extraction, and lyophilization of the 1% extract yielded a white powder (62 mg) which was gel filtered on Sephadex G-15 (1.1 × 110 cm). Fractions eluting between 53 and 58 mL were lyophilized to yield 54 mg of homogeneous **KKI-69** (87%).

Acetylarginylseryl[^{3}H]valinamide, KKI-70. Peptide **KKI-70** was synthesized on 3.0 g of 4-methylbenzhydrylamine resin using standard procedures. HF cleavage, extraction, and concentration of the 1% extract yielded a white solid (21 mg) which was purified to homogeneity by HPLC.

Acetylseryl[^{3}H]prolylphenylalaninamide, KKI-72. Peptide **KKI-71** was synthesized on 3.0 g of 4-methylbenzhydrylamine resin using standard procedures. HF cleavage, extraction, and concentration of the EtOAc extract yielded a white solid (20 mg) which was gel filtered on Sephadex G-15 (1.1 × 110 cm). Fractions eluting between 79 and 83 mL were lyophilized to yield 15 mg of homogeneous **KKI-71** (75%).

Acetylseryl[^{3}H]prolinamide, KKI-72. Peptide **KKI-72** was synthesized on 3.0 g of 4-methylbenzhydrylamine resin using standard procedures. HF cleavage, extraction, and concentration of the EtOAc extract yielded a white solid (15 mg) which was gel filtered on Sephadex G-15 (1.1 × 110 cm). Fractions eluting between 93 and 97 mL were lyophilized to yield 8 mg of homogeneous **KKI-72** (53%).

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Supplementary Material Available: A description of the computer programs and the use of BIOMEK 1000 for K_i determinations (11 pages). Ordering information is given on any current masthead page.

Synthesis and Pharmacological Evaluation of Enantiomerically Pure 4-Deoxy-4-fluoromuscarines

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Four isomers of [(4-fluoro-5-methyl-tetrahydrofuran-2-yl)methyl]trimethylammonium iodide (4-deoxy-4-fluoromuscarines) were prepared in enantiomerically and diastereomerically pure form from (*S*)-(−)-methyl 4-methylphenyl sulfoxide, ethyl fluoroacetate, and allyl bromide. Their absolute configurations were assigned by ^{1}H NMR analyses. The four optically pure compounds were tested in vitro on guinea pig and their muscarinic potency was evaluated at M_3 (ileum and bladder) and M_2 (heart) muscarinic receptor subtypes. Compound **1a**, the most potent isomer of the series, was also tested in vivo on pithed rat and its muscarinic activity at the M_1 receptor subtype was compared with that of muscarine. Moreover, affinity and relative efficacy were calculated in vitro for this compound at M_2 (heart force and rate) and M_3 (ileum and bladder) receptors in order to investigate muscarinic receptor heterogeneity. The 4-deoxy-4-fluoromuscarines display a similar trend of potency as the corresponding muscarines and compound **1a** shows differences in the affinity constants among the studied tissues. Replacement of a hydroxyl group for a fluorine atom in the 4 position of muscarine produces 1 order of magnitude increase in affinity for cardiac M_2 muscarinic receptors controlling rate, while the affinity at cardiac M_2 muscarinic receptors controlling force is unchanged, opening the possibility of a further classification of cardiac muscarinic receptors.

Fluorine-substituted analogues of naturally occurring and biologically active organic compounds have become the focus of increasing interest for the purpose of creating new drugs.[1a,b] Moreover, there are a number of new fluorinated products which are useful probes for studying biochemical processes and there may also be a future for some of them in clinical diagnostics.[1c-f] Introduction of fluorine atoms allows preparation of modified structures which differ only slightly in their steric hinderance from the corresponding naturally occurring molecules. As a result, several of these fluorinated analogs retain the biological activity of the parent compounds.[1g,h]

Considerable attention has been recently devoted to investigations on muscarinic receptors.[2] Many of these efforts have involved exploration of the drug–receptor interactions for novel structures in order to better distinguish the different muscarinic receptor subtypes and their presence and role in different tissues.[3] Some of us have been already involved in those studies[4] and have recently developed new synthetic methods for the construction of fluoroorganic molecules in their optically pure forms.[5] We expanded our efforts by synthesizing and testing a number

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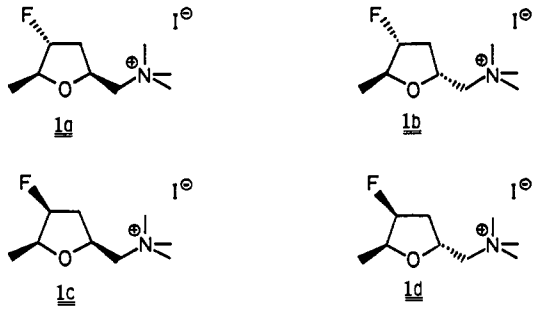
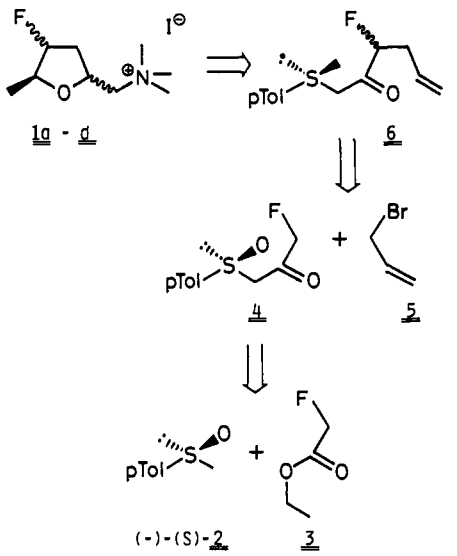


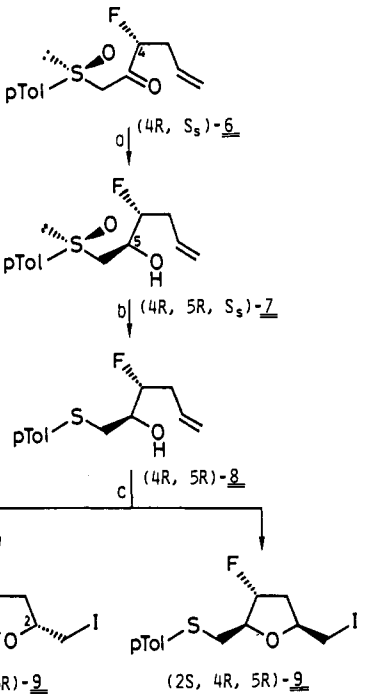
Figure 1.

Scheme I



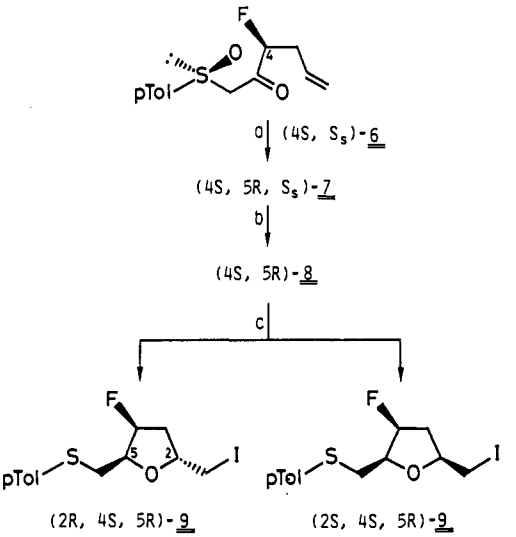
of fluorinated analogs of the muscarines as muscarinic agonists.

