Progress toward the Development of a Safe and Effective Agent for Treating Reentrant Cardiac Arrhythmias: Synthesis and Evaluation of Ibutilide Analogues with Enhanced Metabolic Stability and Diminished Proarrhythmic Potential

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A series of ibutilide analogues with fluorine substituents on the heptyl side chain was prepared and evaluated for class III antiarrhythmic activity, metabolic stability, and proarrhythmic potential. It was found that fluorine substituents stabilized the side chain to metabolic oxidation. Many of the compounds also retained the ability to increase the refractoriness of cardiac tissue at both slow and fast pacing rates. The potential for producing polymorphic ventricular tachycardia in the rabbit model was dependent on the chirality of the benzylic carbon. The *S*-enantiomers generally had less proarrhythmic activity than the corresponding racemates. One compound from this series (**45E**, trecetilide fumarate) had excellent antiarrhythmic activity and metabolic stability and was devoid of proarrhythmic activity in the rabbit model. It was chosen for further development.

Introduction

Cardiac arrhythmias continue to represent a major source of human morbidity and mortality. It has been estimated that 2.2 million Americans have intermittent or sustained atrial fibrillation (AF)[1] which is associated with symptoms such as palpitations and chest discomfort and a high incidence of stroke and heart failure.[2] Results from the Framingham Heart Study have demonstrated a marked increase in mortality risk associated with this arrhythmia,[3] a result that has also been documented in the Manitoba Study.[4] Atrial flutter (AFL) is a related arrhythmia that is often associated with or preceded by AF.[5] Ventricular tachyarrhythmias, which are often a consequence of structural heart disease, are a major risk factor for ventricular fibrillation and sudden cardiac death (SCD). It has been estimated that SCD can account for more than 300 000 deaths annually in the United States.[6] All of these arrhythmias appear to result from the reentry of an activation wave front into newly excitable tissue in a suitable reentrant circuit.[7] Such a circuit can occur when the myocardium manifests unidirectional conduction block and the wavelength (product of the conduction velocity of the circulating wave front and the effective refractory period (ERP) of the reentrant circuit) is shorter than the length of the circuit pathway.[7] From a historical standpoint, therapy for cardiac arrhythmias began with the discovery in 1914 that a cinchona alkaloid preparation alleviated the arrhythmias of a patient that was being treated for malaria.

Quinidine, the active component of this mixture, was subsequently introduced for the treatment of cardiac arrhythmias in 1918.[8] In the 1950s the development of techniques for evaluating electrophysiologic parameters in vivo led to the recognition that a significant property of antiarrhythmic agents was the ability to prolong the ERP of relevant cardiac tissues.[9] It was also established that quinidine prolonged the ERP in ventricular myocardium, and it became accepted that this was a consequence of its primary effect: the ability to slow conduction by depressing the maximal rate of rise of the cardiac action potential.[9] In the Vaughan Williams classification,[10] this sodium channel-mediated activity became known as the class I mechanism for antiarrhythmic activity. Class I antiarrhythmic agents such as procainamide, lidocaine, and disopyramide were found to markedly suppress premature ventricular contractions (PVCs) which were believed to be a risk factor for SCD after a myocardial infarction (MI), and research during the next two decades was devoted to optimizing this activity.[9] This research culminated in the development of encainide, flecainide, and moricizine which, in 1989, were evaluated for their ability to reduce the rate of death from arrhythmia in patients with asymptomatic or mildly symptomatic ventricular arrhythmias after a MI. Although these class I agents effectively controlled the PVCs in this patient population, this pivotal Cardiac Arrhythmia Suppression Trial (CAST) was terminated prematurely when it was found that the death rate in the treated group exceeded that

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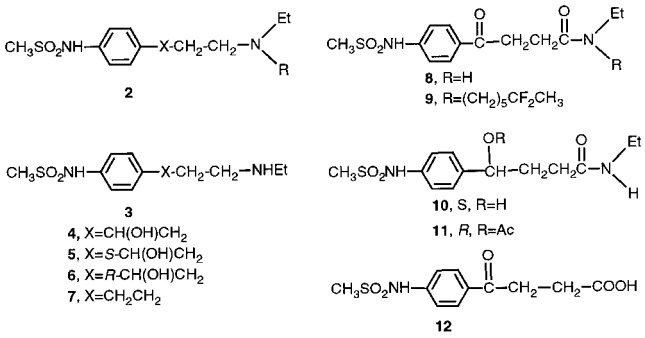
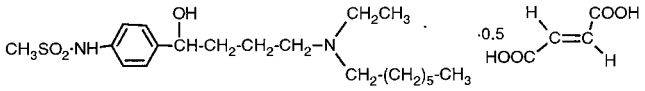
in the control group.[11,12] Subsequent analysis has suggested that class I antiarrhythmic agents predispose patients with acute myocardial ischemia to lethal arrhythmias. This appears to explain the increased mortality observed in the CAST study.[13] As a result, the use of class I agents for treating cardiac arrhythmias appears to be diminishing.[14]

Early studies with sotalol[15] and amiodarone[16] established that prolongation of the action potential duration, reflected in a prolongation of the QTc interval in the electrocardiogram, was a second method for increasing the ERP of cardiac tissue. Compounds with this mechanism of antiarrhythmic action became known as class III agents.[10] Since this time a number of compounds with relatively pure class III antiarrhythmic activity have been investigated.[17] Many of these have excellent activity for treating reentrant arrhythmias in both atrial and ventricular tissues.[17−19] Unfortunately, class III antiarrhythmic activity is associated with the precipitation of a potentially serious polymorphic ventricular tachyarrhythmia (PVT), known as torsade de pointes, in a small but significant percentage of treated patients.[20] This was perhaps anticipated by the discoveries of the Jervell and Lange−Nielsen (JLN) and Romano−Ward syndromes which are characterized by a marked prolongation of the QT interval and are often associated with syncope, seizures, or sudden death due to torsade de pointes.[21,22] In recent years these syndromes, collectively known as the congenital long-QT syndrome (LQTS), have been the subject of a series of revolutionary clinical discoveries. It is now known that LQTS is the result of inherited mutations that have been identified both in the fast sodium channel: I_{Na} (LQT_3, *SCN5A*) and in the repolarizing potassium channels: I_{Kr} (LQT_2, *HERG*), I_{Ks} (LQT_1, *KVLQT1*), and the I_{Ks} β-subunit, min K (LQT_5, *KCNE1*). Mutations in *SCN5A* can block the complete deactivation of I_{Na} thus providing a slow depolarizing sodium current, while mutations of the delayed rectifier potassium channels can slow repolarization of the action potential.[22] Historically it had been assumed that these mutations were nearly all expressed in the ECG (high penetrance) as a prolonged QTc interval which is a criterion for the clinical diagnosis of LQTS; but, several recent studies have identified families with mutations of *KVLQT1* and *HERG* genes that have a very low penetrance of the disease.[23−25] These mutations can, however, interact with QT prolonging agents to provide a marked prolongation of the QT interval, the acquired long-QT syndrome.[23] The results of these studies have major implications for the identification and treatment of individuals with these genetic abnormalities.[25] They suggest that the traditional clinical approach for identification of affected individuals may be inadequate and that the abnormality may be more widespread than originally thought. They also may have implications for the use of medications that prolong the QT interval. It might be possible, for example, to use genetic screening to identify individuals who might have an adverse reaction to such medications.[26,27]

Clinical studies of the intravenously administered class III antiarrhythmic agent, ibutilide, have found an incidence of torsade de pointes, both sustained and nonsustained, of about 4−8%. Almost without exception, however, these proarrhythmic events have occurred either during or shortly after infusion of the drug, are time-limited, and are easily controlled.[28] This suggests that initial administration of the antiarrhythmic agent in-hospital[29] might be used as an alternative method to identify patients who might be susceptible to the induction of torsade de pointes by these agents. This approach appears to have been successfully employed in the DIAMOND study of the use of dofetilide for the treatment of patients with clinical congestive heart failure and MI.[30]

Chart 1





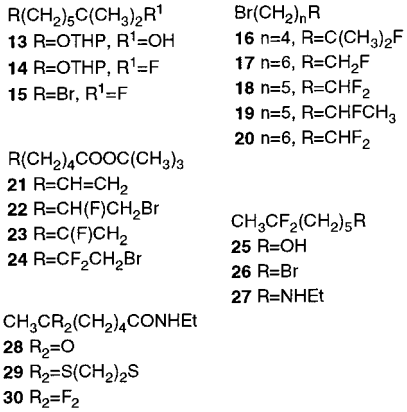
ibutilide fumarate (**1E**)

Ibutilide fumarate (**1E**, Corvert), our first class III antiarrhythmic agent from this series,[31] was introduced on the U.S. market in 1996 for the rapid conversion of AF and AFL to normal sinus rhythm. Although ibutilide is effective for the treatment of both atrial[32] and ventricular[33] tachyarrhythmias, it is limited to intravenous administration due to rapid first-pass metabolism.[32] Because of this limitation, we investigated a series of analogues designed to retain ibutilide's useful antiarrhythmic activity but prevent its rapid hepatic metabolism. In humans ibutilide is metabolized primarily by ω-oxidation of the heptyl side chain first to the alcohol and then to the carboxylic acid which is further metabolized by the β-oxidation pathway.[34] We thus concentrated our attention on modifications of the heptyl side chain that were intended to retard or prevent its metabolism. These included the incorporation of alkyl, cycloalkyl, hydroxy, acetoxy, and fluoro substituents.[35] Fluorine substitution yielded especially interesting compounds that are the subject of this report.

Chemistry

Most of the compounds in this series **2** (Table 1) were prepared by alkylating an amine **3** (Chart 1) with an appropriately substituted alkyl bromide (RBr) in refluxing acetonitrile. Sodium bicarbonate was the preferred base for this reaction. Initial evaluation suggested that stronger bases would give substantial amounts of products resulting from alkylation of the sulfonamide in addition to the basic nitrogen. Procedures A and B in the Experimental Section describe this reaction. Products from procedure B were isolated as the crystal-

Chart 2



line fumaric acid (**E**) salts. Products from procedure A were generally not crystalline, but in some cases crystalline salts were subsequently prepared. In all cases the crystalline salts were hemifumarates and are designated by the **E** suffix. Preparation of the water-soluble amine intermediate **4** for this alkylation was accomplished by lithium aluminum hydride (LAH) reduction of the ketoamide **8**. The corresponding *S*-alcohol **5** was obtained by first reducing **8** with (−)-B-chlorodiisopinocamphenylborane to give **10** which was obtained optically pure by recrystallization from solvents such as acetonitrile−*tert*-butyl methyl ether. Further reduction of **10** with sodium bis(2-methoxyethoxy)aluminum hydride using a nonaqueous workup gave **5**. Assignment of the *S*-configuration to this compound was based on related published work from this laboratory.[36] Preparation of the *R*-enantiomer **6** was accomplished by sodium bis(2-methoxyethoxy)aluminum hydride reduction of **11**, the byproduct from the preparation of **10** from the racemate by a lipase-mediated acetylation.[37] The amine **7** was prepared by LAH reduction of the corresponding amide **51**.

Fluorine was generally incorporated into the side-chain intermediates (RBr), used in the preparations of **2**, by the reaction of diethylaminosulfur trifluoride (DAST) with the appropriately substituted alcohols or aldehydes. For example, the reaction of **13**[38] (Chart 2) with DAST gave **14** which was deprotected and converted to the bromide **15** with triphenylphosphine and *N*-bromosuccinimide (NBS) (procedure C). Similar preparations to give **16**−**20** are detailed in the Experimental Section. Side-chain intermediate **26** was prepared by first alkylating *tert*-butyl acetate with 5-bromo-1-pentene to give **21** which was allowed to react with NBS and triethylamine trihydrofluoride[39] to give **22** in 75% yield. Dehydrobromination of **22** with potassium *tert*-butoxide in THF gave **23** which was resubjected to the bromofluorination conditions to give **24**. LAH reduction of **24** gave **25** which was converted to the bromide **26** by procedure C.

The olefin **50E** (Table 1) was prepared by dehydrating the corresponding alcohol **36** with trifluoroacetic acid. Assignment of the *E*-stereochemistry for this compound was based on its ^{1}H NMR. Compound **37** (Table 1) was prepared by condensing **12** with **27** and reducing the resulting ketoamide **9** with LAH. The amine **27** was prepared from *N*-ethyl-5-acetylvaleramide (**28**) using the method of Sondej and Katzenellenbogen[40] to introduce the fluorine atoms. Thus, the ethylene dithioketal **29** was prepared and treated with 1,3-dibromo-5,5-dimethylhydantoin and hydrogen fluoride−pyridine to give **30** which was reduced with LAH to give **27**.

Results and Discussion

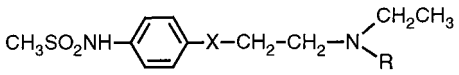
Our initial evaluation of the cardiac electrophysiology of potential antiarrhythmic agents was carried out with rabbit heart preparations.[31,41] This methodology allowed us to evaluate the effects of test compounds on conduction velocity, refractoriness, and contractility of the tissue at both a slow (1 Hz) and fast (3 Hz) pacing rate. Effects on right atrial automaticity were also evaluated. In general, compounds in this series have had little effect on the conduction velocity or contractility of cardiac tissue, and since we are primarily interested in their potential class III antiarrhythmic activity for this discussion, we have only recorded data supporting effects on refractoriness in Table 1. We have also documented in Table 1 the concentration-dependent effects of these compounds on right atrial automaticity.

Metabolic stability was initially evaluated in vitro by incubating the compounds with human liver microsomes. The *R*-(+)-enantiomer **31E** of ibutilide served as a control in these experiments, and the data were normalized to this compound as described in the Experimental Section and recorded in Table 1. Values greater than 1 indicate greater metabolic stability than **31E** in this evaluation.

When we began this study, it was becoming apparent that the propensity to cause PVT would be a potential detriment to any antiarrhythmic agent with the class III mechanism of action.[20] We, therefore, made evaluation of the proarrhythmic potential of these compounds an integral part of the program. For this purpose, we chose the anesthetized rabbit model that had been developed by Carlsson and co-workers[42] for studying the induction of early after depolarization (EAD) and torsade de pointes by agents that prolong the QT interval. EADs, depolarizing processes that occur before the action potential repolarization is complete, are associated with the initiation of PVT.[42] Using a modification of this procedure, it was found that ibutilide was less effective than several other class III agents studied for inducing EADs and PVT in anesthetized and methoxamine-treated rabbits.[43] That is, statistically fewer rabbits developed EADs and PVT when treated with ibutilide. The endpoint for this determination, therefore, became the number of animals that developed EADs and PVT when treated with the test compound. These data and the EAD amplitudes are recorded in Table 2. The maximum prolongations of the QTc and $MAPD_{90}$ which are measures of the class III efficacy are also recorded.

