6 ($CH_2$), 26.3 ($CH_2$). Anal. ($C_{12}H_{16}O_3$) C, H.

**Methyl 2-*oxo*-5-Phenyl-pentanoate (34).** Compound **33** (0.20 g, 0.96 mmol) was dissolved in $CH_2Cl_2$ (20 mL) and treated with Dess−Martin periodinane (0. 43 g) under stirring for 40 min. The organic phase was washed with brine and dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure and the residual oil was purified by flash column chromatography on silica gel eluting with EtOAc−petroleum ether (bp 40−60 °C) 3/7 to give 0.195 g (99%) of the title compound as an yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.31−7.15 (5H, m, Ph), 3.85 (3H, s, $OCH_3$), 2.86 (2H, t, $J$ = 6.6 Hz, $CH_2$), 2.63 (t, $J$ = 6.6 Hz, 2H, $CH_2$), 1.71−1.62 (2H, m, $CH_2$). $^{13}$C NMR: 194.0 (CO), 161.2 (COO), 141.8 (Ph), 128.3 (Ph), 128.0 (Ph), 125.8 (Ph), 52.8 ($OCH_3$), 35.5 ($CH_2$), 30.5 ($CH_2$), 22.5 ($CH_2$). Anal. ($C_{12}H_{14}O_3$) C, H.

**Methyl 2,2-Difluoro-5-phenyl-pentanoate (35).** A solution of compound **34** (0.404 g, 1.67 mmol) in $CH_2Cl_2$ (3.3 mL) was treated dropwise with DAST (0.489 mL, 3.6 mmol) at room temperature. After heating at 55 °C for 5 h, it was poured into $H_2O$, cautiously neutralized by the addition of solid $K_2CO_3$, and extracted with $CHCl_3$ (2 × 15 mL). The organic solvent was dried over $Na_2SO_4$, filtered, and evaporated and the crude product purified by flash column chromatography on silica gel eluting with EtOAc−petroleum ether (bp 40−60 °C) 1/9 to give 0.202 g (50%) of the title compound as an yellowish oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.32−7.12 (5H, m, Ph), 4.10 (3H, s, $OCH_3$), 2.69 (2H, t, $J$ = 7.4 Hz, $PhCH_2$), 2.21−1.90 (2H, m, $CH_2CF_2$), 1.80−1.72 (2H, m, $CH_2$). $^{13}$C NMR: $\delta$ 164.2 (t, $J_{C-C-F}$ = 33 Hz, COO), 140.9 (Ph), 128.4 (Ph), 128.3 (Ph), 126.1 (Ph), 116.2 (t, $J_{C-F}$ = 248 Hz, $CF_2$), 52.7 ($OCH_3$), 34.9 ($CH_2$), 33.8 (t, $J_{C-C-F}$ = 23 Hz, $CH_2CF_2$), 23.0 (t, $J_{C-C-C-F}$ = 2.4 Hz, $CH_2CH_2CF_2$). $^{19}$F NMR: $\delta$ −28.0 (2F, t, $J$ = 17 Hz, $CF_2$). MS (ESI) *m*/*z* (%): 229 ($M^+$ + 1, 100). Anal. ($C_{12}H_{14}F_2O_2$) C, H.

**In Vitro $PLA_2$ Assays.** Phospholipase $A_2$ activity was determined using the previously described modified Dole assay[20] with buffer and substrate conditions optimized for each enzyme as described previously:[20,21,24,25] (i) GIVA cPLA$_2$ substrate mixed-micelles were composed of 400 $\mu$M Triton X-100, 97 $\mu$M PAPC, 1.8 $\mu$M $^{14}$C-labeled PAPC, and 3 $\mu$M $PIP_2$ in buffer containing 100 mM HEPES pH 7.5, 90 $\mu$M $CaCl_2$, 2 mM DTT, and 0.1 mg/mL BSA, (ii) GVIA iPLA$_2$ substrate mixed-micelles were composed of 400 $\mu$M Triton X-100, 99 $\mu$M DPPC, and 1.5 $\mu$M $^{14}$C-labeled DPPC in buffer containing 200 mM HEPES pH 7.0, 1 mM ATP, 2 mM DTT, and 0.1 mg/ml BSA, and (iii) GV sPLA$_2$ substrate mixed-micelles were composed of 400 $\mu$M Triton X-100, 99 $\mu$M DPPC, and 1.5 $\mu$M $^{14}$C-labeled DPPC in buffer containing 50 mM Tris pH 8.0 and 5 mM $CaCl_2$.