Scheme II[a]



[a] (a) Diisobutylaluminum hydride, tetrahydrofuran, −78 °C; (b) sodium iodide, trifluoroacetic anhydride, acetone, −40 °C; (c) iodine, sodium hydrogen carbonate, dichloromethane, room temperature.

Scheme III[a]



[a] (a) Diisobutylaluminum hydride, tetrahydrofuran, −78 °C; (b) sodium iodide, trifluoroacetic anhydride, acetone, −40 °C; (c) iodine, sodium hydrogen carbonate, dichloromethane, room temperature.

This paper reports the asymmetric synthesis of all possible stereoisomers of (5*S*)-muscarine in which the hydroxyl group has been replaced by a fluorine atom, specifically (2*S*,4*R*,5*S*)-[(4-fluoro-5-methyltetrahydrofuran-2-yl)methyl]trimethylammonium iodide (**1a** or 4-deoxy-4-fluoromuscarine),[6] the (2*R*,4*R*,5*S*)-stereoisomer (**1b**[6] or 4-deoxy-4-fluoro-*allo*-muscarine), the (2*S*,4*S*,5*S*)-stereoisomer (**1c** or 4-deoxy-4-fluoro-*epi*-muscarine), and finally the (2*R*,4*S*,5*S*)-stereoisomer (**1d** or

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4-deoxy-4-fluoro-*epiallo*-muscarine) (Figure 1).

The compounds were tested in vitro on guinea pig tissues and their muscarinic potency evaluated at M_3 (ileum and bladder) and M_2 (heart) muscarinic receptor subtypes in order to further define the role of the hydroxyl group in the drug–receptor interaction.

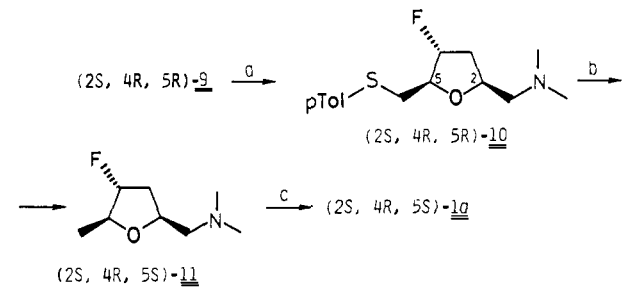
Chemistry

The semisynthetic approach to deoxyfluoromuscarines **1a–d** required the stereoselective substitution of the hydroxyl residue of muscarines with fluorine. Such a transformation could be realized by treatment of the free hydroxyl group with sulfur tetrafluoride or (diethylamido)sulfur trifluoride[7] or of its triflate with fluoride ion.[8] However, reported stereoselective routes to enantiomerically and diastereoisomerically pure muscarines usually are not straightforward[9] and so we decided to undertake a total asymmetric synthesis of fluoromuscarines **1a–d** starting from easily available sources of chirality and of fluorocarbon units.

A retrosynthetic analysis of the alkaloid showed how the six-carbon framework of the molecule could be divided into three parts: a one-carbon unit (corresponding to the exocyclic methyl), a two-carbon unit (bearing the heterocyclic oxygen and the fluorine atom), and a three-carbon unit (on which the heterocyclic oxygen and the nitrogen substituent would be inserted later on in the synthetic route) (Scheme I).

The three building blocks corresponding to these three pieces are (−)-(*S*)-methyl 4-methylphenyl sulfoxide (**2**), ethyl fluoroacetate (**3**), and allyl bromide (**5**). Methyl 4-methylphenyl sulfoxide (**2**) also furnished the chiral auxiliary sulfinyl group which is the source of chirality in the whole process. It is easily obtainable in both enantiomeric forms from the two commercially available (+)- and (−)-menthyl sulfinates through the Andersen procedure.[10]

Scheme IV[a]



[a] (a) Dimethylamine, ethanol, 90 °C; (b) hydrogen, Raney nickel (Fluka), ethanol, reflux; (c) methyl iodide, ethanol, room temperature.

The protocol for the preparation of each one of the four possible stereoisomers of (5*S*)-muscarines is outlined in Schemes II and III. The lithium anion of (−)-(*S*)-methyl 4-methylphenyl sulfoxide (**2**) [prepared by treatment with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C] was acylated with ethyl fluoroacetate (**3**) to give (−)-(*S*)-1-fluoro-3-[(4-methylphenyl)sulfinyl]propan-2-one (**4**) in 83% yield. The 1,3-dilithium derivative of this sulfinyl ketone **4** was formed with 2 equiv of LDA in THF at −78 °C and treated with 1 equiv of allyl bromide.[5c] ($4R,R_S$)-4-Fluorohexenone **6** and its ($4S,S_S$)-diastereoisomer were obtained in 41% and 24% yields, respectively, by flash chromatographic purification of the reaction mixture.[5d]

Both diastereoisomeric ketones ($4R,S_S$)-**6** and ($4S,S_S$)-**6** were treated separately with diisobutylaluminum hydride (DIBAH) and the reduction of the carbonyl occurred in both cases with high asymmetric induction[11] under control of the chirality of the sulfinyl auxiliary group (Scheme II).

As already observed on several other similar substrates, the two sulfinyl alcohols having the (*R*)-absolute configuration at the carbinol stereocenter were obtained with complete diastereoselection and in nearly quantitative yields[5c] independently of the configuration of the α-fluorinated carbon. Deoxygenation[12] of the sulfinyl residue of the so formed alcohols ($4R,5R,S_S$)-**7** and ($4S,5R,S_S$)-**7**

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Table I. Selected Physical Data of Compounds 1a–d, 9, 10

compound	mp, °C (solvent)	$[\alpha]^{20}_D$, deg (*c*, solvent[a])
(2*S*,4*R*,5*R*)-**9**	liq	−10.5 (1.05, A)
(2*R*,4*R*,5*R*)-**9**	58–60 (EtOH)	+24.6 (1.05, A)
(2*R*,4*S*,5*R*)-**9**	liq	+80.2 (1.01, A)
(2*S*,4*S*,5*R*)-**9**	44–46 (EtOH)	+16.8 (0.87, A)
(2*S*,4*R*,5*R*)-**10**	liq	+23.6 (1.30, A)
(2*R*,4*R*,5*R*)-**10**	123–125 (EtOH/pentane)	−24.6 (0.82, A)
(2*R*,4*S*,5*R*)-**10**	liq	+66.9 (0.89, A)
(2*S*,4*S*,5*R*)-**10**	liq	+69.9 (1.42, A)
(2*S*,4*R*,5*S*)-**1a**	158–160 (acetone/(i-Pr)$_2$O)	+10.5 (1.01, B)
(2*R*,4*R*,5*S*)-**1b**	221–223 (acetone)	−28.4 (1.00, B)
(2*S*,4*S*,5*S*)-**1c**	180–182 (EtOH/n-hex)	+41.7 (0.82, B)
(2*R*,4*S*,5*S*)-**1d**	163–165 (acetone)	+16.8[b] (1.08, B)

[a] Solvent: A = $CHCl_3$, B = EtOH. [b] λ = 365 nm.

(trifluoroacetic anhydride and sodium iodide in acetone solution) afforded, respectively, the sulfenyl hexenols (4*R*,5*R*)-**8** and (4*S*,5*R*)-**8** (95% isolated yields).