It is well-known that fluorine can replace a hydrogen without introducing major steric changes in the resulting molecule;[44] however, because of its inductive effect, fluorine would be expected to retard electrophilic oxidation of the substituted carbon by enzymes such as cytochrome P450.[45] We, thus, expected that fluorine substitution of the terminal carbon of ibutilide's heptyl side chain would give a compound with interesting properties. This fluoro-substituted derivative had concentration-dependent effects on ERP_1 that were very

Table 1. In Vitro Evaluation of Potential Efficacy and Stability



2

			electrophysiology[a]				
no.	X	R	concn[b]	ERP1 (*N*, SEM)	ERP3 (*N*, SEM)	rate (*N*, SEM)	metabolism[l]
1E[h,j,m]	$CH(OH)CH_2$	$(CH_2)_6CH_3$	10^{-7}	1.1 (8, 3.0)	3.0 (8, 1.1)	3.0 (4, 3.0)	NE[k]
			10^{-6}	12.0[e] (8, 4.9)	8.0 (8, 1.9)	−8.0 (4, 2.0)	
			10^{-5}	17.9[e] (8, 4.1)	16.0[e] (8, 2.1)	−21.9 (4, 0.9)	
31E[i,j]	(*R*)-$CH(OH)CH_2$	$(CH_2)_6CH_3$	10^{-7}	4.1 (6, 0.9)	4.0 (6, 0.9)	−2.0 (3, 4.2)	1
			10^{-6}	7.1 (6, 2.0)	6.0 (6, 2.0)	−13.9[e] (3, 5.1)	
			10^{-5}	12.9[e] (6, 1.9)	13.0[e] (6, 1.8)	−19.0 (3, 4.1)	
32E[i,j]	(*S*)-$CH(OH)CH_2$	$(CH_2)_6CH_3$	10^{-7}	−1.0 (6, 1.9)	−2.9 (6, 4.9)	−0.9 (3, 2.7)	NE
			10^{-6}	1.9 (6, 2.0)	4.9 (6, 1.0)	−12.0[e] (3, 2.0)	
			10^{-5}	9.0 (6, 2.9)	7.0 (6, 4.1)	−32.2[e] (3, 5.0)	
33E	$CH(OH)CH_2$	$(CH_2)_6CH_2F$	10^{-7}	4.3 (3, 8.0)	7.3 (3, 7.5)	−5.2 (2, 2.7)	4.2
			10^{-6}	14.7 (3, 9.0)	10.5 (3, 5.5)	−17.4 (2, 3.6)	
			10^{-5}	21.6 (3, 7.2)	21.6 (3, 7.1)	−20.4 (2, 2.5)	
34E	$CH(OH)CH_2$	$(CH_2)_6CHF_2$	10^{-7}	24.0[e] (3, 7.8)	5.5 (3, 3.6)	−26.1 (2, 0.19)	≥20
			10^{-6}	31.7[e] (3, 8.6)	1.6 (3, 2.9)	−31.4 (2, 0.23)	
			10^{-5}	40.6[f] (3, 10.9)	22.4 (3, 13.2)	−35.1 (2, 0.26)	
35E	$CH(OH)CH_2$	$(CH_2)_5CHF_2$	10^{-7}	15.6 (3, 6.4)	0.70 (3, 5.3)	−10.5 (2, 1.2)	≥20
			10^{-6}	33.1[e] (3, 16.8)	3.2 (3, 4.6)	−25.2 (2, 2.7)	
			10^{-5}	34.6[e] (3, 12.5)	5.3 (3, 5.4)	−31.9 (2, 0.15)	
36	$CH(OH)CH_2$	$(CH_2)_5CH(F)CH_3$	10^{-7}	35.6[d] (3, 7.2)	10.3 (3, 5.8)	−6.3 (2, 4.4)	13
			10^{-6}	67.6[d] (3, 11.7)	17.6[e] (3, 11.4)	−11.0 (2, 4.2)	
			10^{-5}	80.8[d] (3, 11.7)	29.7[e] (3, 7.0)	−26.4 (2, 1.1)	
37	$CH(OH)CH_2$	$(CH_2)_5CF_2CH_3$	10^{-7}	8.8 (4, 4.1)	6.0 (4, 4.6)	−6.9 (2, 1.0)	NE
			10^{-6}	22.6[f] (4, 4.9)	16.0[e] (4, 12.7)	−22.3 (2, 1.3)	
			10^{-5}	22.8 (4, 8.7)	18.6 (4, 11.9)	−23.9 (2, 1.3)	
38	$CH(OH)CH_2$	$(CH_2)_5C(CH_3)_2F$	10^{-6}	0.4 (4, 1.1)	6.2 (4, 2.6)	−5.5 (2, 3.7)	≥20
			10^{-5}	16.1 (4, 5.4)	24.0[e] (4, 3.0)	−21.7 (2, 2.6)	
39	$CH(OH)CH_2$	$(CH_2)_4C(CH_3)_2F$	10^{-7}	−1.0 (3, 4.7)	5.1 (3, 6.3)	0.0 (2, 0.00)	NE
			10^{-6}	6.5 (3, 7.1)	6.4 (3, 3.2)	−4.0 (2, 0.96)	
			10^{-5}	18.2 (3, 11.6)	14.2 (3, 8.9)	−28.7 (2, 2.9)	
40E	(*S*)-$CH(OH)CH_2$	$(CH_2)_6CH_2F$	10^{-7}	21.5 (4, 3.7)	18.1[e] (4, 6.5)	−2.4 (2, 1.4)	4
			10^{-6}	47.6[e] (4, 16.4)	33.5[e] (4, 12.3)	−5.7 (2, 9.7)	
			10^{-5}	43.5[e] (4, 18.5)	26.1 (4, 21.3)	−28.3 (2, 7.6)	
41E	(*S*)-$CH(OH)CH_2$	$(CH_2)_5CH(F)CH_3$	10^{-7}	0.52 (7, 7.8)	−13.4 (6, 4.6)	−1.9 (4, 1.6)	≥20
			10^{-6}	17.8 (7, 12.2)	−7.1 (7, 5.7)	−22.6 (4, 5.5)	
			10^{-5}	30.7 (7, 8.2)	8.7 (7, 8.9)	−38.5 (4, 6.0)	
42E	(*S*)-$CH(OH)CH_2$	$(CH_2)_6CHF_2$	10^{-7}	13.7[e] (4, 2.5)	8.2 (4, 3.1)	−5.6 (2, 3.2)	NE
			10^{-6}	33.5[f] (4, 3.7)	10.4 (4, 3.7)	−14.5 (2, 9.5)	
			10^{-5}	28.8[e] (4, 5.3)	15.5 (4, 5.6)	−27.1 (2, 5.6)	
43E	(*S*)-$CH(OH)CH_2$	$(CH_2)_5CHF_2$	10^{-7}	18.6[d] (8, 2.6)	1.4 (8, 2.2)	−13.5[e] (6, 2.2)	NE
			10^{-6}	47.0[d] (8, 7.1)	6.5 (8, 3.2)	−29.8[d] (6, 3.5)	
			10^{-5}	51.0[d] (8, 7.4)	31.1 (8, 9.0)	−36.2[d] (6, 4.3)	
44	(*S*)-$CH(OH)CH_2$	$(CH_2)_5CF_2CH_3$	10^{-7}	8.6[e] (8, 3.5)	9.5 (8, 3.0)	−4.6 (6, 0.78)	NE
			10^{-6}	35.6[d] (8, 6.5)	22.7[e] (8, 6.6)	−23.1[d] (6, 2.4)	
			10^{-5}	48.0[d] (8, 10.3)	40.3[e] (8, 11.7)	−37.3[d] (6, 3.1)	
45E	(*S*)-$CH(OH)CH_2$	$(CH_2)_5C(CH_3)_2F$	10^{-7}	2.5 (9, 1.3)	8.0 (9, 3.5)	−3.2 (6, 0.85)	≥20[c]
			10^{-6}	14.4 (9, 3.4)	10.0 (9, 2.0)	−15.3[e] (6, 2.0)	
			10^{-5}	38.9[d] (9, 6.0)	27.7[e] (9, 3.4)	−35.6[d] (6, 3.7)	
46E	(*R*)-$CH(OH)CH_2$	$(CH_2)_5C(CH_3)_2F$	10^{-7}	3.8 (9, 2.2)	5.1 (9, 2.2)	−4.7 (6, 1.1)	NE
			10^{-6}	17.6[e] (9, 3.5)	15.9[e] (9, 4.6)	−19.1[e] (6, 3.0)	
			10^{-5}	27.9[e] (9, 5.8)	40.6[e] (9, 7.6)	−31.6[d] (6, 2.6)	
47	CH_2CH_2	$(CH_2)_5CH(F)CH_3$	10^{-7}	17.8[f] (4, 5.0)	12.7[e] (4, 3.8)	−9.6 (2, 1.8)	3
			10^{-6}	50.1[d] (4, 9.4)	29.2[e] (4, 8.5)	−27.7 (2, 4.1)	
			10^{-5}	*g*	*g*	−43.0 (2, 4.8)	
48	CH_2CH_2	$(CH_2)_6CH_2F$	10^{-7}	8.1 (4, 2.8)	4.1 (4, 2.4)	−6.0 (2, 1.1)	1
			10^{-6}	22.0 (4, 6.7)	14.8 (4, 4.2)	−22.8 (2, 3.8)	
			10^{-5}	29.5 (4, 5.4)	30.4 (4, 1.3)	−32.5 (2, 0.26)	
49	CH_2CH_2	$(CH_2)_5C(CH_3)_2F$	10^{-7}	8.7[e] (7, 3.7)	4.9 (7, 3.9)	−0.45 (4, 1.7)	3
			10^{-6}	23.8[d] (7, 4.8)	19.9 (7, 3.7)	−12.1 (4, 5.8)	
			10^{-5}	45.5[d] (7, 9.8)	50.1[e] (5, 11.0)	−23.0 (3, 0.73)	
50E	(*E*)-CH=CH	$(CH_2)_5CH(F)CH_3$	10^{-7}	10.2 (4, 3.7)	3.7 (4, 5.8)	−5.6 (2, 1.2)	3
			10^{-6}	22.3[e] (4, 6.4)	7.7 (4, 7.9)	−14.6 (2, 1.6)	
			10^{-5}	34.6[e] (4, 7.0)	26.0 (4, 6.2)	−30.2 (2, 4.6)	

[a] Effective refractory period evaluated at 1.0 and 3.0 Hz (ERP1 and ERP3) on right ventricular papillary muscles and change in rate of spontaneously beating right atria (rate) from isolated rabbit myocardium. Data expressed as mean percent change from baseline for the number of tissues (*N*) ± the standard error of the mean (SEM). [b] Molar concentration of the test compound. [c] Determined on the free base (**45**). [d] Statistically different from control ($p < 0.0005$). [e] Statistically different from control ($p < 0.05$). [f] Statistically different from control ($p < 0.005$). [g] Tissues were too refractory to follow the primary stimulus. [h] Ref 31. [i] Ref 36. [j] Some of these data have been reported in ref 41. [k] Not evaluated. [l] Stability relative to **31E** when incubated with human liver microsomes. [m] **E** designates the hemifumarate salt.

Table 2. In Vivo Evaluation of Potential Efficacy and Safety in the Rabbit Proarrhythmia Model

no.	QTc[a]	$MAPD_{90}$[d]	EAD[e]	EAD amplitude[f]	PVT[g]
1E[l,m]	85[b] (0.25−5.0)[j]	65[b] (0.5−1.0)[j]	4/4 (1.7 ± 1.0)[i]	15 (3.9 ± 1.5)[c]	2/16 (1.0 ± 0.9)[h]
31E	112[b] (0.25)	69[b] (0.25−1.0)	4/10 (0.2 ± 0.02)	11 (0.3 ± 0.05)	2/10 (0.3 ± 0.1)
32E	145[b] (0.25)	105[b] (0.25−5.0)	3/10 (1.6 ± 1.0)	22 (1.6 ± 1.0)	1/10 (0.2)
33E	142[b] (0.25−0.5)	128[b] (0.25−0.5)	4/6 (0.3 ± 0.07)	52 (0.8 ± 0.3)	1/6 (2.0)
34E	71[b] (0.25)	48[b] (0.25)	2/6 (0.3 ± 0.05)	11 (0.3 ± 0.05)	2/6 (0.3 ± 0.1)
36E	166[b] (0.25)	143[b] (0.25)	4/6 (0.3 ± 0.1)	63 (0.3 ± 0.1)	3/6 (0.2 ± 0.02)
37	96[b] (0.25)	118[b] (0.25−1.0)	2/6 (0.4 ± 0.04)	15 (0.7 ± 0.2)	2/6 (0.7 ± 0.3)
38	136[b] (0.25)	96[b] (0.5−1.0)	5/6 (0.9 ± 0.4)	35 (1.5 ± 0.6)	1/6 (0.25)
39	174[b] (0.25−1.0)	178[b] (0.25−2.0)	4/4 (1.4 ± 0.8)	64 (3.3 ± 0.7)	2/4 (3.6 ± 1.8)
40E[k]	105[b] (0.1−0.25)	76[b] (0.1−5.0)	1/24 (0.25)	4 (0.25)	1/24 (0.9)
41E[k]	130[b] (0.1−0.25)	90[b] (0.1−1.0)	4/24 (0.2 ± 0.03)	10 (0.5 ± 0.1)	1/24 (0.4)
42E	118[b] (0.1−0.25)	58[b] (0.1−0.5)	3/6 (0.5)	20 (0.5)	2/6 (0.25 ± 0.2)
43E	154[b] (0.1−0.25)	123[b] (0.25−0.5)	3/6 (0.2 ± 0.04)	29 (0.25)	2/6 (0.3 ± 0.1)
44	106[b] (0.1−1.0)	92[b] (0.1−0.25)	3/16 (0.3 ± 0.05)	24 (0.3 ± 0.02)	2/16 (0.3 ± 0.2)
45[k]	83[b] (0.1−1.0)	69[b] (0.1−5.0)	0/24		0/24
46E	92[b] (0.1−0.25)	59[b] (0.1−0.25)	6/24 (0.5 ± 0.3)	10 (0.5 ± 0.3)	2/24 (0.27 ± 0.02)
47	94[b] (0.25−0.5)	56[b] (0.5−1.0)	4/16 (0.2 ± 0.03)	13 (0.4 ± 0.2)	2/16 (1.1 ± 0.1)
48	96[b] (0.1−0.5)	52[b] (0.1−2.0)	1/16 (1.0)	6 (1.0)	1/16 (0.1)
49	105[b] (0.25−5.0)	90[b] (0.25−5.0)	0/16		0/16
50E	75 (2.0)	133[b] (0.5−2.0)	4/4 (0.3 ± 0.06)	91 (0.4 ± 0.2)	3/4 (1.5 ± 0.8)

[a] Maximum increase in QTc interval (ms) from the methoxamine infusion baseline. [b] Statistically significant, $p \leq 0.05$. [c] Mean accumulated dose (mg/kg) of test compound when this value was measured. [d] Maximum increase in the ventricular monophasic action potential duration at 90% repolarization (ms) from the methoxamine infusion baseline. [e] Ratio of the number of animals that developed early after depolarization to the total number of animals evaluated. [f] Maximum EAD amplitude (% of monophasic action potential plateau height). [g] Ratio of the number of animals that developed polymorphic ventricular tachycardia to the total number of animals evaluated. [h] Mean dose of test compound (mg/kg) when PVTs were observed. [i] Mean dose (mg/kg) of test compound at which the EADs began to develop. [j] Mean dose (mg/kg) of test compound at which a statistically significant increase was first observed and the dose for the maximum increase. [k] Both male and female rabbits were used for this evaluation. [l] Some of these data have been published in ref 43. [m] **E** designates the hemifumarate salt.

similar to those of ibutilide (compare **33E** to **1E** in Table 1). In addition, like ibutilide it was equally effective at the fast pacing rate (ERP_3). This absence of a decline in activity at the increased pacing rate, which is also known as reverse use dependence and is encountered with many class III antiarrhythmic agents, is expected to be a beneficial property for compounds that are intended to treat tachyarrhythmias.[46] Unfortunately, although **33E** was more stable than ibutilide, it was still metabolized quite rapidly by human liver microsomes (Table 1). It was also found to have an unacceptable propensity to produce EADs and PVT in the rabbit proarrhythmia model (Table 2). The addition of a second fluorine to the terminous of the ibutilide side chain gave a compound (**34E**) with excellent stability and very potent activity on ERP_1; however, this activity was greatly diminished at the faster pacing rate, and **34E** retained a considerable proarrhythmic potential. The corresponding compound with a six-carbon side chain (**35E**) also had good ERP_1 activity but poor activity on ERP_3. When the fluorine was moved to the ω-1 position of the seven-carbon side chain to give **36**, very potent activity on ERP_1 was obtained. This compound also retained diminished but potent activity on ERP_3. It was surprisingly more stable than the compound (**33E**) with a terminal fluorine, but it had enhanced proarrhythmic potential. Addition of a second fluorine to the ω-1 carbon gave a compound (**37**) with very interesting activity on both ERP_1 and ERP_3, but unfortunately, it retained some proarrhythmic potential. When a methyl group was added to the ω-1 position of **36** a compound (**38**) with good activity on both ERP_1 and ERP_3 and excellent stability was obtained. It still, however, retained some proarrhythmic potential. The corresponding compound (**39**) with a six-carbon side chain also had interesting activity on both ERP_1 and ERP_3 but high potential for proarrhythmic activity.