**In Vitro $PLA_2$ Inhibition Studies.** Initial screening of compounds at 0.091 mol fraction inhibitor in mixed-micelles was carried out. We considered compounds displaying 25% or less inhibition to have no inhibitory affect (designated N.D.). We report average percent inhibition (and standard error, $n$ = 3) for compounds displaying more than 25% and less than 90% enzyme inhibition. If percent inhibition was greater than 90%, we determined its $X_I(50)$ by plotting percent inhibition vs inhibitor molar fraction (7 points; typically 0.005−0.091 mol fraction). Inhibition curves were modeled in Graphpad Prism using either a linear ($x$, $y$ intercept = 0) or nonlinear regression (one-site binding model, hyperbola, BMAX = 100) to calculate the reported $X_I(50)$ and associated error values.

**Acknowledgment.** This work was supported by NIH GM 20,501 and GM64611 (E.A.D.). The project is cofunded by the European Social Fund and National Resources (EPEAEK II) (G.K.).

**Supporting Information Available:** Elemental analysis results for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Schaloske, R. H.; Dennis, E. A. The phospholipase A(2) superfamily and its group numbering system. *Biochim. Biophys. Acta* **2006**, *1761*, 1246–1259.
(2) Kudo, I.; Murakami, M. Phospholipase A(2) enzymes. *Prostaglandins Other Lipid Mediators* **2002**, *68−69*, 3–58.
(3) Leslie, C. C. Regulation of the specific release of arachidonic acid by cytosolic phospholipase A2. *Prostaglandins Leukotrienes Essent. Fatty Acids* **2004**, *70*, 373–376.
(4) Winstead, M. V.; Balsinde, J.; Dennis, E. A. Calcium-independent phospholipase A(2): structure and function. *Biochim. Biophys. Acta* **2000**, *1488*, 28–39.
(5) Balsinde, J.; Balboa, M. A. Cellular regulation and proposed biological functions of group VIA calcium-independent phospholipase A(2) in activated cells. *Cell. Signalling* **2005**, *17*, 1052–1062.

(6) Berg, O. G.; Gelb, M. H.; Tsai, M.-D.; Jain, M. K. Interfacial enzymology: The secreted phospholipase $A_2$-paradigm. *Chem. Rev.* **2001**, *101*, 2613–2654.

(7) Balestrieri, B.; Arm, J. P. Group V $sPLA_2$: Classical and novel functions. *Biochim. Biophys. Acta* **2006**, *1761*, 1280–1288.

(8) Mounier, C. M.; Ghomashchi, F.; Lindsay, M. R.; James, S.; Singer, A. G.; Parton, R. G.; Gelb, M. H. Arachidonic acid release from mammalian cells transfected with human groups IIA and X secreted phospholipase $A_2$ occurs predominantly during the secretory process and with the involvement of cytosolic phospholipase $A_2$-$\alpha$. *J. Biol. Chem.* **2004**, *279*, 25024–25038.

(9) Satake, Y.; Diaz, B. L.; Balestrieri, B.; Lam, B. K.; Kanaoka, Y.; Grusby, M. J.; Arm, J. P. Role of group V phospholipase A2 in zymosan-induced eicosanoid generation and vascular permeability revealed by targeted gene disruption. *J. Biol. Chem.* **2004**, *279*, 16488–16494.

(10) Shirai, Y.; Balsinde, J.; Dennis, E. A. Localization and functional interrelationships among cytosolic Group IV, secreted Group V, and $Ca^{2+}$-independent Group VI phospholipase A2s in P388D1 macrophages using GFP/RFP constructs. *Biochim. Biophys. Acta* **2005**, *1735*, 119–129.

(11) Magrioti, V.; Kokotos, G. Synthetic inhibitors of Group IVA and Group VIA phospholipase $A_2$. *Anti-Inflammatory Anti-Allergy Agents Med. Chem.* **2006**, *5*, 189–203.

(12) Reid, R. C. Inhibitors of secretory phospholipase $A_2$ Group IIA. *Curr. Med. Chem* **2005**, *12*, 3011–3026.