The cyclization of the γ-hydroxyolefin (4*R*,5*R*)-**8** promoted by iodine[13] in tetrachloromethane in the presence of sodium hydrogen carbonate was quite sluggish. After 3 days at room temperature it furnished the (2*S*,4*R*,5*R*)-2-(iodomethyl)tetrahydrofuran **9**, the (2*R*,4*R*,5*R*)-epimer **9**, and unreacted alcohol (4*R*,5*R*)-**8** in a 36:24:40 mixture, probably the equilibrium mixture.

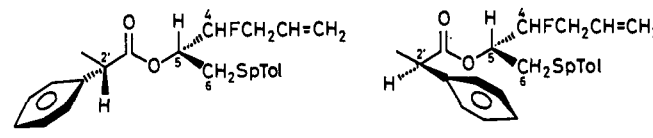
Enantiomerically and diastereoisomerically pure (iodomethyl)tetrahydrofurans **9** were obtained from the reaction mixture by flash chromatography and the unreacted alcohol **8** was recycled. Under the conditions described above, iodine-promoted cyclization of the diastereoisomeric γ-hydroxyalkene (4*S*,5*R*)-**8** furnished a mixture of iodomethyltetrahydrofurans (2*S*,4*S*,5*R*)-**9** and (2*R*,4*S*,5*R*)-**9** which could be separated in pure form by HPLC (Scheme III).

The final steps to fluoromuscarine **1a**, reported in Scheme IV, involve iodine substitution by nitrogen, reductive elimination of the sulfur residue by hydrogen on Raney nickel, and quaternization of nitrogen.

The direct substitution of iodine by dimethylamine was the best way, among the ones tested, for introducing the nitrogen. The (2*S*,4*R*,5*R*)-(iodomethyl)tetrahydrofuran **9** gave the [(dimethylamino)methyl]tetrahydrofuran (2*S*,4*R*,5*R*)-**10** in 80% yield after chromatographic purification when heated for 3 h at about 90 °C in an autoclave in the presence of excess dimethylamine. Similarly, the [(dimethylamino)methyl]tetrahydrofurans (2*R*,4*R*,5*R*)-**10**, (2*S*,4*S*,5*R*)-**10**, and (2*R*,4*S*,5*R*)-**10** were obtained in optically pure form and in 70%, 77%, and 94% yields, respectively, from the corresponding iodomethyl derivatives **9**.

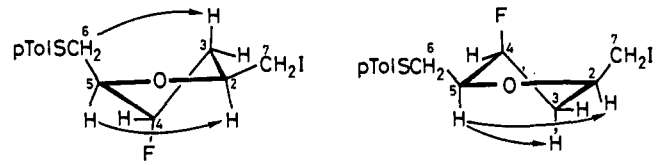
The (4-methylphenyl)sulfenyl group was removed from the (2*S*,4*R*,5*R*)-2-[(dimethylamino)methyl] derivative **10** by heating at reflux for a few minutes an ethanolic solution of the compound under a hydrogen atmosphere in the presence of Raney nickel. After the usual workup the crude (2*S*,4*R*,5*S*)-5-methyltetrahydrofuran **11** was treated with an excess of methyl iodide in ethanol at 0 °C for about 1 h. The final product, (2*S*,4*R*,5*S*)-[(4-fluoro-5-methyltetrahydrofuran-2-yl)methyl]-*N*,*N*,*N*-trimethylammonium iodide (**1a**, the deoxyfluoromuscarine of Figure 1), was isolated in 78% overall yield from (2*S*,4*R*,5*R*)-**10** after crystallization from acetone/diisopropyl ether (Table I).

The three other epimers (2*R*,4*R*,5*S*)-[(4-fluoro-5-methyltetrahydrofuran-2-yl)methyl]-*N*,*N*,*N*-trimethylammonium iodide (**1b**, 4-deoxy-4-fluoro-*allo*-muscarine), (2*S*,4*S*,5*S*)-[(4-fluoro-5-methyltetrahydrofuran-2-yl)methyl]-*N*,*N*,*N*-trimethylammonium iodide (**1c**, 4-deoxy-4-fluoro-*epi*-muscarine), and (2*R*,4*S*,5*S*)-[(4-fluoro-5-methyltetrahydrofuran-2-yl)methyl]-*N*,*N*,*N*-trimethylammonium iodide (**1d**, 4-deoxy-4-fluoro-*epiallo*-muscarine) were obtained from the corresponding tetrahydrofuran derivatives (2*R*,4*R*,5*R*)-**10**, (2*S*,4*S*,5*R*)-**10**, and (2*R*,4*S*,5*R*)-**10** in 70%, 70%, and 75% yields, respectively.



(4S, 5R, 2'S)-12 (4S, 5R, 2'R)-12

Figure 2.



(2S, 4R, 5R)-9 (2S, 4S, 5R)-9

Figure 3.

The ^1H, ^{13}C, and ^{19}F NMR spectra of the title compounds and of their precursors were fully in agreement with the proposed structures.

The absolute configuration at C-5 of the 4-deoxy-4-fluoromuscarines **1a–d** followed from that established for the esters obtained by reacting the corresponding sulfenyl alcohols **8** with (*R*)- and (*S*)-2-phenylpropionic acids.[14]

For the diastereoisomers **12** reported in Figure 2, as well as for (4*R*,5*R*,2′*R*)-**12** and (4*R*,5*R*,2′*S*)-**12**, the shielding effects exerted by the phenyl ring of the esterifying acids on the protons of the $CHFCH_2CH{=}CH_2$ grouping in (4*S*,5*R*,2′*S*)-**12** ($\Delta\delta$ = 0.07–0.31 ppm) and on the 6-methylene protons in (4*S*,5*R*,2′*R*)-**12** ($\Delta\delta$ = 0.08 and 0.17 ppm) parallel those observed for analogous compounds, thus proving *R* as the absolute configuration at C-5. The stereochemistry at C-2 and C-4 was established by the NOE experiments shown in Figure 3 and by coupling constant analysis carried out on the iodo derivatives **9**. In particular, for the (2*S*,4*R*,5*R*)-**9** epimer the NOE observed

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Table II. Potencies and Intrinsic Activities of 4-Deoxy-4-fluoromuscarines and Muscarine at M_2 and M_3 Muscarinic Receptors in the Guinea Pig

	heart (force), M_2		ileum, M_3		bladder, M_3	
	pD_2[a]	intr act.[b]	pD_2[a]	intr act.[b]	pD_2[a]	intr act.[b]
1a	6.73 ± 0.08	0.98	7.36 ± 0.03	0.95	5.66 ± 0.03	0.88
1b	5.59 ± 0.11	0.97	5.93 ± 0.06	0.92	4.45 ± 0.12	0.74
1c	4.43 ± 0.14	0.76	5.02 ± 0.27	0.98	3.74 ± 0.09	0.76
1d	4.07 ± 0.18	0.72	4.64 ± 0.05	0.98	3.92 ± 0.09	0.52
m[c]	6.69 ± 0.05	1.00	7.10 ± 0.11	1.00	5.69 ± 0.06	1.00

[a] $-\log ED_{50}$. The results are the mean ± SEM, and the number of observations varies between 6 and 10. [b] Intrinsic activity, measured as the ratio between the maximum response of the compound and the maximum response of muscarine. [c] (±)-Muscarine.

between H-5, assumed as α, and H-2 (1.5%), but not with H_2-7, allowed the assignment of the (*S*)-configuration to C-2. Furthermore, the NOE observed between the β-disposed H-6 proton at δ 2.85 and H-3 at δ 1.83 (1%), but not with the other H-3 at 2.34, allowed the location of this proton on the β-side of the molecule. The observed values of 10.4 and 39.2 Hz for the coupling constants between the last proton with H-2α and F-4 respectively require the tetrahydrofuran ring preferentially to adopt the half-chair-like conformation shown in Figure 3 in which these atoms are pseudoaxially disposed. It follows that the chirality at C-4 is *R*.