In the course of our studies with ibutilide, we had prepared and evaluated its enantiomers (**31E** and **32E**).[36,41] In the rabbit proarrhythmia model it appeared that the *S*-enantiomer (**32E**) was somewhat less proarrhythmic than either the *R*-enantiomer (**31E**) or ibutilide (**1E**, compare in Table 2). Similar results had also been obtained for artilide[36] and its *S*-entantiomer (data not shown). We, therefore, investigated the *S*-enantiomers of key members of this series to determine if we could obtain compounds with improved activity in the rabbit model of proarrhythmia. On the basis of studies with ibutilide,[41] we anticipated that the activities of these compounds on ERP_1 and ERP_3 would be similar to those of the racemates. For the most part this appeared to be the case (compare the *S*-enantiomers **40E**, **41E**, **42E**, **43E**, **44**, and **45E** with the corresponding racemates **33E**, **36**, **34E**, **35E**, **37**, and **38** in Table 1). Compounds **44** and **45E** had exceptional activity in this test system with only a slight decrease in activity at the high pacing rate. Even more interesting, however, was the apparent reduction of the proarrhythmic potential for several of these compounds in the rabbit model (compare **40E**, **41E**, **44**, and **45** with **33E**, **36E**, **37**, and **38**, respectively, in Table 2). With compound **45** in particular, even though there was a statistically significant lengthening of both QTc and $MAPD_{90}$, it was not possible to elicit either EADs or PVT with this procedure. Evaluation of the *R*-enantiomer (**46E**) of this interesting compound demonstrated that it had activity similar to that of **45E** for enhancing ERP_1 and ERP_3 but retained proarrhythmic potential in the rabbit model. The prolongation of QTc and $MAPD_{90}$ by **46E** in this model was very similar to that produced by **45** which suggested that these measures of antiarrhythmic efficacy were not correlated with the compound's ability to produce PVT in this model. In this regard it is interesting that Carlsson et al.[42] found that the K_{ATP}

agonist, pinacidil, was able to block the EADs and PVT induced by clofilium in their methoxamine-treated rabbits without altering the prolonged monophasic action potential.

During the course of these experiments, we had occasion to look at several compounds in which the alcohol had been either reduced (**47**−**49**) or dehydrated (**50E**). These compounds generally had interesting activity on ERP_1 and ERP_3, and **49** like **45** had no proarrhythmic activity in the rabbit model. Unfortunately, these compounds had poor metabolic stability and were not considered further.

With regard to the mechanism of action for this series of class III antiarrhythmic agents, it is known that the cardiac action potential is the result of an intricate balance between ion currents that flow into and out of cardiac cells. These currents are established by an array of ion channels that can vary depending on the animal species and the type of cardiac tissue investigated. Initial depolarization of the ventricular myocyte is achieved by a rapid influx of sodium (I_{Na}) through the fast sodium channel. This is immediately followed by a transient outward current (I_{to}) which contributes to the repolarization process and is carried by two separate channels. The plateau of the action potential is maintained by a balance between an inward calcium current carried by the L-type and T-type calcium channels and an outward potassium current that is carried by three different delayed rectifier channels (I_{Kr}, I_{Ks}, and I_{kur}). Final repolarization of the cell is facilitated by the inward rectifier potassium current (I_{K1}). The adenosine triphosphate-regulated potassium channel (K_{ATP}) is also present and is probably especially important during ischemia.[47] Class III antiarrhythmic activity has been achieved either by enhancing an inward plateau current or by blocking an outward repolarizing current. Many of the classical class III antiarrhythmic agents such as D-sotalol, sematilide, E4031, and dofetilide block the rapidly activating delayed rectifier (I_{Kr}) which is believed to be the basis for their activity.[48] On the other hand, it has been reported that low, physiologically relevant concentrations of ibutilide enhance a late inward current in guinea pig ventricular cells[49] and human atrial cells.[50] It was proposed that this current is carried by sodium through the L-type Ca^{2+} channels that in the absence of ibutilide are impermeable to sodium.[50] At higher concentrations in guinea pig ventricular cells, ibutilide was found to increase a dofetilide-resistant, time-independent outward current that reversed its effect on the APD to give a bell-shaped concentration−response curve.[51] High concentrations of ibutilide have also been reported to give a concentration-dependent block of I_{to} in human atrial cells.[50] In a study by Lynch and co-workers[48] the displacement of high affinity [^{3}H]dofetilide binding in guinea pig ventricular myocytes was used to measure the interaction of several class III antiarrhythmic agents with I_{Kr}. It was found that there was a good correspondence between the K_i values of several selective I_{Kr} blockers in the binding assay and the measured EC_{25} values for increasing ERP by 25% over baseline in guinea pig papillary muscles. In this study ibutilide was found to have one of the lowest K_i values (16 ± 7 nM) for displacing high affinity [^{3}H]dofetilide binding but a greater than 10-fold higher EC_{25} value (185.8 nM) for increasing ERP in guinea pig papillary muscles. The authors suggested that this lack of correspondence may have been due to the possibility that ibutilide has a combination of effects in addition to those on I_{Kr}. Mouse atrial tumor myocytes (AT-1 cells) have also been used to evaluate the activity of ibutilide on I_{Kr}. In this study ibutilide was found to be a potent blocker of I_{Kr} with activity that was qualitatively similar to that of dofetilide.[52] More recently the I_{Kr} blocking properties of ibutilide were studied on rabbit sinoatrial (SA) node and atrioventricular (AV) node cells.[53] On the basis of these studies, it would appear that there is no general consensus regarding the mechanism of action for ibutilide and by inference for other members of the ibutilide family. We suspect that the activity of these compounds on cardiac cells is the result of agonist or antagonist activities on several different ion channels. If, for example, a compound could enhance an inward plateau current it would prolong the duration of the action potential and the ERP which would block reentrant arrhythmias. If at the same time it could enhance a delayed rectifier or inward rectifier potassium current, it would increase the rate of repolarization which might prevent the formation of EADs and PVT. A compound that could block I_{Kr} but enhance I_{K1} might have a similar effect. As mentioned above it has been shown that the K_{ATP} agonist, pinacidil, can prevent EADs and PVT induced by clofilium in the rabbit proarrhythmia model.[42] It has also been reported that pinacidil can prevent EADs caused by Bay K 8644 or ketanserin in canine ventricular myocytes.[54] High concentrations of ibutilide that elicited an outward potassium current were also reported to prevent EADs caused by the I_{Kr} blocker, E-4031.[51] We believe that the different effects on ERP_1, ERP_3, EADs, and PVT produced by the compounds in this series are the result of slightly different net effects on the ion currents that generate the action potential.

Because of its very interesting activity profile, **45E** was chosen for further evaluation in two canine models of reentrant arrhythmias. In the first, a model of inducible atrial tachycardia that resembles AFL was created by introducing a Y-shaped lesion in the right atrium according to the method of Frame and co-workers.[55] In this model, the arrhythmia which results from a reentrant cycle in the atrial tissue above the tricuspid ring[55,56] is stable, is highly reproducible, and can be consistently induced, terminated, and reinitiated by rapid atrial pacing. It is characterized by a relatively long excitable gap and incomplete recovery of excitability; it, thus, lends itself to the evaluation of antiarrhythmic agents that increase the refractoriness of atrial tissue, thereby increasing the wavelength of the circulating wave front and reducing the excitable gap. In this model, orally administered ibutilide in doses of 0.25−1.0 mg/kg was found to significantly increase the atrial effective refractory period (AERP) and prevent induction of AFL for 4−6 h.[57] Intravenous administration of ibutilide in a second study at a mean dose of 6 ± 1 μg/kg terminated AFL and prevented its reinduction in all of the eight animals studied. This effect was accompanied by a statistically significant increase in both AERP and atrial flutter cycle length (AFLCL).[58] In their original description of this AFL model Frame

Table 3. Heart Rate and Electrophysiologic Parameters Measured at Baseline and Just After AFL Termination by **45E**

	HR[d] (bpm)	QT[b] (ms)	AERP[e] (ms)	VERP[f] (ms)	AFLCl[g] (ms)
baseline	125 ± 8	186 ± 4	116 ± 3	122 ± 3	151 ± 4
termination (0.48 ± 0.12)[a]	108 ± 12	202 ± 8	149 ± 10[c]	138 ± 2[c]	165 ± 9

[a] Mean dose of **45E** at AFL termination (μmol/kg). [b] QT interval determined at a paced cycle length of 300 ms. [c] Statistically significant, $p \leq 0.05$ vs baseline. [d] Heart rate. [e] Atrial effective refractory period. [f] Ventricular effective refractory period. [g] Atrial flutter cycle length.

Table 4. Effects of Intravenous **45E** on HR, QT Interval, AERP, and VERP, Measured at Baseline and After AFL Termination

dose[c]	n[d]	HR[e] (bpm)	QT[a] (ms)	AERP[f] (ms)	VERP[g] (ms)
baseline	8	124 ± 7	186 ± 4	118 ± 4	122 ± 3
0.24	3	128 ± 10	196 ± 8	160 ± 16[b]	142 ± 3[b]
0.6	7	111 ± 9	208 ± 6[b]	153 ± 9[b]	141 ± 3[b]
1.2	8	114 ± 8	212 ± 7[b]	160 ± 9[b]	144 ± 2[b]
2.4	8	113 ± 7	213 ± 6[b]	166 ± 8[b]	143 ± 2[b]
4.8	8	118 ± 9	207 ± 8[b]	166 ± 9[b]	142 ± 3[b]
7.2	8	127 ± 11	205 ± 9	162 ± 7[b]	140 ± 5[b]
9.6	8	114 ± 7	204 ± 8	165 ± 6[b]	139 ± 4[b]
12.0	8	122 ± 6	200 ± 9	164 ± 6[b]	137 ± 3[b]

[a] QT interval determined at a paced cycle length of 300 ms. [b] Statistically significant, $p \leq 0.05$ vs baseline. [c] Cumulative dose of **45E** (μmol/kg). [d] Number of animals. [e] Heart rate. [f] Atrial effective refractory period. [g] Ventricular effective refractory period.

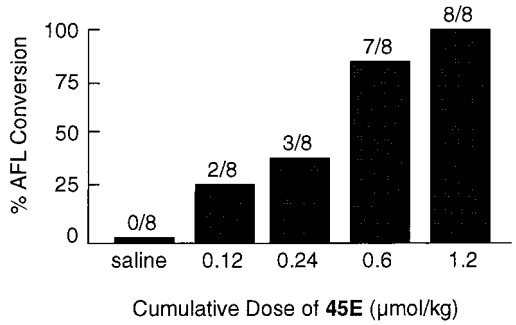


Figure 1. Effects of intravenous **45E** on AFL termination.

and co-workers[55] suggested that it might be a useful model for the common form of human AFL. Since ibutilide has been shown to be especially effective for terminating AFL in humans,[32] its excellent activity in this model also suggests the utility of the model for predicting the potential efficacy of antiarrhythmic candidates for treating human AFL.

Results from the evaluation of **45E** in this model are shown in Tables 3 and 4. Figure 1 shows the effect of dose on arrhythmia termination. Intravenous doses of **45E** were administered periodically to eight animals with established arrhythmias so that cumulative doses of 0.24−12.0 μmol/kg were obtained. It was found that the arrhythmias were terminated in all of the animals after a mean effective dose of 0.48 ± 0.12 μmol/kg. At this time a statistically significant increase in both AERP and ventricular effective refractory period (VERP) but not AFLCL had been achieved. A statistically significant increase in paced QT interval was also obtained after a cumulative dose of 0.6 μmol/kg. It is noteworthy that maximum values of AERP and VERP and of QT were obtained at 0.24 and 0.6 μmol/kg, respectively. No additional change in these values was obtained with increasing cumulative doses of **45E**. In these conscious animals no significant change in heart rate (HR) and no adverse effects were observed through the highest dose tested.

Compound **45E** was also evaluated in the canine 24-h infarction model. In this model the left anterior descending coronary artery (LAD) is permanently ligated in two stages to give a well-defined area of ischemic tissue. As the infarct develops it generates a series of spontaneous ventricular arrhythmias. In the early acute phase, 30 min following coronary occlusion, the arrhythmias are believed to result from both reentrant and nonreentrant mechanisms; however, after 6−8 h and lasting for 2−3 days, the spontaneous arrhythmias (PVCs) result from nonreentrant ectopic depolarizations in the ventricle. Class IC antiarrhythmic agents such as encainide, but not class III agents, are particularly effective for treating these spontaneous arrhythmias.[59] Twenty-four hours after the occlusion, ventricular tachyarrhythmias can be induced by programmed electrical stimulation (PES). These arrhythmias are primarily due to reentry in ischemia-damaged tissue bordering the infarct. Class III antiarrhythmic agents such as ibutilide are very effective for preventing the initiation of this type of arrhythmia.[59] Compound **45E** was administered intravenously to 11 animals to give cumulative doses of 0.24, 0.72, and 2.4 μmol/kg. Hemodynamic and electrophysiologic parameters were measured at baseline and 15 min after each dose. The results are presented in Table 5. There was a dose-dependent increase in cardiac refractoriness which reached statistical significance at 0.72 μmol/kg for AERP and at 2.4 μmol/kg for VERP. The latter was accompanied by a significant increase in the QT interval and in the ventricular $MAPD_{90}$. Other ECG intervals (P, PQ, and QRS) were not significantly affected by **45E** (data not shown). Although there was a dose-dependent decrease in HR and idioventricular heart rate (IVR) which became significant for HR at 2.4 μmol/kg, **45E** had no effect on BP. As expected **45E** which does not have class I antiarrhythmic activity also had no effect on the PVCs. In this experiment 8 animals served as saline-treated controls. No significant changes in any of the measured parameters were observed in this group. At the end of the experiment each of the control animals received an intravenous dose of 2.4 μmol/kg of **45E**. The responses to this treatment mirrored those obtained with the high dose in the drug-treated group. Effects of **45E** on PES-induced arrhythmias are shown in Table 6. At baseline in the drug-treated group arrhythmias could not be induced (NI) in 3 animals, nonsustained ventricular tachycardia (NSVT) was obtained in 3 animals, and sustained ventricular tachycardia (SVT) was obtained in 5 animals. After the 0.24 μmol/kg dose of **45E**, 8 animals were NI, 2 had NSVT, and 1 had SVT. The 0.72 μmol/kg dose level gave 9 NI animals and 2 animals with SVT. When 2.4 μmol/kg of **45E** had been administered, 10 animals were NI and 1 of the previous SVT animals had NSVT. In the saline control group 3−4 animals were NI, 3−4 were induced to SVT, and 1 animal consistently went into ventricular fibrillation (VF). After administration of 2.4 μmol/kg of **45E**, 7 animals became NI and the VF animal was induced to SVT.