(13) Seno, K.; Okuno, T.; Nishi, K.; Murakami, Y.; Yamada, K.; Nakamoto, S.; Ono, T. Pyrrolidine inhibitors of human cytosolic phospholipase $A_2$. Part 2: synthesis of potent and crystallized 4-triphenylmethylthio derivative "Pyrrophenone". *Bioorg. Med. Chem. Lett.* **2001**, *11*, 587–590.

(14) Ludwig, J.; Bovens, S.; Brauch, C.; Elfringhoff, A. S.; Lehr, M. Design and synthesis of 1-indol-1-yl-propan-2-ones as inhibitors of human cytosolic phospholipase A(2)alpha. *J. Med. Chem.* **2006**, *49*, 2611–2620.

(15) Hess, M.; Elfringhoff, A. S.; Lehr, M. 1-(5-Carboxy- and 5-carbamoylindol-1-yl)propan-2-ones as inhibitors of human cytosolic phospholipase $A_2\alpha$: Bioisosteric replacement of the carboxylic acid and carboxamide moiety. *Bioorg. Med. Chem.* **2007**, *15*, 2883–2891.

(16) Fritsche, A.; Elfringhoff, A. S.; Fabian, J.; Lehr, M. 1-(2-Carboxyindol-5-yloxy)propan-2-ones as inhibitors of human cytosolic phospholipase $A_2\alpha$: Synthesis, biological activity, metabolic stability, and solubility. *Bioorg. Med. Chem.* **2008**, *16*, 3489–3500.

(17) Lee, K. L.; Foley, M. A.; Chen, L. R.; Behnke, M. L.; Lovering, F. E.; Kirincich, S. J.; Wang, W. H.; Shim, J.; Tam, S.; Shen, M. W. H.; Khor, S. P.; Xu, X.; Goodwin, D. G.; Ramarao, M. K.; Nickerson-Nutter, C.; Donahue, F.; Ku, M. S.; Clark, J. D.; Mckew, J. C. Discovery of ecopladib, an indole inhibitor of cytosolic phospholipase A(2)alpha. *J. Med. Chem.* **2007**, *50*, 1380–1400.

(18) Lee, K. L.; Behnke, M. L.; Foley, M. A.; Chen, L.; Wang, W.; Vargas, R.; Nunez, J.; Tam, S.; Mollova, N.; Xu, X.; Shen, M. W. H.; Ramarao, M. K.; Goodwin, D. G.; Nickerson-Nutter, C. L.; Abraham, W. M.; Williams, C.; Clark, J. D.; McKew, J. C. Benzenesulfonamide indole inhibitors of cytosolic phospholipase $A_2\alpha$: Optimization of in vitro potency and rat pharmacokinetics for oral efficacy. *Bioorg. Med. Chem.* **2008**, *16*, 1345–1358.

(19) McKew, J. C.; Lee, K. L.; Shen, M. W. H.; Thakker, P.; Foley, M. A.; Behnke, M. L.; Hu, B.; Sum, F.-W.; Tam, S.; Hu, Y.; Chen, L.; Kirincich, S. J.; Michalak, R.; Thomason, J.; Ipek, M.; Wu, K.; Wooder, L.; Ramarao, M. K.; Murphy, E. A.; Goodwin, D. G.; Albert, L.; Xu, X.; Donahue, F.; Ku, M. S.; Keith, J.; Nickerson-Nutter, C. L.; Abraham, W. M.; Williams, C.; Hegen, M.; Clark, J. D. Indole cytosolic phospholipase $A_2$ $\alpha$ inhibitors: Discovery and in vitro and in vivo characterization of 4-{3-[5-Chloro-2-(2-{[(3,4-dichlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoic acid, efipladib. *J. Med. Chem.* **2008**, *51*, 3388–3413.

(20) Kokotos, G.; Kotsovolou, S.; Six, D. A.; Constantinou-Kokotou, V.; Beltzner, C. C.; Dennis, E. A. Novel 2-oxoamide inhibitors of human Group IVA phospholipase $A_2$. *J. Med. Chem.* **2002**, *45*, 2891–2893.