Finally, the coupling observed between H-3β and F-4α is higher than the maximum value expected for a cis H,F coupling (ca. 31 Hz),[15] thus proving not only a *trans* relationship between these atoms but also suggesting a dihedral angle of ca. 170°.

For (2*S*,4*S*,5*R*)-**9**, irradiation of H-5, assumed as α, enhanced, inter alia, H-2 (1.5%) and H-3 at δ 2.40 (1%) while no significant enhancement was observed for H_2-7 and the C-3 proton at δ 2.25. This fact indicates that H-2 and H-3 at δ 2.40 are on the α-side of the molecule and that C-2 has the (*S*)-configuration. Here again, the presence of a coupling of 37.8 Hz between H-3α and F-4 implies that these atoms are trans pseudoaxially disposed, thus suggesting that the tetrahydrofuran ring preferentially adopts an half-chair-like conformation, inverted with respect to that assumed by the C-4 epimer. As a consequence, the chirality at C-4 is *S*.

It is interesting to note that optical rotation of compounds 1 strictly parallels those of corresponding muscarine isomers. This confirms the structural assignments made through spectroscopic technique and further proves the ability of fluorine to mimic a hydroxyl residue.

Results and Discussion

The four isomers of deoxyfluoromuscarines **1a–d** have the same absolute configuration at C-5 and differ from each with regard to stereochemistry at the other centers. They were tested in vitro for their muscarinic activity on guinea pig heart, ileum, and bladder in order to evaluate their potency at M_2 and M_3 muscarinic receptor subtypes, respectively. These results were compared with those of muscarine (Table II) to investigate the effects of the replacement of a hydroxyl group for a fluorine atom in the 4 position on the receptor–ligand interaction. Moreover, we compared the potency trend of the four 4-deoxy-4-fluoromuscarines on the M_2 and M_3 muscarinic receptor subtypes with the trend for muscarine on these subtypes.

Table III. Potencies of Muscarine and 1a at Cardiac M_2 Receptors Mediating Bradycardia and at Ganglionic M_1 Receptors Mediating Tachycardia in the Pithed Rat

	ED_{50},[a] μg/kg pithed rat	
	decrease in heart rate (M_2)	increase in heart rate (M_1)
(±)-muscarine	3.7 ± 0.46	2.5 ± 0.23
1a	23.5 ± 3.1	4.5 ± 0.70

[a] The results are the mean ± SEM, and the number of observations varies between five and nine.

Table II shows that substitution of the hydroxy group of muscarine with a fluorine atom does not have major consequences on the potency of the compounds. This table also shows that all the agonists display the same trend of potency at the investigated tissues: ileum > heart > bladder. Compounds **1a–d** show a pattern of activity at ileum and heart (fluoromuscarine > *allo* > *epi* > *epiallo*) which is quite similar to that at bladder (fluoromuscarine > *allo* > *epiallo* > *epi*).

Apparently, compound **1a** has a pharmacological action quite similar to that of muscarine, it possesses all the requisites for strong muscarinic potency, and it stands in a unique position among the four isomers, the other ones being nevertheless endowed with interesting muscarinic potency.

A closer inspection of Table II shows that in all three tested tissues, compound **1a**, carrying the methyl and aminomethylene residue in a cis relationship, shows a higher potency than **1b**. The same trend was observed for diastereoisomeric muscarines, 1,3-dioxolanes, and 1,3-oxathiolanes.[16–18]

It is well-known that the activity of the muscarine diastereoisomers decreases whenever the 4-hydroxyl group is cis to the substituents on C-2 and C-5. A similar effect of the chirality in position 4 was observed also in 1,3-oxathiolane *S*-oxides.[19] Compounds **1a** and **1b** are more potent that **1c** and **1d**, respectively. The former couple of products carry the fluorine on C-4, in the same position of the exocyclic oxygen of the more active diastereoisomers of muscarines and 1,3-oxathiolane *S*-oxides. Fluorine therefore mimics the hydroxyl of muscarines and the sulfinyl oxygen of oxathiolane *S*-oxides. The hydrogen of the hydroxyl group of muscarine is not involved in a hydrogen bond and the contribution of the hydroxyl to the

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Table IV. Pharmacological Parameters of (±)-Muscarine and 1a in the Guinea Pig

	tissue	−log ED_{50}[a]	−log K_D[a]	rel affinity[b]	K_D/ED_{50}	e_r[c]	% receptor occupied at ED_{50}
m[d]	heart r[e]	6.42 ± 0.04	4.61 ± 0.19	1.0	65.8	1.00	1.52
	heart f[e]	6.69 ± 0.05	4.70 ± 0.10	1.0	98.0	1.00	1.01
	ileum	7.10 ± 0.11	5.95 ± 0.10	1.0	14.1	1.00	6.62
	bladder	5.69 ± 0.06	4.62 ± 0.09	1.0	11.8	1.00	7.85
1a	heart r[e]	6.87 ± 0.04	5.77 ± 0.17	14.5	12.6	0.21	7.36
	heart f[e]	6.73 ± 0.08	4.67 ± 0.12	0.93	115.0	1.17	0.86
	ileum	7.36 ± 0.03	5.72 ± 0.11	0.59	43.7	2.96	2.24
	bladder	5.66 ± 0.03	4.39 ± 0.09	0.59	18.6	1.54	5.11

[a] The results are the mean ± SEM, and the number of observations varies between 6 and 10. [b] (±)-Muscarine = 1. [c] Relative efficacy ((±)-muscarine = 1). [d] (±)-Muscarine. [e] r = atria rate, f = atria force.

binding comes either through a dipole–dipole interaction[4] or through an acceptor role of the oxygen in an hydrogen bond.[17,20] It has already been demonstrated that fluorine is capable of interacting significantly with proton donors also in enzymatic sites.[21,22] Compound **1a** and muscarine were also tested in vivo on pithed rat in order to evaluate their muscarinic activity at ganglionic M_1 and cardiac (heart rate) M_2 receptors. In fact, these two agonists produced biphasic heart rate responses which partly overlap in the pithed rat, where the initial bradycardic effects are mediated by cardiac M_2 receptors and are followed by a secondary increase in heart rate which is mediated by ganglionic M_1 receptors. The suitable use of selective antimuscarinic compounds as pirenzepine and methoctramine, as recently reported by Angeli et al.,[23] allows the measurement of the unmixed agonist potencies at M_2 and M_1 receptors, respectively. Compound **1a** and muscarine are equipotent in increasing heart rate (M_1) while a 6-fold difference in decreasing heart rate (M_2) exists between them, muscarine being the more active (Table III). Compound **1a**, in fact, shows a slight selectivity (5-fold) for M_1 muscarinic receptors while muscarine is confirmed to be a nonselective (M_1/M_2) agonist.[23]

It is well-known that comparing only potencies of an agonist on different tissues is not sufficient to speculate on differentiation among receptor subtypes, while differences in K_D and relative efficacy (e_r) can be indicative of receptor heterogeneity.[24] To this end we have further investigated compound **1a** (and muscarine for comparison), and in addition to potency, other pharmacological parameters, reported in Table IV, have been determined.[25]