Table 5. Effects of **45E** and Saline Control on Hemodynamic and Electrophysiologic Parameters in the Canine 24-h Infarction Model

dose	HR[g] (bpm)	IVR[h] (bpm)	BP[i] (mmHg)	QT[j] (ms)	AERP[k] (ms)	atrial $MAPD_{90}$[l] (ms)	VERP[m] (ms)	ventricular[n] $MAPD_{90}$ (ms)	PVCs[f]
Compound **45E** ($n = 11$)[a]									
baseline	152 ± 5	144 ± 8	115 ± 5	210 ± 5	135 ± 4	140 ± 9	157 ± 4	160 ± 4	87 ± 14
0.24[b]	155 ± 5	138 ± 9	112 ± 3	211 ± 6	149 ± 6	148 ± 9	162 ± 5	162 ± 5	68 ± 17
0.72	146 ± 6	130 ± 8	115 ± 4	218 ± 6	166 ± 8[c]	146 ± 10	170 ± 7	170 ± 7	57 ± 17
2.4	135 ± 8[c]	124 ± 11	119 ± 5	240 ± 6[c]	194 ± 9[c]	163 ± 11	185 ± 9[c]	185 ± 9[c]	73 ± 14
Saline Control ($n = 8$)[a]									
baseline	162 ± 9	150 ± 8	122 ± 6	210 ± 7	128 ± 4	159 ± 11	151 ± 5	166 ± 6	105 ± 19
1[d]	158 ± 7	155 ± 7	114 ± 6	212 ± 7	132 ± 3	158 ± 12	152 ± 7	164 ± 8	111 ± 14
2	149 ± 6	147 ± 8	119 ± 9	216 ± 8	132 ± 3	159 ± 14	151 ± 7	172 ± 12	86 ± 21
3	153 ± 10	148 ± 10	117 ± 7	203 ± 8	144 ± 13	156 ± 13	150 ± 7	171 ± 9	85 ± 21
45E (2.4)[e]	127 ± 10[c]	111 ± 11[c]	111 ± 7	238 ± 9[c]	179 ± 7[c]	209 ± 13[c]	180 ± 6[c]	201 ± 12[c]	53 ± 16

[a] Number of animals. [b] Cumulative intravenous dose of **45E** (μmol/kg). [c] Statistically significant, $p \leq 0.05$ vs baseline. [d] Vehicle dose number [e] Single intravenous dose of **45E** (μmol/kg). [f] Spontaneous arrhythmias, number per minute. [g] Heart rate. [h] Idioventricular heart rate. [i] Blood pressure. [j] QT interval. [k] Atrial effective refractory period. [l] Atrial monophasic action potential duration recorded at 90% repolarization. [m] Ventricular effective refractory period. [n] Ventricular monophasic action potential duration recorded at 90% repolarization.

Table 6. Effects of **45E** and Saline Control on PES-Induced Arrhythmias

dose	NI[a,f]	NSVT[a,g]	SVT[a,h]	VF[a,i]
Compound **45E** ($n = 11$)[e]				
baseline	3	3	5	0
0.24[b]	8	2	1	0
0.72	9	0	2	0
2.4	10	1	0	0
Saline Control ($n = 8$)[e]				
baseline	3	1	3	1
1[d]	4	0	3	1
2	3	0	4	1
3	4	0	3	1
45E (2.4)[c]	7	0	1	0

[a] Number of animals in this arrhythmia category after PES. [b] Cumulative intravenous dose of **45E** (μmol/kg). [c] Single intravenous dose of **45E** (μmol/kg). [d] Vehicle dose number. [e] Number of animals. [f] Noninducible. [g] Nonsustained ventricular tachycardia. [h] Sustained ventricular tachycardia. [i] Ventricular fibrillation.

Conclusions

We prepared a series of compounds in which the heptyl side chain of ibutilide was modified by fluorine substitution to prevent its rapid metabolism. Like ibutilide many of these compounds prolonged cardic refractoriness in vitro and in addition had increased stability when incubated with human liver microsomes. However, they retained the ability to induce EADs and PVT in a rabbit proarrhythmia model. It was found that the *S*-enantiomers of these alcohols were generally less proarrhythmic than the racemates. One of these enantiomers (**45E**, trecetilide fumarate) was devoid of proarrhythmic activity in this model. Further evaluation of **45E** demonstrated that it had excellent activity in canine models of reentrant AFL and ventricular tachyarrhythmias. This compound is currently undergoing clinical evaluation for the treatment of atrial arrhythmias.[60]

Experimental Section

Chemistry. Melting points taken in capillary tubes are uncorrected. Preparative flash chromatography was carried out on Kieselgel (230−400 mesh ASTM silica gel) from EM Reagents and low-pressure chromatography on silica gel 60 (70−230 mesh ASTM) from EM Reagents. The progress of reactions and the purity of products were evaluated by TLC on silica gel GF 240-μm slides from Analtech, Inc., Newark, DE. Unless otherwise indicated, IR spectra were determined on mineral oil mulls. ^{1}H NMR spectra were obtained on 300-MHz instruments using tetramethylsilane as an internal standard; other physical and analytical data were obtained by the physical and analytical chemistry group at Pharmacia.

***(S)*-(−)-*N*-[4-[4-[Ethyl(6-fluoro-6-methylheptyl)amino]-1-hydroxybutyl]phenyl]methanesulfonamide (45). Procedure A.** A stirred mixture of **5** (6.00 g, 0.0210 mol), **15** (5.12 g, 0.0231 mol), $NaHCO_3$ (3.52 g, 0.0419 mol) and acetonitrile (180 mL) was refluxed under nitrogen for 16 h, cooled and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel with 5% MeOH−0.5% NH_4OH−CH_2Cl_2. A solution of the product in EtOAc was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated to give 7.00 g (80.0%) of **45**: ^{1}H NMR ($CDCl_3$) δ 1.10 (t, $J = 7.2$ Hz, 3H), 1.30 (s, 3H), 1.37 (s, 3H), 1.30−1.70 (m, 11H), 1.95 (m, 1H), 2.39−2.76 (m, 6H), 2.92 (s, 3H), 4.60 (m, 1H), 7.16 (d, $J = 8.5$ Hz, 2H), 7.33 (d, $J = 8.5$ Hz, 2H); MS (EI) *m*/*z* (relative intensity) 416 (M^+, 5.3), 401 (2.9), 396 (2.1), 337 (20.5), 317 (9.1), 299 (52.6), 188 (100), 168 (74.5), 72 (28.3); HRMS (FAB) calcd for $C_{21}H_{38}FN_2O_3S$ 417.2587 $(M + H)^+$, found 417.2602.

***(S)*-(−)-*N*-[4-[4-[Ethyl(7-fluoroheptyl)amino]-1-hydroxybutyl]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1) Salt (40E). Procedure B.** A stirred mixture of **5** (2.58 g, 0.00900 mol), **17** (2.0 g, 0.010 mol), $NaHCO_3$ (1.68 g, 0.0200 mol) and acetonitrile (80 mL) was refluxed, under nitrogen for 18 h and then concentrated in vacuo. A mixture of the residue and water was extracted with EtOAc; the extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with 0.3% NH_4OH−6% MeOH−$CHCl_3$. A solution of the product in EtOAc was washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated to give 1.93 g (4.76 mmol) of the free base. This was combined with 0.276 g (2.38 mmol) of fumaric acid and the salt was crystallized from acetone to give 1.78 g (42.9%) of **40E:** mp 126−127 °C; $[\alpha]^{24}_D$ −15° (*c* 0.997, EtOH); MS *m*/*z* (relative intensity) 402 (M^+, 4.9), 323 (16.6), 299 (26.4), 232 (28.1), 174 (100), 91 (22.1); IR 3369, 2748, 2708, 1614, 1576 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] δ 1.00 (t, 3H) 1.2−1.7 (m, 14H), 2.58 (m, 6H), 2.94 (s, 3H), 3.62 (br s, 2H), 4.33 (t, 1H), 4.50 (m, 2H), 6.46 (s, 1H), 7.15 (d, 2H), 7.26 (d, 2H). Anal. ($C_{22}H_{37}FN_2O_5S$) C, H, N, S.

***N*-[4-[4-[Ethyl(7-fluoroheptyl)amino]-1-hydroxybutyl]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1) Salt (33E).** As described in procedure B, **4** (1.30 g, 0.00454 mol) was alkylated with **17**, the product was flash chromatographed on silica gel with 7.5% MeOH−0.5% NH_4OH−$CHCl_3$ and the salt was crystallized from acetone to give 1.06 g (50.7%) of **33E**: mp 136.5−137.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 0.99 (t, $J = 7.1$ Hz, 3H), 1.25−1.70 (m, 14H), 2.57 (m, 6H), 2.94 (s, 3H), 4.34 (t, $J = 6.1$ Hz, 1H), 4.50 (m, 2H), 6.48 (s, 1H), 7.15 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 8.5$ Hz, 2H); IR 3380 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 402 (M^+, 7.0), 174 (100). Anal. ($C_{22}H_{37}FN_2O_5S$) C, H, N, S.

***N*-[4-[4-[(7,7-Difluoroheptyl)ethylamino]-1-hydroxybutyl]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1) Salt (34E).** As described in procedure B, **4** (1.0 g, 0.0035 mol) was alkylated with **20**, the product was flash chromatographed on silica gel with 10% MeOH−0.5% NH_4OH−$CHCl_3$ and the salt was crystallized from acetone to give 0.69 g (41%) of **34E**: mp 147−148 °C; IR 3375 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 0.99 (t, J = 7.0 Hz, 3H), 1.23−1.60 (m, 12H), 1.79 (m, 2H), 2.59 (m, 6H), 2.94 (s, 3H), 3.63 (br s), 4.49 (t, 1H), 5.87, 6.05, 6.25 (t, t, t, 1H), 6.46 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H); MS (EI) *m/z* (relative intensity) 420 (M^+, 7.2), 405 (1.3), 341 (21.2) 299 (34.3), 269 (7.0), 240 (13.2), 192 (100). Anal. ($C_{22}H_{36}F_2N_2O_5S$) C, H, N, S.

***N*-[4-[4-[(6,6-Difluorohexyl)ethylamino]-1-hydroxybutyl]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1 Salt) (35E).** As described in procedure B, **4** (1.33 g, 0.00466 mol) was alkylated with **18**, the product was flash chromatographed on silica gel with 10% MeOH−0.5% NH_4OH−$CHCl_3$ and the salt was crystallized from acetone−Et_2O to give 0.7 g (32%) of **35E**: mp 88−90 °C; IR 3323 cm^{-1}; MS (EI) *m/z* (relative intensity) 406 (M^+, 6.6), 327 (19.1), 299 (30.0), 178 (100): ^1H NMR [$(CD_3)_2SO$] δ 1.00 (t, J = 7.1 Hz, 3H), 1.26−1.59 (m, 10H), 1.79 (m, 2H), 2.59 (m, 6H), 2.94 (s, 3H), 3.69 (br s), 4.49 (t, 1H), 5.87, 6.05, 6.24 (t, t, t, 1H), 6.46 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H). Anal. ($C_{21}H_{34}F_2N_2O_5S$) C, H, N, S.

***N*-[4-[4-[Ethyl(6-fluoroheptyl)amino]-1-hydroxybutyl]phenyl]methanesulfonamide (36).** Alkylation of **4** (1.65 g, 0.00578 mol) with **19** (1.23 g, 0.00624 mol) as described in procedure A and flash chromatography of the product on silica gel with 5% MeOH−0.25% NH_4OH−$CHCl_3$ gave 1.54 g (66.4%) of **36**: ^1H NMR ($CDCl_3$) δ 1.10 (t, J = 7.1 Hz, 3H), 1.32 (d, d, J = 6.1, 24.0 Hz, 3H), 1.27−1.76 (m, 11H), 1.98 (m, 1H), 2.48 (m, 5H), 2.68 (m, 1H), 2.95 (s, 3H), 4.60 (m, 1H), 4.60, 4.73 (m, m, 1H), 7.16 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H); MS (EI) *m/z* (relative intensity) 402 (M^+, 11.4), 323 (32.1) 299 (47.2), 174 (100); HRMS calcd for $C_{20}H_{35}FN_2O_3S$ 402.2352, found 402,2347.

***N*-[4-[4-[Ethyl(6-fluoroheptyl)amino]-1-hydroxybutyl]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1 Salt) (36E).** A solution of **36** (2.5 g, 0.0062 mol) in EtOAc was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated. A solution of the residue in acetonitrile was treated with fumaric acid (0.36 g, 0.0031 mol) and crystallized to give 2.1 g (73.5%) of **36E**: mp 119−122 °C; ^1H NMR [$(CD_3)_2SO$] δ 0.99 (t, 3H), 1.20−1.60 (m, 15H), 2.94 (s, 3H), 4.50 (m, 1H), 4.57, 4.72 (m, m, 1H), 6.47 (s, 1H), 7.16 (d, 2H), 7.26 (d, 2H). Anal. ($C_{22}H_{37}FN_2O_5S$) C, H, N, S.

***N*-[4-[4-[(6,6-Difluoroheptyl)ethylamino]-1-hydroxybutyl]phenyl]methanesulfonamide (37).** An ice-cold, stirred suspension of $LiAlH_4$ (0.11 g, 2.89 mmol) in THF (2 mL) under nitrogen was treated dropwise with a solution of **9** (0.379 g, 0.877 mol) in THF (5 mL), kept in the bath for 2.5 h and then treated carefully with a saturated aqueous solution of potassium sodium tartrate (1.4 mL). This mixture was stirred for 20 min and filtered through Celite. The filtrate was concentrated and the residue was chromatographed on silica gel with 5% MeOH−0.5% NH_4OH−CH_2Cl_2 to give 0.228 g (61.8%) of **37**, an oil: ^1H NMR ($CDCl_3$) δ 1.12 (t, J = 7.1 Hz, 3H), 1.35 (m, 2H), 1.58 (t, J = 18.4 Hz, 3H), 1.47−1.97 (m, 10H), 2.60 (m, 6H), 2.95 (s, 3H), 4.60 (m, 1H), 7.18 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H); MS (EI) *m/z* (relative intensity) 420 (M^+, 9.7), 405 (2.5), 341 (26.3), 299 (40.6), 192 (100); HRMS (EI) calcd for $C_{20}H_{34}F_2N_2O_3S$ 420.2258, found 420.2265.

***N*-[4-[4-[Ethyl(6-fluoro-6-methylheptyl)amino]-1-hydroxybutyl]phenyl]methanesulfonamide (38).** As described in procedure A, **4** (0.37 g, 0.00128 mol) was allowed to react with **15** in refluxing acetonitrile. The product was chromatographed on silica gel with 10% MeOH−CH_2Cl_2 to give 0.332 g (62.3%) of **38**: ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.36 (m, 7H), 1.37 (s, 3H), 1.76 (m, 8H), 2.95 (s, 3H), 2.97 (m, 6H), 4.65 (m, 1H), 7.24 (m, 4H); MS (EI) *m/z* (relative intensity) 416 (M^+, 3.4), 401 (1.8), 396 (8.9), 381 (2.0), 337 (10.2), 317 (22.9), 299 (59.3), 269 (8.5), 240 (17.1), 188 (36.1), 168 (100); HRMS (FAB) calcd for $C_{21}H_{38}FN_2O_3S$ 417.2587 ($M + H^+$), found 417.2579.

***N*-[4-[4-[Ethyl(5-fluoro-5-methylhexyl)amino]-1-hydroxybutyl]phenyl]methanesulfonamide (39).** As described in procedure A, **4** (0.889 g, 0.00311 mol) was allowed to react with **16** in refluxing acetonitrile. The product was chromatographed on silica gel with 10% MeOH−1% NH_4OH−$CHCl_3$ to give 0.530 g (50.9%) of **39**: ^1H NMR ($CDCl_3$) δ 1.19 (t, J = 7.09 Hz, 3H), 1.30 (s, 3H), 1.37 (s, 3H), 1.44 (m, 2H), 1.73 (m, 8H), 2.73 (m, 6H), 2.95 (s, 3H), 4.62 (m, 1H), 7.21 (d, J = 8.50 Hz, 2H), 7.30 (d, J = 8.45 Hz, 2H); MS (EI) *m/z* (relative intensity) 402 (M^+, 14.3), 387 (5.7), 323 (36.0), 299 (55.5), 174 (100); HRMS (EI) calcd for $C_{20}H_{33}FN_2O_3S$ 402.2352, found 402.2350.