(21) Kokotos, G.; Six, D. A.; Loukas, V.; Smith, T.; Constantinou-Kokotou, V.; Hadjipavlou-Litina, D.; Kotsovolou, S.; Chiou, A.; Beltzner, C. C.; Dennis, E. A. Inhibition of Group IVA cytosolic phospholipase $A_2$ by novel 2-oxoamides in vitro, in cells and in vivo. *J. Med. Chem.* **2004**, *47*, 3615–3628.

(22) Constantinou-Kokotou, V.; Peristeraki, A.; Kokotos, C. G.; Six, D. A.; Dennis, E. A. Synthesis and activity of 2-oxoamides containing long chain beta-amino acids. *J. Pept. Sci.* **2005**, *11*, 431–435.

(23) Yaksh, T. L.; Kokotos, G.; Svensson, C. I.; Stephens, D.; Kokotos, C. G.; Fitzsimmons, B.; Hadjipavlou-Litina, D.; Hua, X.-Y.; Dennis, E. A. Systemic and intrathecal effects of a novel series of phospholipase A(2) inhibitors on hyperalgesia and spinal prostaglandin E-2 release. *J. Pharmacol. Exp. Ther.* **2006**, *316*, 466–475.

(24) Stephens, D.; Barbayianni, E.; Constantinou-Kokotou, V.; Peristeraki, A.; Six, D. A.; Cooper, J.; Harkewicz, R.; Deems, R. A.; Dennis, E. A.; Kokotos, G. Differential inhibition of Group IVA and Group VIA phospholipases A(2) by 2-oxoamides. *J. Med. Chem.* **2006**, *49*, 2821–2828.

(25) Six, D. A.; Barbayianni, E.; Loukas, V.; Constantinou-Kokotou, V.; Hadjipavlou-Litina, D.; Stephens, D.; Wong, A. C.; Magrioti, V.; Moutevelis-Minakakis, P.; Baker, S.; Dennis, E. A.; Kokotos, G. Structure−activity relationship of 2-oxoamide inhibition of group IVA cytosolic phospholipase $A_2$ and group V secreted phopholipase $A_2$. *J. Med. Chem.* **2007**, *50*, 4222–4235.

(26) Moutevelis-Minakakis, P.; Neokosmidi, A.; Filippakou, M.; Stephens, D.; Dennis, E. A.; Kokotos, G. Synthesis of lipophilic 2-oxoamides based on $\gamma$-aminobutyric and $\delta$-aminovaleric analogues and their activity against phospholipase $A_2$. *J. Pept. Sci.* **2007**, *13*, 634–641.

(27) Street, I. P.; Lin, H.-K.; Laliberte, F.; Ghomashchi, F.; Wang, Z.; Perrier, H.; Tremblay, N. M.; Huang, Z.; Weech, P. K.; Gelb, M. H. Slow- and tight-binding inhibitors of the 85-kDa human phospholipase $A_2$. *Biochemistry* **1993**, *32*, 5935–5940.

(28) Trimble, L. A.; Street, I. P.; Perrier, H.; Tremblay, N. M.; Weech, P. K.; Bernstein, M. A. NMR structural studies of the tight complex between a trifluoromethyl ketone inhibitor and the 85-kDa human phospholipase $A_2$. *Biochemistry* **1993**, *32*, 12560–12565.

(29) Amandi-Burgermeister, E.; Tibes, U.; Kaiser, B. M.; Friebe, W. G.; Scheuer, W. V. Suppression of cytokine synthesis, integrin expression and chronic inflammation by inhibitors of cytosolic phospholipase $A_2$. *Eur. J. Pharmacol.* **1997**, *326*, 237–250.

(30) Conde-Frieboes, K.; Reynolds, L. J.; Lio, Y.-C.; Hale, M. R.; Wasserman, H. H.; Dennis, E. A. Activated ketones as inhibitors of intracellular $Ca^{2+}$-dependent and $Ca^{2+}$-independent phospholipase $A_2$. *J. Am. Chem. Soc.* **1996**, *118*, 5519–5525.

(31) Ghomashchi, F.; Loo, R.; Balsinde, J.; Bartoli, F.; Apitz-Castro, R.; Clark, J. D.; Dennis, E. A.; Gelb, M. H. Trifluoromethyl ketones and methyl fluorophosphonates as inhibitors of group IV and VI phospholipases $A_2$: structure−function studies with vesicle, micelle, and membrane assays. *Biochim. Biophys. Acta* **1999**, *1420*, 45–56.