Guinea pig heart rate was studied too, in order to compare the in vivo and in vitro potency of compound **1a** and muscarine at this tissue. Both agonists exhibit the largest number of spare receptors (K_D/ED_{50}) on atria (force) and a small amount of bladder accordingly to the results obtained by other authors.[24,26-28]

Furchgott[29] suggests that differences of at least 0.5 in −log K_D are indicative of receptor heterogeneity. Table IV indicates that the two agonists show the same trend of affinity at the studied tissues, discriminating between ileum on one hand and heart and bladder on the other, with the only exception being the affinity of **1a** for the heart. In fact, while muscarine displays a significantly higher affinity for ileum than for heart (force and rate) and bladder,[24] compound **1a** shows similar affinities for ileum and heart (rate) which are 1 order of magnitude higher than those for bladder and heart (force). Moreover, among the investigated tissues, compound 1a shows a significantly lower relative efficacy on heart (rate) compared to the other tissues. The fact that on the heart (rate) muscarine displays a higher ED_{50} than that of compound **1a** in vivo (6-fold) and a slight lower one in vitro (2.8-fold) could be due to differences in metabolism and kinetics between these two agonists in the two preparations.

The total results suggest that the replacement of a hydroxyl group for the fluorine atom in the 4 position of muscarine does not greatly influence the pharmacological behavior of the molecule and causes some change only in the receptor–ligand interaction of the cardiac M_2 muscarinic receptors of the atria (rate).

Finally, the comparison between the affinities and relative efficacies upon heart rate and force in vitro led us to conclude that these two M_2 cardiac effects could be mediated by different muscarinic receptor subtypes, as also

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reported by other authors.[30-34] Moreover muscarine and compound 1a seem to exhibit some differences between the M_3 muscarinic receptors of ileum and bladder and between ileum (M_3) and heart (M_2).

Experimental Section

Materials. (-)-(*S*)-Methyl-4-methylphenyl sulfoxide was prepared by a slightly modified Andersen procedure[10] from commercially available (Aldrich) (1*S*,2*R*,5*S*)-(+)-menthyl (*R*)-4-methylphenylsulfinate. Tetrahydrofuran was freshly distilled from lithium aluminium hydride; diisopropylamine was distilled from calcium hydride and stored over molecular sieves (4 Å); in all other cases commercially available reagent-grade solvents were employed without purification. Flash column chromatography was performed, unless otherwise stated, on silica gel as described in a previous paper.[35] ^1H, ^{13}C, and ^{19}F NMR were recorded with a Bruker AC 250 or a Bruker CPX-300 spectrometer. Unless otherwise stated, $CDCl_3$ was used as solvent, $[\alpha]_D$ values were obtained on a Jasco DIP-181 polarimeter. Melting points are uncorrected and were obtained on a capillary apparatus. Thin-layer chromatographies were run on silica gel 60 F_{254}. Elemental analyses were within 0.2%, 0.3%, and 0.3% for C, H, and N, respectively. Chemical shifts and coupling constants of compounds 1, 9, and 10 are reported in Table 1 (^1H and ^{19}F NMR) and Table 2 (^{13}C NMR) of the supplementary material.

(4*R*)-4-Fluoro-5-oxo-6-[(*S*)-(4-methylphenyl)sulfinyl]-hex-1-ene (6) and (4*S*,*S*$_S$)-6. A solution of (-)-(*S*)-methyl 4-methylphenyl sulfoxide (2) (7.5 g, 50 mmol) in dry tetrahydrofuran (100 mL) was added dropwise at -75 °C under argon to a stirred solution of LDA (52.5 mmol) in the same solvent (100 mL). Ethyl fluoroacetate (5.3 mL, 52 mmol) was added at the same temperature to the yellowish solution obtained. After 5 min, 200 mL of a saturated aqueous solution of ammonium chloride was added, the mixture was extracted with ethyl acetate, the collected organic phases were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure.

The residue was crystallized from ethyl acetate to give 9.1 g (85% yield) of pure (-)-(*S*)-1-fluoro-3-[(4-methylphenyl)-sulfinyl]propan-2-one (4): mp 120–122 °C, white crystals; $[\alpha]^{20}_D$ -229° (*c* 1.0, $CHCl_3$); flash chromatography, ethyl acetate/*n*-hexane 1:1; ^1H NMR (DMSO-d_6) δ 2.38 (br s, 3 H, Me), 4.03 (dd, J = 14.5 and 2.5 Hz, 1 H, CH_aS), 4.21 (dd, J = 14.5 and 1.5 Hz, 1 H, CH_bS), 5.03 (d, J = 46.5 Hz, 2 H, CH_2F), 7.40 and 7.59 (m, 4 H, ArH). Anal. ($C_{10}H_{11}FO_2S$) C, H.

This fluorosulfinyl acetone 4 (2.1 g, 10.0 mmol) was dissolved in anhydrous tetrahydrofuran (80 mL) and the solution obtained was added at -78 °C under argon to a solution of LDA (22.0 mmol), in the same solvent (40 mL). After 3 min allyl bromide (1.0 mL, 12 mmol) was added dropwise, the reaction mixture was stirred for 5 min, then a saturated aqueous solution of ammonium chloride (50 mL) was added, the mixture was extracted with ethyl acetate, the collected organic phases were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was flash-chromatographed (*n*-pentane/diethyl ether 4:6) to give (4*R*)-4-fluoro-5-oxo-6-[(*S*)-(4-methylphenyl)sulfinyl]hex-1-ene (6) (1.04 g, 41% yield) and (4*S*,*S*$_S$)-6 (0.61 g, 24% yield) as pure compounds. (4*R*,*S*$_S$)-6: $[\alpha]^{20}_D$ -175° (*c* 1.0, $CHCl_3$); ^1H NMR δ 2.45 and 2.70 (m, 2 H, H_2-3), 2.46 (br s, 3 H, Me), 4.06 (d, J = 3.0 Hz, 2 H, H_2-6), 4.78 (m, 1 H, H-4), 5.15 and 5.18 (m, 2 H, H_2-1), 5.75 (m, 1 H, H-2), 7.36 and 7.60 (m, 4 H, ArH); ^{19}F NMR δ -194.3. Anal. ($C_{13}H_{15}FO_2S$) C, H. (4*S*,*S*$_S$)-6: $[\alpha]^{20}_D$ -230° (*c* 1.0, $CHCl_3$); ^1H NMR δ 2.43 (br s, 3 H, Me), 2.43 and 2.48 (m, 2 H, H_2-3), 3.91 (dd, J = 14.7 and 2.7 Hz, 1 H, H-6a), 4.17 (dd, J = 14.7 and 3.5 Hz, 1 H, H-6b), 4.78 (ddd, J = 49.0, 7.2, and 4.4 Hz, 1 H, H-4), 5.12 (m, 2 H, H_2-1), 5.70 (m, 1 H, H-2), 7.34 and 7.57 (m, 4 H, ArH); ^{19}F NMR δ -191.6. Anal. ($C_{13}H_{15}FO_2S$) C, H.