(*S*)-(−)-*N*-[4-[4-[Ethyl(6-fluoroheptyl)amino]-1-hydroxybutyl]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1) Salt (41E). As described in procedure B, **5** (2.58 g, 0.00900 mol) was alkylated with **19,** the product was flash chromatographed on silica gel with 6% MeOH−0.3% NH_4OH−$CHCl_3$ and the salt was crystallized from acetone to give 1.26 g (30.5%) of **41E**: mp 109−110.5 °C; $[\alpha]^{24}_D$ −14° (*c* 0.980, EtOH); MS *m/z* (relative intensity) 402 (M^+ 4.9), 323 (19.2), 299 (34.5), 240 (15.3), 174 (100) 162 (10.8); IR 3315, 3097, 3025, 2758, 2712, 2507, 1614, 1570 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 0.99 (t, 3H) 1.21−1.55 (m, 15H), 2.55 (m, 6H), 2.94 (s, 3H), 3.51 (br s), 4.49 (m, 1H), 4.56 (m, 0.5H), 4.71 (m, 0.5H), 6.46 (s, 1H), 7.16 (d, 2H), 7.26 (d, 2H). Anal. ($C_{22}H_{37}FN_2O_5S$) C, H, N, S.

(*S*)-(−)-*N*-[4-[4-[(7,7-Difluoroheptyl)ethylamino]-1-hydroxybutyl]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1) Salt (42E). According to procedure B the alkylation of **5** (3.64 g, 0.0127 mol) with **20** (2.74 g, 0.0127 mol) and crystallization of the salt from acetone gave 2.61 g (42.8%) of **42E**: mp 109−111 °C; $[\alpha]^{24}_D$ −14° (*c* 1.00, EtOH); MS (EI) *m/z* (relative intensity) 420 (M^+, 4.3), 341 (13.3), 299 (23.7), 192 (100), 72 (42.8), 58 (33.4); IR 3363 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 1.00 (t, J = 7.1 Hz, 3H), 1.27−1.58 (m, 12H), 1.78 (m, 2H), 2.56 (m, 6H), 2.94 (s, 3H), 4.49 (t, 1H), 5.87, 6.05. 6.23 (t,t,t, 1H), 6.47 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H). Anal. ($C_{22}H_{36}F_2N_2O_5S$) C, H, N, S.

(*S*)-(−)-*N*-[4-[4-[(6,6-Difluorohexyl)ethylamino]-1-hydroxybutyl]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1) Salt (43E). As described in procedure B, **5** (3.53 g, 0.0123 mol) was alkylated with **18**, the product was chromatographed on silica gel with 5% MeOH−0.25% NH_4OH−$CHCl_3$ and the salt was crystallized from acetone to give 1.98 g (34.7%) of **43E**: mp 110−111 °C; $[\alpha]^{24}_D$ −14° (*c* 0.996, EtOH); IR (Nujol) 3347, 3085, 2754, 2627, 2510, 1614, 1571 cm^{-1}; MS (EI) *m/z* (relative intensity) 406 (M^+, 2.6), 327 (8.0), 299 (11.4), 270 (7.7), 178 (100); ^1H NMR [$(CD_3)_2SO$] δ 0.99 (t, J = 7.1 Hz, 3H), 1.30−1.57 (m, 10H), 1.79 (m, 1H), 2.56 (s, 6H), 2.94 (s, 3H), 4.49 (t, 1H), 5.87, 6.05, 6.25 (t,t,t, 1H), 6.47 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H). Anal. ($C_{21}H_{34}F_2N_2O_5S$) C, H, N, S.

(*S*)-(−)-*N*-[4-[4-[Ethyl(6,6-difluoroheptyl)amino]-1-hydroxybutyl]phenyl]methanesulfonamide (44). According to procedure A, **5** (3.33 g, 0.0116 mol) was allowed to react with **26** (2.75 g, 0.0128 mol) and the product was chromatographed on silica gel with mixtures of MeOH−NH_4OH−CH_2Cl_2 containing 3−5% MeOH and 0.3−0.5% NH_4OH to give 2.84 g (58.2%) of **44**: ^1H NMR ($CDCl_3$) δ 1.12 (t, J = 7.12 Hz, 3H), 1.58 (t, J = 18.4 Hz, 3H), 1.28−2.00 (m, 14H), 2.39−2.81 (m, 6H), 2.94 (s, 3H), 4.59 (d, 1H), 7.18 (d, J = 8.48 Hz, 2H), 7.33 (d, J = 8.46 Hz, 2H); ^{19}F NMR (282.2 MHz, $CDCl_3$) δ −94.83 (6 peaks); MS *m/z* (relative intensity) 420 (M^+ 3.0), 405 (0.8), 341 (9.7), 299 (17.1), 220 (1.0), 192 (100), 72 (36.5); HRMS (EI) calcd for $C_{20}H_{34}N_2O_3F_2$ 420.2258, found 420.2266; $[\alpha]_D^{24}$ −16° (*c* 0.6598, EtOH); IR (film) 3255, 3155, 1614, 1512 cm^{-1}.

(*S*)-(−)-*N*-[4-[4-[Ethyl(6-fluoro-6-methylheptyl)amino]-1-hydroxybutyl]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1 Salt) (45E). A solution of **45** (6.68 g, 0.0160 mol) in acetone (200 mL), under nitrogen was treated with fumaric acid (0.93 g, 0.0080 mol) and warmed to obtain solution. The resulting salt was crystallized from acetone to give 3.99 g (52.5%) of **45E**: mp 135.5−137 °C; $[\alpha]^{24}_D$ −14° (*c* 0.934, EtOH); IR 3320, 3094, 3021, 2752, 2704, 2511, 1575,

1512 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 1.00 (t, 3H), 1.25 (s, 3H), 1.32 (s, 3H), 1.23−1.61 (m, 12H), 2.59 (m, 6H), 2.95 (s, 3H), 3.49 (br s), 4.49 (t, 1H), 6.47 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H). Anal. ($C_{23}H_{39}FN_2O_5S$) C, H, F, N, S.

(*R*)-(+)-*N*-[4-[4-[Ethyl(6-fluoro-6-methylheptyl)amino]-1-hydroxybutyl]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1) Salt (46E). According to procedure B, the alkylation of **6** (2.5 g, 0.00873 mol) with **15**, flash chromatography of the product on silica gel with 8% MeOH−0.4% NH_4OH−$CHCl_3$ and crystallization of the salt from acetone gave 0.521 g (12.6%) of **46E** which was identical to **45E** in all respects except for the sign of its rotation: mp 135−137 °C; $[\alpha]^{24}_D$ +14° (*c* 0.9697, EtOH); MS *m*/*z* (relative intensity) 416 (M^+, 9.4), 401 (4.5), 337 (30.8), 299 (58.7), 269 (13.5), 240 (24.6), 188 (100), 168 (31.0), 269 (13.5), 240 (24.6), 188 (100), 168 (31.0), 162 (17.3), 144 (15.0), 98 (30.0); IR 3317, 1575 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 0.95 (t, 3H) 1.27 (d, J = 21.5 Hz, 6H), 1.23−1.58 (m, 12H), 2.52 (m, 6H), 2.92 (s, 3H), 3.35 (br s), 4.46 (t, 1H), 6.46 (s, 1H), 7.13 (d, 2H), 7.25 (d, 2H). Anal. ($C_{23}H_{39}FN_2O_5S$) C, H, N.

***N*-[4-[4-[Ethyl(6-fluoroheptyl)amino]butyl]phenyl]-methanesulfonamide (47).** Alkylation of **7** (1.11 g, 0.00411 mol) with **19** (0.900 g, 0.00457 mol) as described in procedure A and flash chromatography of the product over silica gel with 5% MeOH−0.25% NH_4OH−$CHCl_3$ gave 0.94 g (59.2%) of **47**: ^1H NMR ($CDCl_3$) δ 1.01 (t, J = 7.1 Hz, 3H), 1.31 (d,d J = 6.16, 24.1 Hz, 3H), 1.26−1.68 (m, 12H), 2.38−2.63 (m, 8H), 2.98 (s, 3H), 4.56, 4.72 (m,m, 1H), 7.16 (s, 4H); FAB MS *m*/*z* (relative intensity) 387 (M + H^+, 100), 369 (11.9), 283 (31.9), 184 (5.6), 174 (59.9), 160 (6.9); HRMS (FAB) calcd for $C_{20}H_{36}FN_2O_2S$ 387.2481 (M + H^+), found 387.2483.

***N*-[4-[4-[Ethyl(7-fluoroheptyl)amino]butyl]phenyl]-methanesulfonamide (48).** Alkylation of **7** (3.51 g, 0.0130 mol) with **17** (3.40 g, 0.0173 mol) as described in procedure A and chromatography of the product on silica gel with 5% MeOH−0.25% NH_4OH−$CHCl_3$ gave 2.38 g (47.4%) of **48**: ^1H NMR ($CDCl_3$) δ 1.01 (t, J = 7.1 Hz, 3H), 1.23−1.76 (m, 14H), 2.38−2.63 (m, 8H), 2.98 (s, 3H), 4.44 (t,t, J = 47.3, 6.11 Hz, 2H), 7.15 (s, 4H); MS (EI) *m*/*z* (relative intensity) 386 (M^+, 4.3), 371 (3.0), 307 (8.0), 283 (88.4), 174 (100), 102 (25.1); HRMS (EI) calcd for $C_{20}H_{35}FN_2O_2S$ 386.2403, found 386.2395.

***N*-[4-[4-[Ethyl(6-fluoro-6-methylheptyl)amino]butyl]-phenyl]methanesulfonamide (49).** Alkylation of **7** (2.0 g, 0.0074 mol) with **15** (1.72 g, 0.00814 mol) as described in procedure A and chromatography of the product on silica gel with 4% MeOH−0.4% NH_4OH−CH_2Cl_2 gave 2.59 g (87.4%) of **49**: ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.1 Hz, 3H), 1.30 (s, 3H), 1.37 (s, 3H), 1.38 (m, 4H), 1.60 (m, 8H), 2.61 (m, 6H), 2.71 (m, 2H), 2.98 (s, 3H), 7.17 (d,d, J = 8.6 Hz, 4H); MS (EI) *m*/*z* (relative intensity) 400 (M^+, 2.9), 3.85 (4.8), 380 (3.7), 365 (2.1), 321 (3.5), 301 (6.7), 283 (100), 188 (50.3), 168 (48.0), 72 (27.4); HRMS (FAB) calcd for $C_{21}H_{38}N_2O_2FS$ 401.2638 (M + H^+), found 401.2645.

(*E*)-*N*-[4-[4-[Ethyl(6-fluoroheptyl)amino]-1-butenyl]phenyl]methanesulfonamide (*E*)-2-Butenedioate (2:1) Salt (50E). A stirred, ice-cold solution of **36** (0.93 g, 2.31 mmol) in 5 mL of CH_2Cl_2, under nitrogen was treated dropwise during 20 min with 3.0 mL of trifluoroacetic acid, kept in the ice bath for 30 min and at ambient temperature for 22 h and concentrated under a stream of nitrogen. The residue was mixed with ice, neutralized with saturated $NaHCO_3$ and extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 5% MeOH−0.25% of NH_4OH−$CHCl_3$ gave 0.29 g (0.76 mmol) of product which was treated with fumaric acid (0.044 g, 0.38 mmol) and crystallized from acetone to give 0.24 g (23.5%) of **50E**: mp 109−111 °C; ^1H NMR [$(CD_3)_2SO$] δ 1.03 (t, J = 7.1 Hz, 3H), 1.20, 1.28 (d, d, J = 6.2 Hz, 3H), 1.42 (m, 8H), 2.36 (m, 2H), 2.63 (m, 9H), 2.97 (s, 3H), 4.56, 4.72 (m, m, 1H), 6.20 (t, t, J = 15 Hz, 9 Hz, 1H), 6.41 (d, J = 15 Hz, 1H), 6.50 (s, 1H), 7.14 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H); IR 2475, 2379, 2299, 1608, 1582 cm^{-1}; MS *m*/*z* (relative intensity) 384 (M^+, 0.1), 369 (0.4), 281 (1.4), 174 (100). Anal. ($C_{22}H_{35}FN_2O_4S$) H, N, S; C: calcd, 59.70; found, 59.28.

***N*-[4-[4-(Ethylamino)-1,4-dioxobutyl]phenyl]methanesulfonamide (8).** A stirred slurry of **12**[31] (20 g, 0.0737 mol) in THF (600 mL) was treated with triethylamine (13.7 mL, 0.0981 mol), cooled to −12 °C and treated, dropwise, with isobutyl chloroformate (12.7 mL, 0.0981 mol). This mixture was stirred at −12 °C for 1.5 h, treated, dropwise, with a solution of ethylamine (4 g, 0.09 mol) and triethylamine (13.7 mL, 0.0981 mol) in THF (173 mL), kept for 3 h at −12 °C and poured into 780 mL of a mixture of ice and 1 N HCl. A stream of nitrogen was bubbled through this mixture for 18 h to remove most of the THF; the resulting solid was collected by filtration, washed with dilute $NaHCO_3$ and water and dried in vacuo to give 14.3 g of product. The filtrate was extracted with EtOAc to give an additional 4 g of product. The combined product was washed with MeOH and dried to give 13.8 g (62.5%) of **8**. A sample, recrystallized from acetonitrile, had: mp 210−213 °C; IR 3375, 3145, 3060, 1667, 1649, 1604 cm^{-1}; MS *m*/*z* (relative intensity) 298 (M^+, 14.3), 254 (8.4), 226 (5.5), 198 (100), 119 (23.5), 100 (13.9): ^1H NMR [$(CD_3)_2NCOD$] δ 1.01 (t, J = 7.2 Hz, 3H), 2.51, (t, J = 6.6 Hz, 2H), 3.12 (t, J = 7.2 Hz, 2H), 3.15 (s, 3H), 3.24 (t, J = 6.6 Hz, 2H). Anal. ($C_{13}H_{18}N_2O_4S$) C, H, N, S.

***N*-[4-[4-(Ethylamino)-1-hydroxybutyl]phenyl]methanesulfonamide (4).** Compound **8** (3.0 g, 0.010 mol) was added, portionwise to an ice-cold, stirred slurry of $LiAlH_4$ (1.15 g, 0.030 mol) in THF (75 mL), under nitrogen. The mixture was stirred in the ice bath for 1 h and at ambient temperature for 2 h; it was then diluted with THF (100 mL), warmed briefly to the reflux temperature and kept at ambient temperature for 18 h. The stirred mixture was treated carefully with 69 mL of saturated potassium sodium tartrate, kept for 1 h, and extracted with EtOAc. The product remained in the aqueous layer which was freeze-dried. The solid residue was extracted with MeOH. The extract was concentrated and the semisolid residue was extracted with CH_2Cl_2. Concentration of this extract gave the crude product which was chromatographed on silica gel (300 g) with 10−20% MeOH−1% NH_4OH−$CHCl_3$ and crystallized from MeOH−EtOAc to give 540 mg (18.9%) of **4**: mp 178.5−180.5 °C; IR 3387, 3127 cm^{-1}; MS *m*/*z* (relative intensity) 268 (M^+, 9.0), 253 (6.2), 207 (39.5), 162 (70.3), 58 (100); ^1H NMR [$(CD_3)_2SO$] δ 1.00 (t, 3H), 1.4, (m), 1.58 (t), 2.93 (s, 3H), 3.70 (s), 4.46 (t). Anal. ($C_{13}H_{22}N_2O_3S$) C, H, N, S.

(*S*)-(−)-*N*-[4-[4-(Ethylamino)-1-hydroxy-4-oxobutyl]phenyl]methanesulfonamide (10). A stirred mixture of **8** (490.1 g, 1.64 mol) and THF (4 L) was cooled, under nitrogen, to −30 to −35 °C and treated during 1.5 h with a solution of (−)-B-chlorodiisopinocampheylborane (920 g, 2.86 mol) in THF (2 L). The mixture was stirred at −25 °C for 3.5 h, treated with diethanolamine (600 mL) and kept at 0−10 °C for 10 min and at ambient temperature for 18 h. The resulting mixture was concentrated to a slurry while adding MeOH to displace the residual solvent. The concentrate was mixed with MeOH and washed with heptane. The resulting MeOH solution was concentrated and the residual oil was combined with the product from a similar reduction of 53 g (0.178 mol) of **8** and chromatographed on silica gel with mixtures of MeOH−CH_2Cl_2 contining 0−10% MeOH. The product was crystallized from acetonitrile−*tert*-butyl methyl ether at 0 °C to give 71.7 g (13.1%) of **10**: mp 137−138 °C; $[\alpha]_D^{24}$ −16 (*c* 0.95, EtOH]; MS *m*/*z* (relative intensity) 300 (M^+, 3.5), 282 (1.2), 214 (3.2), 200 (4.5), 130 (5.7), 121 (5.0), 101 (14.9), 87 (100), 71 (28.6); IR 3370, 3116, 3053, 3033, 3017, 1642, 1612 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 0.97 (t, J = 7.2 Hz, 3H), 1.78 (m, 2H), 2.07 (m, 2H), 2.95 (s, 3H), 3.02 (m, 2H), 4.46 (m, 1H), 5.26 (d, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.78 (m, 1H), 9.66 (br s, 1H). Anal. ($C_{13}H_{20}N_2O_4S$) C, H, N, S.