(32) Kalyvas, A.; David, S. Cytosolic phospholipase $A_2$ plays a key role in the pathogenesis of multiple sclerosis-like disease. *Neuron* **2004**, *41*, 323–335.

(33) Yeo, J.-F.; Ong, W.-Y.; Ling, S.-F.; Farooqui, A. A. Intracerebroventricular injection of phospholipases A2 inhibitors modulates allodynia after facial carrageenan injection in mice. *Pain* **2004**, *112*, 148–155.

(34) Svensson, C. I.; Lucas, K. K.; Hua, X. Y.; Powell, H. C.; Dennis, E. A.; Yaksh, T. L. Spinal phospholipase A2 in inflammatory hyperalgesia: Role of the small, secretory phospholipase $A_2$. *Neuroscience* **2005**, *133*, 543–553.

(35) Bate, C.; Reid, S.; Williams, A. Phospholipase A2 inhibitors or platelet-activating factor antagonists prevent prion replication. *J. Biol. Chem.* **2004**, *279*, 36405–36411.

(36) Risse, D.; Elfringhoff, A. S.; Lehr, M. Determination of the cell lytic properties of amphiphilic inhibitors of the cytosolic phospholipase A2 against human platelets by measuring the liberation of serotonin with high-performance liquid chromatography and fluorescence detection. *J. Chromatogr., B* **2002**, *769*, 185–190.

(37) Kazuyoshi, Y.; Kenjiro, O.; Mayumi, K.; Sei K. Japanese Patent JP09268153A, 1997.

(38) Banville, J.; Marinier, A.; Gai, Y.; Plamondon, S.; Roy, S.; Balasubramanian, N. U.S. Patent US 6,414,179 B1, 2002.

(39) Banville, J.; Plamondon, S.; Gai, Y.; Balasubramanian, N. U.S. Patent US 6,492,550 B2, 2001.

(40) Banville, J.; Remillard, R.; Balasubramanian, N.; Bouthillier, G.; Martel, A. U.S. Patent US 6,924,391 B2, 2005.

(41) Burke, J. R.; Davern, L. B.; Stanley, P. L.; Gregor, K. R.; Banville, J.; Remillard, R.; Russell, J. W.; Brassil, P. J.; Witmer, M. R.; Johnson, G.; Tredup, J. A.; Tramposch, K. M. BMS-229724 is a tight-binding inhibitor of cytosolic phospholipase A2 that acts at the lipid/water interface and possesses anti-inflammatory activity in skin inflammation models. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 376–385.

(42) Ackermann, E. J.; Conde-Frieboes, K.; Dennis, E. A. Inhibition of macrophage $Ca^{2+}$-independent phospholipase $A_2$ by bromoenol lactone and trifluoromethyl ketones. *J. Biol. Chem.* **1995**, *270*, 445–450.

(43) Müller, K.; Faeh, C.; Diederich, F. Fluorine in pharmaceuticals: Looking beyond intuition. *Science* **2007**, *317*, 1881–1886.

(44) Bohm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. Fluorine in medicinal chemistry. *ChemBioChem* **2004**, *5*, 637–643.

(45) Boivin, J.; El Kaim, L.; Zard, S. Z. A new and efficient synthesis of trifluoromethyl ketones from carboxylic acids. *Tetrahedron* **1995**, *51*, 2573–2584.

(46) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. Fluoro ketone inhibitors of hydrolytic enzymes. *Biochemistry* **1985**, *24*, 1813–1821.

(47) Kokotos, G.; Kotsovolou, S.; Verger, R. Novel trifluoromethyl ketones as potent gastric lipase inhibitors. *ChemBioChem.* **2003**, *4*, 90–95.

(48) Leanna, M. R.; Sowin, T. J.; Morton, H. E. Synthesis of α-amino and α-alkoxy aldehydes via oxoammonium oxidation. *Tetrahedron Lett.* **1992**, *33*, 5029–5032.

(49) Middleton, W. J. New fluorinating reagents. Dialkylaminosulfur fluorides. *J. Org. Chem.* **1975**, *5*, 574–578.