(4*R*,5*R*)-4-Fluoro-5-hydroxy-6-[(*S*)-(4-methylphenyl)-sulfinyl]hex-1-ene (7) and (4*S*,5*R*)-7. A 1.0 N solution of diisobutylaluminum hydride in *n*-hexane (12 mL) was added dropwise to a solution of (4*R*,*S*$_S$)-6 (2.54 g, 10 mmol) in dry tetrahydrofuran (40 mL) with stirring at -60 °C under an argon atmosphere. After 30 min at the same temperature an excess of a saturated aqueous solution of sodium hydrogen carbonate was added, the resulting mixture was stirred for 30 min, and then a 10 N solution of hydrochloric acid was added until pH 5 was reached. Organic products were extracted with ethyl acetate, the collected organic phases were dried with sodium sulfate, and the solvent was removed under reduced pressure to give (4*R*,5*R*)-4-fluoro-5-hydroxy-6-[(*S*)-(4-methylphenyl)sulfinyl]hex-1-ene (7) in nearly pure form and in quantitative yield. Crystallization from diisopropyl ether afforded an analytical sample: $[\alpha]^{20}_D$ -258° (*c* 1.10, $CHCl_3$); mp 99 °C; white crystals; ^1H NMR δ 2.36 and 2.48 (m, 2 H, H_2-3), 2.45 (br s, 3 H, Me), 2.85 (dt, J = 13.5 and 1.8 Hz, 1 H, H-6a), 3.16 (dd, J = 13.5 and 9.5 Hz, 1 H, H-6b), 4.16 (m, 1 H, H-5), 4.42 (dd, J = 3.9 and 1.2 Hz, 1 H, OH-5), 4.47 (dddd, J = 48.0, 7.8, 6.2, and 4.0 Hz, H-4), 5.05 and 5.12 (m, 2 H, H_2-1), 5.75 (m, 1 H, H-2), 7.36 and 7.53 (m, 4 H, ArH); ^{19}F NMR δ -192.3. Anal. ($C_{13}H_{17}FO_2S$) C, H.

The reduction of the (4*S*,*S*$_S$)-ketone 6 with diisobutylaluminum hydride as described above gave the alcohol (4*S*,5*R*,*S*$_S$)-7 in 96% yield: $[\alpha]^{20}_D$ -270° (*c* 1.2, $CHCl_3$); mp 146 °C (diisopropyl ether); white crystals; ^1H NMR δ 2.44 (br s, 3 H, Me), 2.45 and 2.55 (m, 2 H, H_2-3), 2.73 (dd, J = 13.5 and 2.0 Hz, 1 H, H-6a), 3.21 (dd, J = 13.5 and 10.2 Hz, 1 H, H-6b), 3.81 (d, J = 4.6 Hz, 1 H, OH-5), 4.24 (m, 1 H, H-5), 4.36 (m, 1 H, H-4), 5.12 and 5.16 (m, 2 H, H_2-1), 5.75 (m, 1 H, H-2), 7.37 and 7.54 (m, 4 H, ArH); ^{19}F NMR δ -195.2. Anal. ($C_{13}H_{17}FO_2S$) C, H.

(4*R*,5*R*)-4-Fluoro-5-hydroxy-6-[(4-methylphenyl)-sulfenyl]hex-1-ene (8) and (4*S*,5*R*)-8. The crude (4*R*,5*R*,*S*$_S$)-7 (1.28 g, 5.0 mmol) was dissolved in acetone (80 mL), sodium iodide was added (2.40 g, 16.0 mmol), and a solution of trifluoroacetic anhydride (3.5 mL, 25.0 mmol) in the same solvent (35 mL) was added dropwise with stirring at -40 °C under argon. After 10 min an excess of saturated aqueous solutions (saturated sodium sulfite and sodium hydrogen carbonate) was added in the stated order. Acetone was removed under reduced pressure and the aqueous layer was extracted with ethyl ether. The combined organic phases were dried over anhydrous sodium sulfate, and the solvent was removed to give (4*R*,5*R*)-4-fluoro-5-hydroxy-6-[4-methylphenyl)sulfenyl]hex-1-ene (8) in nearly pure form: flash chromatography, *n*-hexane/diethyl ether 85:25; $[\alpha]^{20}_D$ -46° (*c* 0.8, $CHCl_3$); ^1H NMR δ 2.32 (br s, 3 H, Me), 2.40 and 2.51 (m, 2 H, H_2-3), 2.61 (dd, J = 3.7 and 1.0 Hz, 1 H, OH-5), 2.90 (ddd, J = 14.0, 9.1 and 1.0 Hz, H-6a), 3.30 (ddd, J = 14.0, 3.1, and 1.6 Hz, 1 H, H-6b), 3.71 (ddddd, J = 10.5, 9.1, 6.0, 3.7, and 3.1 Hz, 1 H, H-5), 4.47 (m, 1 H, H-4), 5.11 and 5.13 (m, 2 H, H_2-1), 5.82 (m, 1 H, H-2), 7.12 and 7.32 (m, 4 H, ArH); ^{19}F NMR δ -192.4. Anal. ($C_{13}H_{17}FOS$) C, H.

Deoxygenation of the sulfenyl residue of (4*S*,5*R*,*S*$_S$)-7 (1.92 g, 7.5 mmol) with trifluoroacetic anhydride/sodium iodide as described above afforded the sulfenyl alcohol (4*S*,5*R*)-8 in quantitative yield: $[\alpha]^{20}_D$ -21.0° (*c* 0.8, $CHCl_3$); mp 32 °C; white crystals; ^1H NMR δ 2.32 (m, 3 H, Me), 2.41 (dd, J = 5.8 and 1.0 Hz, 1 H, OH-5), 2.45 and 2.54 (m, 2 H, H_2-3), 3.04 (ddd, J = 13.7, 8.0 and 1.0 Hz, 1 H, H-6a), 3.09 (dd, J = 13.7 and 5.5 Hz, 1 H, H-6b), 3.66 (m, 1 H, H-5), 4.60 (dddd, J = 47.4, 7.9, 5.2, and 2.9 Hz, 1 H, H-4), 5.12 and 5.16 (m, 2 H, H_2-1), 5.80 (m, 1 H, H-2), 7.12 and 7.31 (m, 4 H, ArH); ^{19}F NMR δ -198.9. Anal. ($C_{13}H_{17}FOS$) C, H.

(2*S*,4*R*,5*R*)-4-Fluoro-2-iodomethyl-5-[[(4-methylphenyl)sulfenyl]methyl]tetrahydrofuran (9) and

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(2R,4R,5R)-9. A solution of (4R,5R)-4-fluoro-5-hydroxy-6-[(4-methylphenyl)sulfenyl]hex-1-ene (8) (3.00 g, 12.5 mmol) in carbon tetrachloride (100 mL) was added dropwise to a suspension of iodine (5.00 g, 19.7 mmol) and sodium hydrogen carbonate (1.05 g, 12.5 mmol) in carbon tetrachloride (150 mL) at 0 °C under argon. The reaction mixture was stirred at room temperature for 3 days. Then an excess of a saturated aqueous solution of sodium sulfite was added, the organic solvent was removed under reduced pressure, and the aqueous phase was extracted with ethyl acetate (3 × 200 mL). The collected organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give a residue which was represented by a 36:24:40 mixture of (2S,4R,5R)-4-fluoro-2-iodomethyl-5-[[(4-methylphenyl)sulfenyl]methyl]tetrahydrofuran (9), (2R,4R,5R)-9, and unreacted (4R,5R)-8; flash chromatography, petroleum ether/diisopropyl ether 93:7. (2S,4R,5R)-9: R_f = 0.37. (2R,4R,5R)-9: R_f = 0.34. Physical data are reported in Table I and spectral properties as supplementary material.