The chiral purity of this sample of **10** was found to be 99.5% by allowing it to react with 1-naphthyl isocyanate and analyzing the resulting carbamate by HPLC on a Pirkle covalent 5-μm *N*-(3,5-dinitrobenzyl)-D-phenylglycine analytical column with 20% hexane−80% EtOH which contained 0.1% TEA and 0.1% TFA.[36] The mother liquors from this crystallization were concentrated in vacuo and the residue was dissolved in warm CH_3CN and washed with heptane. The resulting CH_3CN

solution was concentrated in vacuo and the residue was crystallized from MeOH−*tert*-butyl methyl ether at 0 °C to give 323 g (59.1%) of additional **10**: mp 138−139.5 °C; $[\alpha]^{24}_D$ −16° (*c* 0.954, EtOH) which had a chiral purity of 99.4% by HPLC.

(*S*)-(−)-*N*-[4-[4-(Ethylamino)-1-hydroxybutyl]phenyl]-methanesulfonamide (5). A 65% solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (44 mL, 0.146 mol) was mixed with THF (100 mL), under nitrogen, and the stirred mixture was treated, portionwise during 1 h 20 min with a suspension of **10** (11.5 g, 0.0381 mol) in THF (360 mL); a slight exothermic reaction raised the temperature of the mixture to 30 °C during the addition. The mixture was stirred at ambient temperature for 18 h, cooled to 4 °C and treated, dropwise with 22.4 mL of 6 M H_2SO_4. The first few drops of acid caused a vigorous reaction. When this was no longer evident, the cooling bath was removed and the remainder of the acid was added during 40 min. After an additional 10 min MeOH (150 mL) was added to the mixture. Since the pH of the mixture was 4, $NaHCO_3$ (2.47 g) was added and stirring was continued for 1.5 h; the pH of the mixture was now 9−10. The solid was collected by filtration and washed successively with 10% MeOH−THF (500 mL), 10% MeOH−CH_2Cl_2 (1 L) and 10% MeOH−$CHCl_3$ (2 L). The filtrates were concentrated and the product was crystallized from acetonitrile to give 7.29 g (66.8%) of **5**: mp 168−170 °C; $[\alpha]^{24}_D$ −20° (*c* 0.8515, MeOH); MS (EI) *m/z* (relative intensity) 286 (M^+, 1.1), 268 (21.0), 253 (47.8), 207 (12.7), 184 (25.1), 162 (32.1), 98 (48.0), 58 (100); ^{1}H NMR [$(CD_3)_2SO$] δ 0.98 (t, J = 7.2 Hz, 3H), 1.40, (m, 2H), 1.59 (m, 2H), 2.48 (m, 4H), 2.92 (s, 3H), 4.45 (t, J = 6.0 Hz, 1H), 4.57 (br s, 2H), 7.12 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H); IR 3478, 3385, 3139, 2651, 2500, 2378, 1605 cm^{-1}. Anal. ($C_{13}H_{22}N_2O_3S$) C, H, N, S.

(*R*)-(+)-*N*-[4-[4-(Ethylamino)-4-oxo-1-acetyoxybutyl]-phenyl]methanesulfonamide (11). This material (**11**) was obtained as a byproduct from the preparation of **10** from the racemate by a lipase mediated acylation. [*Pseudomonas cepaica* (PS-30) supported on Celite and isopropenyl acetate in THF at 40−45 °C. A quantitative conversion of the *R*-enantiomer to the *O*-acetate was obtained.][37] It was recrystallized to constant melting point from EtOAc: mp 102−104 °C; $[\alpha]^{24}_D$ +68° (*c* 0.9785, EtOH); IR 3373, 3288, 1727, 1667, 1649, 1613 cm^{-1}; FAB MS *m/z* (relative intensity) 343 ($M + H^+$, 2.2), 342 (M^+, 4.4), 299 (7.2), 283 (100); ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.2 Hz, 3H), 2.07 (s, 3H), 2.16 (m, 4H), 2.98 (s, 3H), 3.27 (m, 2H), 5.65 (m, 1H), 5.71 (m, 1H), 7.23 (m, 4H), 7.50 (s, 1H). Anal. ($C_{15}H_{22}N_2O_5S$) C, H, N.

(*R*)-(+)-*N*-[4-[4-(Ethylamino)-1-hydroxybutyl]phenyl]-methanesulfonamide (6). A stirred mixture of a 70% toluene solution of sodium bis(2-methoxyethoxy)aluminum hydride (155.7 g, 0.539 mol) in THF (600 mL), under nitrogen was treated, dropwise during 95 min with a solution of **11** (16.0 g, 0.0467 mol) in THF (120 mL) keeping the temperature of the mixture at 21−29 °C. It was kept at ambient temperature for 20 h, cooled in an ice bath and treated dropwise during 50 min with 20 drops of 6 M H_2SO_4; this was accompanied by a vigorous evolution of hydrogen; the temperature of the mixture was maintained at 5−7 °C during this addition. The remainder of a total of 76.5 mL of 6 M H_2SO_4 was then added dropwise during 90 min at ambient temperature. The mixture was stirred for 20 min, treated with MeOH (355 mL) and stirred for 30 min. The pH of the mixture was 4. Solid $NaHCO_3$ (6.0 g) was added and the mixture was stirred for 90 min (pH 7−8) and filtered. The solid was washed with 1.4 L of 20% MeOH−CH_2Cl_2 and the filtrate was concentrated in vacuo. Chromatography of the residue on silica gel with mixtures of MeOH−NH_4OH−$CHCl_3$ containing 10−15% MeOH and 0.5−1% NH_4OH gave the product which was crystallized from acetonitrile to give 3.08 g (23.1%) of **6**: mp 167−169 °C; $[\alpha]^{24}_D$ +18° (*c* 0.9445, MeOH); MS (ES) *m/z* 287 $(M + H)^+$; ^{1}H NMR [$(CD_3)_2SO$] δ 0.96 (t, J = 7.1 Hz, 3H), 1.39, (m, 2H), 1.57 (m, 2H), 2.48 (m, 4H), 2.91 (s, 3H), 4.44 (t, J = 6.3 Hz, 1H), 7.11 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H).

***N*-[4-[4-(Ethylamino)-4-oxobutyl]phenyl]methanesulfonamide (51).** A stirred mixture of 4-[4-(methanesulfonylamino)phenyl]butyric acid[61] (29.9 g, 0.116 mol) and triethylamine (21.5 mL, 0.154 mol) in THF (1300 mL) under nitrogen was cooled in an ice−2-propanol bath and treated dropwise during 10 min with isobutyl chloroformate (20.0 mL, 0.154 mol). It was stirred for 1.25 h and treated during 25 min with a solution of 2 M ethylamine in THF (100 mL) and triethylamine (21.5 mL), stirred for 2.5 h and filtered. The filtrate was concentrated and the residue crystallized from EtOAC to give 14.9 g (45.3%) of **51**: mp 122−123 °C; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.2 Hz, 3H), 1.94, (m, 2H), 2.17 (t, J = 7.2 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 2.99 (s, 3H), 3.30 (m, 2H), 5.48 (br s, 1H), 6.87 (s, 1H), 7.16 (s, 4H); MS *m/z* (relative intensity) 284 (M^+, 27.9), 240 (3.5), 205 (8.2), 132 (26.6), 118 (18.9), 106 (20.7), 87 (100), 72 (69.1); IR 3365, 3141, 1646, 1616 cm^{-1}. Anal. ($C_{13}H_{20}N_2O_3S$) C, H, N, S.

***N*-[4-[4-(Ethylamino)butyl]phenyl]methanesulfonamide (7).** A stirred, ice-cold suspension of $LiAlH_4$ (2.9 g, 0.0763 mol) in THF (68 mL) under nitrogen was treated dropwise during 70 min, with a solution of **51** (9.88 g, 0.0347 mol) in THF (200 mL). The mixture was kept at ambient temperature for 1 h, at reflux for 4.5 h and at ambient temperature for 18 h. It was then cooled in an ice bath, treated cautiously with 125 mL of a saturated aqueous potassium sodium tartrate solution, stirred at ambient temperature for 1 h, and extracted with EtOAc; the extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was crystallized from acetonitrile to give 6.03 g (64.3%) of **7**: mp 108−109 °C; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 3H), 1.52, (m, 2H), 1.61 (m, 2H), 2.64 (m, 6H), 2.96 (s, 3H), 3.42 (br s, 2H), 7.13 (s, 4H); MS (EI) *m/z* (relative intensity) 270 (M^+, 5.1), 255 (3.0), 191 (31.3), 146 (22.0), 58 (100); IR 3101, 2337, 1610, 1505 cm^{-1}. Anal. ($C_{13}H_{22}N_2O_2S$) C, H, N, S.

***N*-Ethyl-5-acetylvaleramide (28).** A stirred solution of 5-acetylvaleric acid (1.00 g, 6.94 mmol) and triethylamine (1.29 mL, 9.23 mmol) in THF (50 mL) was cooled, under nitrogen, in an ice−2-propanol bath (−5 to −10 °C) and treated, dropwise with isobutyl chloroformate (1.2 mL, 9.2 mmol). The thick mixture was kept in the bath for 3 h, treated during 8.5 min with a solution of ethylamine (0.7 mL, 10.4 mmol) and triethylamine (1.29 mL, 9.23 mmol) in THF (15 mL) and stirred for 2.75 h. The solid was collected by filtration and the filtrate was concentrated. Chromatography of the residue on silica gel with 3% MeOH−CH_2Cl_2 and crystallization of the product from Et_2O gave 0.681 g (57.3%) of **28**: mp 55.5−58 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.3 Hz, 3H), 1.61, (m, 4H), 2.15 (s, 3H), 2.18 (m, 2H), 2.48 (m, 2H), 3.30 (m, 2H), 5.67 (br s, 1H). Anal. ($C_9H_{17}NO_2$) C, H, N.

***N*-Ethyl-5-acetylvaleramide Ethylene Dithioketal (29).** According to the method of Sondej and Katzenellenbogen,[40] a stirred mixture of **28** (0.5 g, 2.92 mmol) and 1,2-ethanedithiol (0.49 mL, 5.84 mmol), under nitrogen, was treated with boron trifluoride−acetic acid complex (0.41 mL, 2.9 mmol) and kept at ambient temperature for 15 min. It was then diluted with EtOAc, washed with aqueous $NaHCO_3$, 15% NaOH and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue over silica gel with 1.5% MeOH−0.05% Et_3N−CH_2Cl_2 and crystallization of the product from Et_2O−pentane gave 0.597 g (82.7%) of **29**: mp 54−55 °C; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.3 Hz, 3H), 1.54, (m, 2H), 1.68 (m, 2H), 1.75 (s, 3H), 1.95 (m, 2H), 2.18 (t, J = 7.1 Hz, 2H), 3.31 (m, 6H), 5.46 (br s, 1H); MS (EI) (relative intensity) 247 (M^+, 22.5) 214 (10.5), 203 (2.1), 188 (40.0), 154 (50.1), 119 (100), 87 (47.4); IR 3300, 3206, 3098, 1641 cm^{-1}. Anal. ($C_{11}H_{21}N_1O_1S_2$) C, H, N, S.

***N*-Ethyl-6,6-difluoroheptanamide (30).** According to the method of Sondej and Katzenellenbogen,[40] a stirred suspension of 1,3-dibromo-5,5-dimethylhydantoin (0.116 g, 0.404 mmol) in CH_2Cl_2 (0.8 mL) was cooled, under nitrogen, in a dry ice−acetone bath and treated with hydrogen fluoride−pyridine (0.2 mL) followed by a solution of **29** (0.10 g, 0.40 mmol) in CH_2Cl_2 (0.2 mL). It was kept in the dry ice bath for 10 min and at ambient temperature for 15 min, adsorbed on a basic alumina (3 mL) column and eluted with CH_2Cl_2. The eluate was concentrated and the residue chromatographed on silica gel with 1−2% MeOH−CH_2Cl_2 to give 0.021 g (27%) of crystalline

product **30**: mp 41−42 °C; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.2 Hz, 3H), 1.52, (m, 2H), 1.58 (t, J = 30.7 Hz, 3H), 1.67 (m, 2H) 1.85 (m, 2H), 2.19 (t, J = 7.2 Hz, 2H), 3.30 (m, 2H), 5.51 (br s); MS (EI) *m/z* (relative intensity) 193 (M^+, 1.9), 178 (4.5), 149 (3.4), 129 (6.2), 114 (6.6), 100 (9.9), 87 (100).

(6,6-Difluoroheptyl)ethylamine (27). An ice-cold stirred suspension of $LiAlH_4$ (0.21 g, 5.65 mmol) in THF (5 mL) under nitrogen, was treated dropwise with a solution of **30** (0.464 g, 2.4 mmol) in THF (5 mL) and kept in the ice bath for 10 min, at ambient temperature for 1 h and at 80 °C for 2.5 h. It was then cooled in an ice bath and treated successively with water (0.2 mL), 15% NaOH (0.2 mL) and water (0.6 mL), stirred at ambient temperature for 1 h and filtered through Celite. The filtrate was concentrated and the residue was chromatographed on silica gel with 5% MeOH−0.5% NH_4OH−CH_2Cl_2 to give 0.336 g (78.1%) of **27**: ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.1 Hz, 3H), 1.5, (m, 7H), 1.58 (t, J = 30.7 Hz, 3H), 1.84 (m, 2H) 2.65 (m, 4H).

***N*-[4-[4-[(6,6-Difluoroheptyl)ethylamino]-1,4-dioxobutyl]phenyl]methanesulfonamide (9).** A stirred mixture of **12**[31] (0.56 g, 2.06 mmol) and triethylamine (0.33 mL, 2.38 mmol) in THF (10 mL) was cooled, under nitrogen, in an ice−methanol bath and treated with isobutyl chloroformate (0.31 mL, 2.38 mmol). It was kept in the bath for 2 h, treated with a solution of **27** (0.336 g, 1.87 mmol) and triethylamine (0.33 mL, 2.38 mmol) in THF (0.7 mL), kept in a cold bath for 21 h and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel with 2% MeOH/CH_2Cl_2 to give 0.379 g (46.9%) of **9**: mp 103−108 °C; ^{1}H NMR ($CDCl_3$) δ 1.48 (br m, 14H), 2.82 (m, 2H), 3.01 (s, 3H), 3.27 (m, 2H), 3.42 (m, 4H), 7.21 (d, J = 8.7 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H), 8.61 (d, 1H); MS (EI) *m/z* (relative intensity) 432 (M^+, 9.3), 254 (100), 234 (28.0), 198 (32.8), 178 (49.2), 119 (14.3).

6-Hydroxy-6-methylheptyl THP Ether (13). Compound **13** was prepared in 56% yield by the reaction of the THP ether of 5-hydroxypentylmagnesium chloride with acetone according to the procedure of Buendia.[38] It was purified by silica gel chromatography with mixtures of EtOAc, Et_3N and hexane that contained 10−20% EtOAc and 0.05% Et_3N. It had: ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 6H), 1.5 (m, 14H), 3.40 (m, 1H), 3.52 (m, 1H), 3.73 (m, 1H), 3.87 (m, 1H), 4.58 (m, 1H); MS (CI) *m/z* (relative intensity) 231 (M + H^+, 63.8), 461 (2 M + H^+, 7.1), 213 (100); IR 3436 cm^{-1}.