(50) Singh, R. P.; Cao, G.; Kirchmeier, R. L.; Shreeve, J. M. Cesium fluoride catalysed trifluoromethylation of esters, aldehydes, and ketones with (trifluoromethyl)trimethylsilane. *J. Org. Chem.* **1999**, *64*, 2873–2876.

(51) Creary, X. Reaction of organometallic reagents with ethyl trifluoroacetate and diethyl oxalate. Formation of trifluoromethyl ketones and α-keto esters via stable tetrahedral adducts. *J. Org. Chem.* **1987**, *52*, 5026–5030.

(52) Erni, B.; Khorana, H. G. Fatty acids containing photoactivable carbene precursors. Synthesis and photochemical properties of 3,3-bis(1,1-difluorohexyl)diazirine and 3-(1,1-difluorooctyl)-3*H*-diazirine. *J. Am. Chem. Soc.* **1980**, *102*, 3888–3896.

(53) Middleton, W. J.; Bingham, E. M. α,α-Difluoroarylacetic acids: preparation from (diethylamino)sulphur trifluoride and α-oxoarylacetates. *J. Org. Chem.* **1980**, *45*, 2883–2887.

(54) Yuan, W.; Berman, R. J.; Gelb, M. H. Synthesis and evaluation of phospholipid analogues as inhibitors of cobra venom phospholipase $A_2$. *J. Am. Chem. Soc.* **1987**, *109*, 8071–8081.

(55) Balsinde, J.; Dennis, E. A. Distinct roles in signal transduction for each of the phospholipase $A_2$ enzymes present in P388D1 macrophages. *J. Biol. Chem.* **1996**, *271*, 6758–6765.

(56) Balsinde, J.; Dennis, E. A. Function and inhibition of intracellular calcium-independent phospholipase $A_2$. *J. Biol. Chem.* **1997**, *272*, 16069–16072.

(57) Song, H.; Ramanadham, S.; Bao, S.; Hsu, F.-F.; Turk, J. A bromoenol lactone suicide substrate inactivates group VIA phospholipase $A_2$ by generating a diffiusible bromomethyl keto acid that alkylates cysteine thiols. *Biochemistry* **2006**, *45*, 1061–1073.

(58) López-Vales, R.; Navarro, X.; Shimizu, T.; Baskakis, C.; Kokotos, G.; Constantinou-Kokotou, V.; Stephens, D.; Dennis, E. A.; David, S. Intracellular phospholipase $A_2$ group IVA and group VIA play important roles in Wallerian degeneration and axon regeneration after peripheral nerve injury. *Brain* **2008**, *131*, 2620−2631.

(59) Leung, D.; Du, W.; Hardouin, C.; Cheng, H.; Hwang, I.; Cravatt, B. F.; Boger, D. L. Discovery of an exceptionally potent and selective class of fatty acid amide hydrolase inhibitors enlisting proteome-wide selectivity screening: concurrent optimization of enzyme inhibitor potency and selectivity. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1423–1428.

(60) Pez, D.; Leal, I.; Zuccotto, F.; Boussard, C.; Brun, R.; Croft, S. L.; Yardley, V.; Ruiz Perez, L. M.; Gonzalez Pacanowska, D.; Gilbert, I. H. 2,4-Diaminopyrimidines as inhibitors of leishmanial and trypanosomal dihydrofolate reductase. *Bioorg. Med. Chem.* **2003**, *11*, 4693–4711.

(61) Lwein, A. H.; Szewczyk, J.; Wilson, J. W.; Ivy Carroll, F. Galanthamine analogs: 6*H*-benzofuro[3*a*,3,2,-*e*,*f*][1]benzazepine and 6*H*-benzofuro[3*a*,3,2,-*e*,*f*][3]benzazepine. *Tetrahedron* **2005**, *61*, 7144–7152.

(62) Roda, G.; Riva, S.; Danieli, B. Almond oxynitrilase-catalyzed transformation of aldehydes is strongly influenced by napthyl and alkoxy substituents. *Tetrahedron: Asymmetry* **1999**, *10*, 3939–3949.

(63) Rho, H.-S.; Ko, B.-S. Regioselective deoxygenation of the cyclic thionocarbonates of 2,3-dihydroxy esters with magnesium in methanol. *Synth. Commun.* **1999**, *29*, 2875–2880.

JM800649Q