Similarly, by reacting (4S,5R)-8 as described above, the tetrahydrofurans (2S,4S,5R)-9 and (2R,4S,5R)-9 were obtained in 17% and 68% yield, respectively, after preparative HPLC (silica gel, 10-μm Porasil, *n*-hexane/methylene chloride 1:1). Physical data are reported in Table I and spectral properties are reported in the supplementary material.

(2S,4R,5R)-2-[(Dimethylamino)methyl]-4-fluoro-5-[[(4-methylphenyl)sulfenyl]methyl]tetrahydrofuran (10), (2R,4R,5R)-10, (2R,4S,5R)-10, and (2S,4S,5R)-10. A solution of (2S,4R,5R)-4-fluoro-2-iodomethyl-5-[[(4-methylphenyl)-sulfenyl]methyl]tetrahydrofuran (9) (1.60 g, 4.40 mmol) and dimethylamine (20 mL) in ethanol (140 mL) was heated at 90 °C in an autoclave. After 3.0 h at the same temperature, excess dimethylamine was evaporated at room temperature, ethanol was removed under reduced pressure, the residue was washed with a saturated aqueous solution of potassium carbonate, and organic products were extracted with ethyl acetate. The collected organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure, and the oily residue was flash chromatographed (aluminum oxide, diisopropyl ether/petroleum ether 6:4) to give 1.00 g (80% yield) of (2S,4R,5R)-2-[(dimethylamino)methyl]-4-fluoro-5-[[(4-methylphenyl)sulfenyl]methyl]-tetrahydrofuran (10) in pure form.

Similarly, the pure dimethylamino derivatives (2R,4R,5R)-10 (2S,4S,5R)-10, and (2R,4S,5R)-10 were isolated in 70%, 77%, and 94% yields, respectively, by reacting (2R,4R,5R)-9, (2S,4S,5R)-9, and (2R,4S,5R)-9 as described above and by purifying the crude reaction mixture through flash chromatography (aluminum oxide, *n*-hexane/ethyl acetate 7:3). Physical data of the four diastereoisomeric tetrahydrofurans 10 are reported in Table I and spectral properties are reported in the supplementary material.

(3S,4R,5S)-[(4-Fluoro-5-methyltetrahydrofuran-2-yl)-methyl]-*N,N,N*-trimethylammonium Iodide (1a). A solution of (2S,4R,5R)-2-[(dimethylamino)methyl]-4-fluoro-5-[[(4-methylphenyl)sulfenyl]methyl]tetrahydrofuran (10) (566 mg, 2.0 mmol) in ethanol (20 mL) was heated at reflux for 5 min in the presence of Raney nickel (Fluka) (1.10 g) under a hydrogen atmosphere. The nickel was filtered off and washed twice with ethyl ether, and the collected organic phases were evaporated. The residue was (2S,4R,5S)-2-[(dimethylamino)methyl]-4-fluoro-5-methyltetrahydrofuran (11).

The crude (dimethylamino)methyl derivative 11 was redissolved in EtOH (10 mL) and treated at 0 °C with an excess of methyl iodide (10 mL). After 1 h the solvent and the excess reagent were removed at reduced pressure. The residue was washed twice with petroleum ether and then crystallized from acetone/diisopropyl ether to give the (2S,4R,5S)-[(4-fluoro-5-methyl-tetrahydrofuran-2-yl)methyl]-*N,N,N*-trimethylammonium iodide (1a) in 78% overall yield. Anal. ($C_9H_{19}OFNI$) C, H, N. Physical data are reported in Table I, and spectral data are reported in the supplementary material.

(2R,4S,5S)-2-(Dimethylamino)-4-fluoro-5-methyltetrahydrofuran (11). Starting from (2R,4S,5R)-10, the treatment with Raney nickel gave, as already described, a residue which contained (2R,4S,5S)-11 in nearly pure form. In this case, the compound was isolated and characterized by ^{1}H NMR spectroscopy: ^{1}H NMR δ 1.29 (dd, *J* = 6.5 and 1.9 Hz, 3 H, H_3-6), 1.81 and 2.30 (m, 2 H, H_2-3), 2.31 (s, 6 H, NMe_2), 2.34 and 2.48 (m, 2 H, H_2-7), 4.09 (dddq, *J* = 28.7, 2.8, 0.8, and 6.5 Hz, 1 H, H-5), 4.42 (dddd, *J* = 9.6, 7.6, 6.0, and 4.3 Hz, 1 H, H-2), 4.98 (ddddd, *J* = 53.7, 4.2, 2.8, 1.0, and 0.6 Hz, 1 H, H-4).

(2R,4R,5S)-[(4-Fluoro-5-methyltetrahydrofuran-2-yl)-methyl]-*N,N,N*-trimethylammonium Iodide (1b), (2S,4S,5S)-1c, and (2R,4S,5S)-1d. According to the procedure described above, desulfenylation with Raney nickel and methylation of the nitrogen of (2R,4R,5R)-10, (2S,4S,5R)-10, and (2R,4S,5R)-10 afforded (2R,4R,5S)-[(4-fluoro-5-methyltetrahydrofuran-2-yl)methyl]-*N,N,N*-trimethylammonium iodide (1b), (2S,4S,5S)-1c, and (2R,4S,5S)-1d, respectively, in 70%, 70%, and 75% overall yield. Anal. Calcd ($C_9H_{19}OFNI$) C, 35.64; H, 6.27; N, 4.62. Found: C, 35.72; H, 6.07; N, 4.60. Physical properties are reported in Table I and spectral data are reported in the supplementary material.