6-Fluoro-6-methylheptyl THP Ether (14). A stirred solution of 4.6 mL (34.5 mmol) of DAST in CH_2Cl_2 (12 mL), under nitrogen was cooled in a dry ice−acetone bath and treated during 4−5 min with a solution of **13** (3.97 g, 17.3 mmol) in CH_2Cl_2 (12 mL). The mixture was kept in the dry ice bath for 15 min and in an ice bath for 10 min. It was then mixed with 10% aqueous Na_2CO_2 (60 mL). The layers were separated and the CH_2Cl_2 layer was washed with water, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 2.5% EtOAc−0.05% Et_3N−hexane gave 3.36 g (83.6%) of **14** which had: ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.37 (s, 3H), 1.40 (m, 4H), 1.62 (m, 10H), 3.39 (m, 1H), 3.52 (m, 1H), 3.74 (m, 1H), 3.87 (m, 1H), 4.58 (m, 1H).

6-Fluoro-6-methylheptanol (52). A stirred solution of **14** (3.34 g, 14.4 mmol) and pyridinium tosylate (0.47 g, 1.87 mmol) in absolute EtOH (120 mL) was kept under nitrogen at ambient temperature for 41 h and concentrated in vacuo. A solution of the residue in EtOAc was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue, combined with the product from a previous reaction (0.844 mmol), was chromatographed over silica gel with 5−20% EtOAc−hexane to yield 1.86 g (82.2%) of **52**: ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.38 (s, 3H), 1.41 (m, 5H), 1.59 (m, 4H), 3.65 (t, 2H); MS (EI) *m/z* (relative intensity) 1.28 (12.9), 111 (8.1), 110 (9.5), 95 (41.3); IR 3581, 3345 cm^{-1}.

1-Bromo-6-fluoro-6-methylheptane (15). As described in procedure C, **52** (0.427 g, 0.00288 mol) was allowed to react with NBS and triphenylphosphine. Chromatography of the product on silica gel with 1−3% EtOAc−hexane gave 0.440 g (72.3%) of **15**: ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.38 (s, 3H), 1.44 (m, 4H), 1.62 (m, 2H), 1.88 (m, 2H), 3.42 (t, 2H); MS (EI) *m/z* (relative intensity) 190 (4.2), 135 (6.9), 111 (59.0), 61 (100).

4-Chlorobutyl THP Ether (55). A stirred solution of 4-chloro-1-butanol (23.0 mL, 0.230 mol) and 3,4-dihydro-2*H*-pyran (32.0 mL, 0.351 mol) in Et_2O (500 mL) was treated with 10-camphorsulfonic acid (5.33 g, 0.023 mol) and kept, under nitrogen, at ambient temperature for 18 h. Additional 3,4-dihydro-2*H*-pyran (5 mL, 0.0548 mol) as added and the reaction was continued for 5 h. The mixture was washed with 8% $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The residue was distilled to give **55**: bp 58 °C (0.01 kPa).

5-Hydroxy-5-methylhexyl THP Ether (56). A mechanically stirred refluxing mixture of magnesium turnings (1.27 g, 0.052 mol) and THF (5 mL), under nitrogen, was treated dropwise with a solution of **55** (5.00 g, 0.260 mol) in THF (27 mL). After a small amount of **55** had been added, the reaction was started by the addition of several drops of 1,2-dibromoethane and crushing some of the magnesium. After the addition, the mixture was refluxed for 1 h, cooled in an ice bath, and treated dropwise with a solution of acetone (2.29 mL, 0.0312 mol) in THF (24 mL). This mixture was kept at ambient temperature for 20 h, cooled in an ice bath and treated, dropwise with saturated NH_4Cl (29.5 mL). It was stirred for 1 h and then extracted with EtOAc. The extracts were washed with dilute aqueous NaCl, dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel with 5−20% EtOAc−0.05% Et_3N−hexane to give 1.64 g (29.2%) of **56**: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 6H), 1.58 (s, 13H), 3.47 (m, 2H), 3.82 (m, 2H), 4.58 (m, 1H); MS *m/z* (relative intensity) 115 (18.7), 101 (15.3), 85 (100), 59 (25.3); IR (film) 3452 cm^{-1}.

5-Fluoro-5-methylhexyl THP Ether (57). The reaction of **56** (7.4 mmol) with DAST was carried out as described for the preparation of **14** to give a 75.6% yield of **57**: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.38 (s, 3H), 1.6 (m, 12H), 3.47 (m, 2H), 3.82 (m, 2H), 4.58 (m, 1H).

5-Fluoro-5-methylhexanol (58). A stirred solution of **57** (1.22 g, 5.59 mmol) and 10-camphorsulfonic acid (0.233 g, 1 mmol) in MeOH (144 mL) was kept at ambient temperature, under nitrogen for 20 h and concentrated. The residue was mixed with EtOAc (100 mL), washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with 5−30% EtOAc−hexane to give 0.400 g (53.4%) of **58**: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.36 (s, 3H), 1.58 (m, 6H), 2.72 (s, 1H), 3.64 (t, J = 6.28 Hz, 2H).

1-Bromo-5-fluoro-5-methylhexane (16). Procedure C. A stirred solution of **58** (0.400 g, 2.98 mmol) and triphenylphosphine (0.859 g, 3.28 mmol) in benzene (5.4 mL), under nitrogen, was cooled in an ice bath and treated, portionwise during 20 min, with NBS (0.580 g, 3.28 mmol). The mixture was kept in the ice bath for 30 min and at ambient temperature for 5 h, diluted with pentane (20 mL) and cooled in an ice bath. The solid was collected by filtration and washed with pentane. The filtrate was concentrated and the residue was mixed with pentane, cooled in an ice bath and filtered. The filtrate was concentrated and the residue was mixed with Et_2O, washed with cold 5% sodium thiosulfate, 0.5 N NaOH and brine, dried ($MgSO_4$) and concentrated to give 0.51 g (86.8%) of **16** which was used without further purification in the next reaction.

7-Bromoheptanol (53). A solution of 8-bromo-1-octene (5.0 g, 26 mmol) in a mixture of 25 mL of MeOH and 5 mL of CH_2Cl_2 was cooled to −50 °C and treated with O_3 until a blue color persisted (45 min) and then for an additional 10 min. The cold mixture was purged with N_2, allowed to warm to −20 °C and treated with 1.3 g (34 mmol) of sodium borohydride in portions over 30 min. The mixture was stirred for 30 min at −20 °C then treated dropwise with 20 mL of H_2O. This mixture was stirred for 10 min, and extracted with hexane; the organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated to give 3.65 g (72%) of **53**: ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 9H), 1.85 (m, 2H), 3.41 (t, J = 6.84, 2H), 3.65 (t, J = 6.53 Hz, 2H).

1-Bromo-7-fluoroheptane (17). A stirred solution of **53** (1.53 g 7.85 mmol) in 2.5 mL of CCl_4 was cooled in an ice bath, under nitrogen, an treated with 2.25 mL (17.0 mmol) of DAST; the flask was stoppered, kept in the ice bath for 30 min and at ambient temperature 4.5 h. Additional DAST (0.7 mL, 5.3 mmol) was added and the mixture was stirred at ambient temperature for 18 h. It was then added dropwise to 25 mL of ice water and extracted with hexane. The organic extracts were washed with water, 10% aqueous Na_2CO_3, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed under pressure over silica gel with 4% CH_2Cl_2−hexane to give 0.9 g (53%) of **17**: ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 6H), 1.71 (m, 2H), 1.87 (m, 2H), 3.42 (t, J = 6.84, 2H), 4.37 (t, J = 6.07 Hz, 1H), 4.52 (t, J = 6.07 Hz, 1H).

6-Bromohexanal (54). A stirred solution of oxalyl chloride (6.7 mL, 77 mmol) in 50 mL of CH_2Cl_2, under nitrogen, was cooled to −70 °C, treated dropwise over 15 min with 10.9 mL (154 mmol) of DMSO in 50 mL of CH_2Cl_2, kept at −70 °C for 20 min and treated over 7 min with 6-bromohexanol (6.8 g, 37.6 mmol) in 50 mL of CH_2Cl_2. The mixture was allowed to warm to −20 °C during 2.5 h. It was kept at this temperature for 1.5 h, recooled to −65 °C and treated, dropwise during 5 min with Et_2N (32.1 mL). This mixture was warmed to ambient temperature during 30 min, diluted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$) and concentrated. A solution of the residue in hexane was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 6.38 g (95%) of **54**: ^{1}H NMR ($CDCl_3$) δ 1.42 (m 2H), 1.58 (m, 2H), 1.82 (m, 2H), 2.41 (m, 2H), 3.35 (t, 2H), 9.71 (s, 1H).

1-Bromo-6,6-difluorohexane (18). An ice-cold, stirred solution of **54** (1.0 g, 5.58 mmol) in 1.5 mL of CCl_4, under nitrogen was treated with 1.5 mL (1.8 g, 11.2 mmol) of DAST. The flask was stoppered, kept in the ice bath for 90 min and at ambient temperature for 18 h. The resulting mixture was added dropwise with stirring to ice water (20 mL), neutralized with Na_2CO_3 and extracted with hexane. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue over silica gel with 2.5% CH_2Cl_2−hexane gave 0.37 g (33%) of **18**: ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 4H), 1.89 (m, 4H), 3.42 (t, J = 6.7 Hz, 2H), 5.63, 5.82, 6.00 (t,t,t, J = 4.4 Hz, 1H).

Ethyl 6-Hydroxyheptanoate (59). A solution of 6-methyl-ϵ-caprolactone[62] (18.94 g, 0.148 mol) in 65 mL of absolute EtOH was treated with 0.8 mL of concentrated H_2SO_4, stirred at ambient temperature for 7 h and concentrated in vacuo. The residue was treated with ice, neutralized with dilute $NaHCO_3$ and extracted with Et_2O. The extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Distillation of the residue (24.4 g) combined with 6.2 g of product from a previous reaction gave 18.5 g, bp 96 °C (0.29 kPa), and 6.73 g, bp 91 °C (0.1 kPa), of **59**: ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 6.21 Hz, 3H), 1.26 (t, J = 7.08 Hz, 3H) 1.43 (m, 5H), 1.65 (m, 2H), 2.32 (t, J = 7.37 Hz, 2H), 3.81 (m, 1H), 4.12 (q, J = 7.19 Hz, 2H).

Ethyl 6-Fluoroheptanoate (60). A stirred solution **59** (18.4 g, 0.106 mol) in 200 mL of CH_2Cl_2, under nitrogen, was cooled in a dry ice−acetone bath and treated dropwise with a solution of 30 mL (0.225 mol) of DAST in CH_2Cl_2 (195 mL) over 1 h. The mixture was kept at −70 °C for 1 h, warmed to 5 °C during 2 h 40 min and poured into a stirred mixture of 600 mL of 10% Na_2CO_3 and 200 mL of ice. This was extracted with Et_2O; the extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Distillation of the residue gave 7.16 g (38.5%) of **60**: bp 76−78 °C (0.77 kPa); ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 4.5H), 1.35 (d, J = 6.11 Hz, 1.5H), 1.57 (m, 6H), 2.32 (t, J = 7.32 Hz, 2H) 4.13 (q, J = 7.13 Hz, 2H), 4.57, 4.72 (m,m, 1H).

6-Fluoroheptanol (61). A solution of **60** (10.4 g, 0.059 mol) in Et_2O (35 mL) was added during 45 min, under nitrogen, to a stirred ice-cold mixture of $LiAlH_4$ (3.64 g, 0.096 mol) in Et_2O (200 mL). The mixture was kept in the ice bath for 15 min and allowed to warm to ambient temperature during 100 min. It was again cooled in an ice bath and treated during 40 min with saturated aqueous Na_2SO_4 (35 mL). This mixture was filtered through Na_2SO_4 and the filtrate was concentrated. Distillation of the residue gave 5.38 g (68%) of **61**: bp 85−87 °C (1.2 kPa); ^{1}H NMR ($CDCl_3$) δ 1.27, 1.35 (d,d, J = 6.16 Hz, 3H), 1.55 (m, 9H), 3.65 (t, J = 6.48 Hz, 2H) 4.58, 4.73 (m,m, 1H).

1-Bromo-6-fluoroheptane (19). In the manner described in procedure C, **61** (4.8 g, 0.0358 mol) was allowed to react with NBS and triphenylphosphine to give 6.6 g (93.6%) of **19**: ^{1}H NMR ($CDCl_3$) δ 1.22, 1.28 (d,d, J = 6.21 Hz, 3H), 1.57 (m, 6H), 1.88 (m, 2H), 3.42 (t, J = 6.8 Hz, 2H) 4.57, 4.73 (m,m, 1H).

1-Bromoheptanal (62). A solution of 8-bromo-1-octene (5.0 g, 0.026 mol) in MeOH (25 mL) and CH_2Cl_2 (5 mL) was cooled to −40 to −60 °C, treated during 40 min with excess ozone and purged with a stream of nitrogen. It was then treated with dimethyl sulfide (2.5 mL), warmed to −10 °C during 3 h and concentrated. The residue was mixed with water and extracted with hexane; the extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue on silica gel with 5−10% EtOAc−hexane gave 1.75 g (34.9%) of **62**: ^{1}H NMR ($CDCl_3$) δ 1.41 (m, 4H), 1.63 (m, 2H), 1.87 (m, 2H), 2.45 (m, 2H), 3.41 (m, 2H), 9.78 (s, 1H).

1-Bromo-7,7-difluoroheptane (20). A stirred solution of **62** (0.65 g, 3.4 mmol) in CCl_4 (1 mL) was cooled in an ice bath, under nitrogen, and treated with DAST (1.0 mL, 7.6 mmol). The flask was stoppered and the mixture was kept at ambient temperature for 7 h, mixed with ice, neutralized with 10% aqueous $NaCO_3$, and extracted with hexane. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue on silica gel with 5% CH_2Cl_2−hexane gave 0.53 g (72.5%) of **20**: ^{1}H NMR ($CDCl_3$) δ 1.47 (m, 6H), 1.84 (m, 4H), 3.41 (t, J = 6.7 Hz, 2H), 5.61, 5.80, 5.99 (t,t,t, J = 4.5 Hz, 1H).

6-Heptenoic Acid *tert*-Butyl Ester (21).[63] A stirred solution of diisopropylamine (15.4 g, 0.152 mol) in THF (150 mL) was cooled in an ice bath, under nitrogen and treated dropwise during 14 min with 1.6 N *n*-butyllithium in hexane (95.3 mL, 0.152 mol). This mixture was kept in the ice bath for 20 min and then cooled in a dry ice−acetone bath and treated dropwise during 10 min with a solution of *tert*-butyl acetate (17.7 g, 0.152 mol) in THF (25 mL). This mixture was stirred for 45 min and then treated dropwise during 15 min with a solution of 5-bromo-1-pentene (25.0 g, 0.168 mol) in hexamethylphosphoramide (27 g, 0.152 mol). Stirring was continued for 1 h when the mixture was warmed in an ice bath for 1.5 h and at ambient temperature for 1.5 h. It was treated, dropwise, during 10 min with saturated aqueous NH_4Cl (75 mL) and mixed with Et_2O (280 mL). The aqueous layer was extracted with Et_2O and the organic solution was dried ($MgSO_4$) and concentrated in vacuo. Distillation of the oily residue gave 12.8 g (45.8%) of **21**: bp 45−56 °C (0.09 kPa); ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 2H), 1.44 (s, 9H), 1.60 (m, 2H), 2.06 (m, 2H), 2.22 (m, 2H), 4.98 (m, 2H), 5.80 (m. 1H).

7-Bromo-6-fluoroheptanoic Acid *tert*-Butyl Ester (22).[39] A stirred mixture of **21** (22.1 g, 0.120 mol), and NBS (25.6 g, 0.144 mol) in CH_2Cl_2 (63 mL) was cooled in an ice bath under nitrogen and treated dropwise during 21 min with a solution of triethylamine trihydrofluoride (38.6 g, 0.240 mol) in CH_2Cl_2 (63 mL). This mixture was kept in the ice bath for 4.5 h; the solid slowly dissolved during 4 h and then the solution became yellow. The mixture was poured into ice water (1 L) and the pH was adjusted to 9 with about 36.5 mL of NH_4OH. It was extracted with CH_2Cl_2. The extract was washed successively with cold 0.1 N HCl and aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated in vacuo. Distillation of the residue gave 25.3 g (76.6%) of **22**: bp 94−102 °C (0.03−0.08 kPa); MS (EI) *m*/*z* (relative intensity) 267 (0.13), 226 (0.40), 209 (8.6), 207 (3.4), 189 (0.72), 129 (21.9), 101 (7.0), 57 (100); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.62 (m, 6H), 2.24 (t, J = 7.3 Hz, 2H), 3.48 (m, 2H), 4.57, 4.73 (m,m, 1H); ^{19}F NMR (282.203 MHz, $CDCl_3$) δ −4.97 (13 peaks CHF), −36.60 (6 peaks, CH_2F). The area under the CH_2F peaks was 4% of the total area.

6-Fluoro-6-heptenoic Acid *tert*-Butyl Ester (23). A stirred 1 M solution of potassium *tert*-butoxide in THF (107 mL, 0.107 mol) was cooled, under nitrogen in an ice bath, and

treated dropwise during 17 min with **22** (25.3 g, 0.0893 mol) and about 10 mL of THF. A dark precipitate formed during the addition. The mixture was kept in the ice bath for 50 min, poured into ice water (250 mL), and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), concentrated and distilled to give 15.5 g (85.8%) of **23**: bp 46−49 °C (0.009−0.02 kPa); MS (EI) *m/z* (relative intensity) 146 (4.0), 129 (21.5), 109 (1.8), 81 (19.0), 57 (100); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.54 (m, 4H), 2.21 (m, 4H), 4.22 (d,d, J = 2.77, 50.3 Hz, 1H), 4.50 (d,d, J = 2.66, 17.6 Hz, 1H).

7-Bromo-6,6-difluoroheptanoic Acid *tert*-Butyl Ester (24). A stirred mixture of **23** (15.6 g, 0.0772 mol) and NBS (16.5 g, 0.0926 mol) in CH_2Cl_2 (40 mL) was cooled under nitrogen in an ice bath. A solution of triethylamine trihydrofluoride (24.9 g, 25.2 mL, 0.154 mol) in CH_2Cl_2 (40 mL) was then added dropwise. After about 25 mL of this solution had been added the temperature of the mixture began to rise and very quickly reached 35 °C; the addition was stopped and a light yellow solution was obtained. When the temperature again reached 5 °C, the remaining triethylamine trihydrofluoride solution was added; no additional increase in temperature was observed; the addition required 23 min. The mixture was kept in the ice bath for 4 h; by TLC the reaction was not complete. Additional NBS (3.4 g, 0.019 mol) and after 35 min, a solution of triethylamine trihydrofluoride (6.3 mL, 0.039 mol) in CH_2Cl_2 (10 mL) were added. The mixture was kept in the ice bath for 55 min and poured into ice water (600 mL). The pH was adjusted to 9 with NH_4OH and the mixture was extracted with CH_2Cl_2. The extract was washed with cold 0.1 N HCl and aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated. Distillation of the residue under reduced pressure separated unreacted **23** from the product which was mixed with hexane, filtered to remove a solid impurity, concentrated and redistilled to give 7.78 g (33.5%) of **24**: bp 84−87 °C (0.01−0.02 kPa); FAB MS *m/z* (relative intensity) 301 (M + H^+, 13.2) 245 (17.4), 227 (14.9), 57 (100); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.52 (m, 2H), 1.66 (m, 2H), 2.05 (m, 2H), 2.25 (t, J = 7.37 Hz, 2H), 3.51 (t, J = 12.9 Hz, 2H); ^{19}F NMR (282.2 MHz, $CDCl_3$) δ −103.08 (9 peaks).

6,6-Difluoro-1-heptanol (25). A stirred 1 M solution of $LiAlH_4$ in THF (54.4 mL, 0.054 mol) was cooled in an ice bath, under nitrogen, treated dropwise during 15 min with a solution of **24** (7.28 g, 0.0242 mol) in THF (30 mL) and kept at ambient temperature for 5.25 h. It was then treated with additional 1 M $LiAlH_4$ in THF (12 mL, 0.012 mol), kept at ambient temperature for 17 h, cooled in an ice bath and treated with H_2O (2.5 mL), 15% NaOH (2.5 mL) and H_2O (7.5 mL). This mixture was stirred at ambient temperature for 45 min and filtered. The filtrate was concentrated and the residue was combined with the product from a similar 0.00332 mol reaction and chromatographed on silica gel with 15% EtOAc−hexane to give 2.03 g (48.5%) of **25**: ^{1}H NMR ($CDCl_3$) δ 1.52 (m, 10H), 1.85 (m, 2H), 3.65 (t, J = 6.5 Hz, 2H); ^{19}F NMR (282.2 MHz, $CDCl_3$) δ −79.82 (12 peaks); MS (NH_3-CI) *m/z* (relative intensity) 170 (M + NH_4^+, 100), 52 (40.0).

1-Bromo-6,6-difluoroheptane (26). In the manner described in procedure C, **25** (2.03 g, 0.0133 mol) was allowed to react with NBS and triphenylphosphine to give 2.75 g (96.1%) of **26**: ^{1}H NMR ($CDCl_3$) δ 1.51 (m, 4H), 1.59 (t, J = 18.4 Hz, 3H), 1.88 (m, 4H), 3.42 (t, J = 6.68 Hz, 2H).

Biology. 1. In Vitro Cardiac Electrophysiology. ERPs, the longest coupling intervals between the basic drive impulse S1 and the premature impulse S2 that fail to propogate through the tissue, were determined on right ventricular papillary muscles isolated from New Zealand white rabbits using S1 frequencies of 1 and 3 Hz. Automaticity was measured in beats per minute on isolated right atria which were allowed to contract spontaneously. Working and stock solutions of test compounds were prepared by dissolving the salts in glass distilled water. Compounds evaluated as the free base were first dissolved in ethanol that contained an equivalent of fumaric acid. The solutions were then diluted with distilled water. A detailed description of this procedure has been reported.[31]

2. In Vitro Determination of Metabolic Stability. Materials: Human liver microsomes were prepared according to a standard method of Lu and Levin.[64] A stock NADPH generating system was prepared, consisting of 10 mM β-$NADP^+$, 50 mM trisodium isocitrate, 50 mM magnesium chloride, and 4 units/mL isocitrate dehydrogenase. The test compounds (substrates) were each dissolved in 0.9% sodium chloride or a pH 7.0 buffer.

Methods: The in vitro metabolic stabilities of test compounds were determined in three experiments. Although the conditions varied slightly between the experiments, **31E** was included in each experiment and the data were normalized to this compound. Incubations were prepared at a final volume of 1 mL. Human liver microsomes (1 mg protein), obtained from pooled human liver tissue, were diluted with 50 mM potassium phosphate buffer, pH 7.4. The test compounds were added from stock solutions to a final concentration of 0.4−0.5 μM. Following preincubation at 37 °C, reaction was started by addition of 100 μL NADPH generating system. At various times up to 20 min, 100-μL aliquots were removed and quenched by dilution with 1−2 volumes of acetonitrile containing 2% triethylamine and/or 5−20% methanol. Samples were frozen, and subsequently remaining substrate was quantitated by reversed-phase HPLC (Zorbax stable bond cyano column, 250 × 4.6 mm) using fluorescence detection (225−233 nm excitation, 312−314 nm emission). The rate of disappearance of each compound was calculated by linear regression analysis as the slope of a plot of log(substrate concentration) vs time. The values of the slopes from each series of experiments were normalized by calculating the ratio of **31E** slope/test compound slope. A value greater than 1 indicated that the compound was metabolically more stable than **31E**. Values greater than 20 could not be measured reliably because the compound disappeared too slowly; such compounds were considered to be 'stable' under the assay conditions.

3. In Vivo Evaluation of Proarrhythmia Potential and Class III Antiarrhythmic Efficacy in a Rabbit Model. Male New Zealand white rabbits (2.5−3.5 kg) were anesthetized and instrumented for measurement of heart rate, aortic blood pressure, QT interval, and monophasic action potential duration. They were then allowed to equilibrate for 10 min before baseline measurements were made. Following baseline measurements, the α_1 agonist methoxamine was infused at a constant rate of 10 μg/kg/min at an infusion volume of 12.0 mL/h. After an additional 15 min, the methoxyamine baseline measurements were made and the test compounds, dissolved in 0.1 M fumaric acid in absolute EtOH and diluted with saline, were then administered by a continuous infusion intravenously at the rate of 5 mg/kg during 30 min in an infusion volume of 15 mL. Measurements of heart rate, aortic blood pressure, QTc (QT interval divided by the square root of the R−R interval), and monophasic action potential duration at 90% repolarization ($MAPD_{90}$) were reported at several time intervals to provide dose−response relationships. Data were analyzed as means ± SEM using one-way analysis of variance; differences with $p \leq 0.05$ were considered to be statistically significant. The first incidence of polymorphic ventricular tachycardia (PVT), the occurrence of three or more closely coupled repetitive extrasystoles with a twisting or torsioning QRS morphology, was noted and the administered dose of test compound at this time was determined. The appearance of early after depolarizations (EADs), characterized as secondary upstrokes in the monophasic action potential prior to full repolarization, was also determined and reported as a percentage of the monophasic action potential plateau height. Selected data from these studies are presented in Table 2. Values for QTc and $MAPD_{90}$ are maximum differences from baseline in milliseconds; the dose of test compound that had been administered at the time of this observation is recorded. PVT is reported as the number of animals that experienced the arrhythmia over the total number of animals evaluated with the test compound. The dose of test compound administered at the time that PVT was initiated is presented. The maximum EAD values and the accumulated dose at which they occurred

are also presented. A more detailed description of this procedure has been reported.[43]

4. In Vivo Evaluation of the Antiarrhythmic and Electrophysiologic Effects of 45E on a Chronic Canine Model of AFL. Eight male mongrel dogs weighing 18−24 kg were surgically prepared for this study. A right thoracotomy was performed in the fourth intercostal space, the pericardium was opened and the intercaval section of the right atrium was clamped with a vena cava clamp. The intercaval tissue was incised then sutured with surgical silk. A connecting incision of approximately 3−4 cm which extended along the center of the right atrial free wall was made and sutured. Bipolar platinum pacing and recording electrodes with a 2-mm interelectrode distance were sutured to the right atrium for atrial pacing and measurement of AERP; the electrode leads were exteriorized in the interscapular region. The animals were allowed to recover for 2 weeks prior to evaluation of the test compound. These experiments were conducted in an isolation room which minimized excessive external stimuli. The dogs were fully conscious and loosely restrained in a support sling. They had been acclimated to mock study conditions in the isolation room during 1 week prior to experimentation. A cephalic vein was cannulated for administration of the test compound, and the animal was instrumented for recording the heart rate (HR), recording the lead II ECG, recording the atrial and ventricular effective refractory periods (AERP and VERP), inducing atrial flutter (AFL), and recording measuring atrial flutter cycle length (AFLCL).

AERP and VERP were determined by pacing at a cycle length of 300 ms and interjecting a single premature stimulus every eighth beat. Each drive cycle was separated by a 2-s pause. The cycle length of the premature stimulus was shortened by 10-ms decrements until the ERP was reached.

Induction of AFL was attempted by pacing for 2−3-s intervals at cycle lengths starting at 150 ms and then shortened by 10-ms decrements to a minimum cycle length 50 ms. AFL was considered to be sustained if it did not spontaneously terminate during a 5-min period.

At the start of the experiment, baseline measurements were made and AFL was induced. Compound **45E**, dissolved in saline, was then administered intravenously every 5 min to give cumulative doses of 0.024, 0.06, 0.12, 0.24, 0.6, 1.2, 2.4, 4.8, 7.2, 9.6 and 12.0 μmol/kg. When AFL terminated, the dose of **45E** and the AFLCL were noted and the HR, QT interval, AERP, VERP and ability to reinduce AFL were determined. Following these measurements, doses of **45E** were continued until a total of 12.0 μmol/kg had been administered. Heart rate and electrophysiologic measurements were made 3 min after each dose. Data are presented in Tables 3 and 4 as means ± SEM. They were analyzed using the RS1 statistical package employing a pared *t*-test for equality of means. Differences with $p \leq 0.05$ were considered to be statistically significant.

This canine model of AFL was developed by Frame and coworkers.[55] A more detailed description from our laboratory has been published.[58]

5. In Vivo Evaluation of the Antiarrhythmic Efficacy of 45E on Spontaneous and Induced Ventricular Arrhythmias in the Canine 24-h Infarction Model. The left anterior descending coronary artery (LAD) of 19 male mongrel dogs weighing 16−22 kg was permanently ligated in two stages with surgical silk as described by Harris.[65] The animals were allowed to recover for 24 h when they were prepared for the electrophysiologic evaluation of **45E** and placebo. They were reanesthetized with pentobarbitol and instrumented for the measurement of right atrial and right ventricular $MAPD_{90}$, heart rate (HR), idioventricular heart rate (IVR), mean aortic blood pressure (BP), and the ECG intervals (P, PQ, QRS, and QT). Atrial and ventricular effective refractory periods (AERP and VERP) were determined to the nearest 5 ms using the extra stimulus technique by pacing at a cycle length of 300 ms and interjecting a single premature stimulus every eighth beat. Each drive cycle was separated by a 2-s pause. The cycle length of the premature stimulus was shortened by 5-ms decrements until the ERP, characterized by failure of the stimulus to capture and produce a propogated response, was reached. The atrial and ventricular $MAPD_{90}$ and the QT interval were also recorded at a pacing cycle length of 300 ms. Spontaneous arrhythmias (PVCs) were recorded over three 1-min intervals during a 10-min period. Programmed electrical stimulation (PES) to induce ventricular tachyarrhythmias was performed at a pacing cycle length of 300 ms using a standard protocol of up to three premature stimuli. These arrhythmias were defined as monomorphic ventricular tachycardia characterized by a rapid ventricular rate (greater than 200 bpm) with no discernible P or T wave and a wide QRS complex or as ventricular fibrillation (VF) characterized by irregular chaotic heart rate with no discernible P, Q, R, S or T waves. Responses to PES were recorded as: noninducible (NI) ≤ 15 arrhythmic ventricular beats; nonsustained ventricular tachycardia (NSVT) > 15 beats but spontaneously terminating within 30 s; sustained ventricular tachycardia (SVT) > 30 s of tachycardia requiring pacing conversion or electrical cardioversion (10−20 J internally) for arrhythmia termination; and VF. An initial positive response to PES was repeated to demonstrate its reproducibility. Detailed descriptions of this procedure have been published.[59,66]

Following surgical instrumentation baseline measurements were obtained and attempts to elicit arrhythmias by PES were made. A solution of **45E** (6.0 μmol/mL) in saline was then administered in sequential intravenous doses calculated to deliver cumulative doses of 0.24, 0.72, and 2.4 μmol/kg. Measurements were repeated 15 min following each dose and attempts to elicit ventricular tachycardia by PES were made. Control animals were treated in the same manner with intravenous doses of saline replacing the active compound. Data are presented in Table 5 as means ± SEM. They were analyzed using the RS1 statistical package, employing a paired *t*-test for equality of means. Differences with $p \leq 0.05$ were considered to be statistically significant.

At the end of the experiment the hearts were removed, stained with 2,3,5-triphenyltetrazolium chloride and carefully dissected to separate infarcted and noninfarcted left ventricular tissue. The infarct size, determined as a percentage of the left ventricle by wet weight, was not statistically different between the treatment (30.7 ± 2.0%) and control (30.9 ± 2.0%) groups.

Supporting Information Available: Elemental analyses calculated/found. This material is available free of charge via the Internet at http://pubs.acs.org.

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