2-Phenylpropionic Esters 12 of (4R,5R)-8 and (4S,5R)-8. 4-(Dimethylamino)pyridine (1.2 mg, 0.01 mmol) was added to a dichloromethane solution (0.5 mL) containing the sulfenyl alcohol (4R,5R)-8 (24 mg, 0.10 mmol), (+)-(S)-2-phenylpropionic acid (17 mg, 0.11 mmol), and dicyclohexylcarbodiimide (25 mg, 0.12 mmol). After 4 h at room temperature the dicyclohexylurea was removed by filtration and washed with *n*-hexane. The collected organic phases were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was flash chromatographed (*n*-hexane/diethyl ether 98:2) to give the desired (S)-2-phenylpropionate of the alcohol (4R,5R)-8: ^{1}H NMR δ 1.44 (d, *J* = 7.1 Hz, 3 H, H_3-3′), 1.99 and 2.08 (m, 2 H, H_2-3), 2.33 (br s, 3 H, ArMe), 3.09 and 3.23 (m, 2 H, H_2-6), 3.48 (q, *J* = 7.1 Hz, 1 H, H-2′), 4.54 (m, 1 H, H-4), 4.84 and 4.98 (m, 2 H, H_2-1), 5.03 (m, 1 H, H-5), 5.60 (m, 1 H, H-2), 7.0–7.4 (m, 9 H, ArH). Similarly, by use of (−)-(R)-2-phenylpropionic acid and (4R,5R)-8 the corresponding 2-phenylpropionate 12 of the alcohol (4R,5R)-8 was obtained: ^{1}H NMR δ 1.51 (d, *J* = 7.1 Hz, 3 H, H_3-3′), 2.21 and 2.36 (m, 2 H, H_2-3), 2.30 (br s, 3 H, ArMe), 3.02 (ddd, *J* = 14.3, 7.6, and 1.5 Hz, 1 H, H-6a), 3.07 (ddd, *J* = 14.3, 4.8, and 1.2 Hz, 1 H, H-6b), 3.72 (q, *J* = 7.1 Hz, 1 H, H-2′), 4.66 (ddt, *J* = 47.8, 8.2, and 4.5 Hz, 1 H, H-4), 5.02 and 5.07 (m, 2 H, H_2-1), 5.03 (m, 1 H, H-5), 5.72 (m, 1 H, H-2), 7.0–7.4 (m, 9 H, ArH). When (4S,5R)-8 was esterified with (+)-(S)-2-phenylpropionic acid, the obtained ester 12 showed the following spectrum: ^{1}H NMR δ 1.52 (d, *J* = 7.1 Hz, 1 H, H_3-3′), 1.90 and 2.05 (m, 2 H, H_2-3), 2.31 (br s, 3 H, ArMe), 3.09 (dd, *J* = 14.0 and 7.4 Hz, 1 H, H-6a), 3.18 (ddd, *J* = 14.0, 6.8, and 0.8 Hz, 1 H, H-6b), 3.71 (q, *J* = 7.1 Hz, 1 H, H-2′), 4.73 (dddd, *J* = 46.5, 8.3, 5.2, and 2.1 Hz, 1 H, H-4), 4.78 and 4.95 (m, 2 H, H_2-1), 4.88 (m, 1 H, H-5), 5.53 (m, 1 H, H-2) and 7.0–7.4 (m, 9 H, ArH). The ester 12 obtained from (−)-(R)-2-phenylpropionic acid and the alcohol (4S,5R)-8 showed the following spectrum: ^{1}H NMR δ 1.53 (d, *J* = 7.2 Hz, 3 H, H_3-3′), 2.15 and 2.36 (m, 2 H, H_2-3), 2.30 (br s, 3 H, ArMe), 3.01 (d, *J* = 7.0 Hz, 2 H, H_2-6), 3.78 (q, *J* = 7.2 Hz, 1 H, H-2′), 4.80 (dddd, *J* = 46.7, 8.3, 5.2, and 2.3 Hz, 1 H, H-4), 4.92 (ddt, *J* = 25.5, 2.3, and 6.9 Hz, 1 H, H-5), 5.01 and 5.06 (m, 2 H, H_2-1), 5.70 (m, 1 H, H-2), 7.0–7.4 (m, 9 H, ArH).

Pharmacology. In Vitro Tests. General Considerations. Male guinea pigs (200–300 g) were killed by cervical dislocation and the organs required were set up rapidly under 1 g of tension in 20-mL organ baths containing physiological salt solution (PSS) kept at an appropriate temperature (see below) and aerated with 5% CO_2–95% O_2. Two dose–response curves were constructed by cumulative addition of the reference agonist (muscarine). The concentration of agonist in the organ bath was increased approximately 3-fold at each step, with each addition being made only after the response to the previous addition had attained a maximal level and remained steady. Following 30 min of washing, a new dose–response curve to the agonist under study was obtained. Responses were expressed as a percentage of the maximal response obtained in the control curve. The results are expressed in terms of pD_2, which is the −log ED_{50}, the concentration of agonist required to produce 50% of the maximum contraction. Contractions were recorded by means of a force transducer connected to a two-channel Gemini polygraph.

In all cases, parallel experiments in which tissues received only muscarine were run in order to check for any variation in sensitivity.

Determination of Dissociation Constants. Dissociation constants and relative efficacies for compound 1a and muscarine

were determined as previously described[24,25] according to the method of Furchgott and Bursztyn.[36]

Guinea Pig Ileum. Two-centimer-long portions of terminal ileum were taken at about 5 cm from the ileum–cecum junction and mounted in PSS at 37 °C. The composition of PSS was as follows (mM): NaCl (118), $NaHCO_3$ (23.8), KCl (4.7), $MgSO_4 \cdot 7H_2O$ (1.18), KH_2PO_4 (1.18), $CaCl_2$ (2.52), glucose (11.7). Tension changes were recorded isotonically. Tissues were equilibrated for 30 min, and dose–response curves for muscarine were obtained at 30-min intervals, the first one being discarded and the second one being taken as the control.

Guinea Pig Stimulated Left Atria. The heart was rapidly removed and the right and left atria were separately excised. Left atria were mounted in PSS (the same used for ileum) at 30 °C and stimulated through platinum electrodes by square-wave pulses (1 ms, 1 Hz, 5–10 V). Inotropic activity was recorded isometrically. Tissues were equilibrated for 2 h and a cumulative dose–response curve to muscarine was constructed.

Whole Atria. The right and left atria were removed and equilibrated for 1 h at the above conditions (see Guinea Pig Stimulated Left Atria for PSS and temperature). Contractions were recorded isometrically.

Guinea Pig Bladder. A 2-mm-wide longitudinal strip of bladder from urethra to the apex of the bladder was cut, excluding the portion under the urethra orefice, and mounted in PSS (the same as used for ileum) at 37 °C. Contractions were recorded isometrically. Tissues were equilibrated for 30 min (see the protocol for ileum).

In Vivo Tests. Pithed Rat. Male normotensive rats (270–330 g) were housed five per cage and maintained on a 12 h light/dark cycle. Food and water were available ad libitum. The animals were anesthetized with equithesin (9.6 g of nembutal sodium, 42.6 g of chloral hydrate, 21.2 g of $MgSO_4$, 400 mL of propylene glycol, 50 mL of ethyl alcohol, and water to 1000 mL) at 3 mL/kg of body weight ip. The right jugular vein was cannulated (PE 10 polyethylene tubing) for drug administration. Blood pressure was measured from the left common carotid artery through a PE 50 catheter connected to a pressure transducer (P23 ID, Statham, Hato Rey, Puerto Rico). The heart rate was measured continuously by means of a rate meter (Basile) which was triggered by the blood pressure pulse in the carotid artery. After catheterization of the trachea, heparin (150 IU/kg) was given iv to prevent blood coagulation. Temperature was maintained at approximately 37 °C throughout the experiment by means of an overhead heating lamp. The rats were then pithed by insertion of a steel rod (1.5 mm in diameter) through the skull and foramen magnum down into the spinal canal.[37] The animals were respired artificially by means of a Harvard Apparatus Model 681 rodent respirator at a frequency of 60 cycles/min with a volume of 1 mL/100 g. The preparation was allowed to equilibrate for at least 30 min before drug administration, until mean heart rate had stabilized. The basal heart rate amounted to 300 ± 8 beats/min (n = 50). Changes in heart rate were measured for individual doses of the agonists given iv (0.1 mL/100 g). Full recovery from the pressure and cardiac effects with return to preinjection values are allowed between successive doses. After drug injection, the venous cannula was flushed with 50 μL of isotonic saline solution.

Experimental Protocol. All drugs were dissolved in saline (0.9% w/v) and injected iv in a volume of 0.1 mL/100 g. Because of desensitization phenomena, when muscarine and compound **1a** were employed, only one single dose–response curve was assessed in each preparation. ED_{50} values were determined graphically from the resultant dose–response curves and represent the dose causing 50% of the maximum response of the compound under study. Pretreatment, iv, with antagonists was carried out 20 min before the administration of agonists. This interval was selected because preliminary experiments showed that after this time the antagonistic effects of pirenzepine (50 μg/kg iv) and methoctramine (300 μg/kg iv) were constant during the whole experiment.

Data are presented as means ± SEM of n experiments. Differences between mean values were tested for significance by the Student's t test.

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Supplementary Material Available: ^1H, ^{19}F, and ^{13}C NMR spectral data for compounds **1a–d**, **9**, and **10** (2 pages). Ordering information is given on any current masthead page.

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