Synthesis of Some Highly Functionalized Thiophene-3-carboxylates and Alcohols

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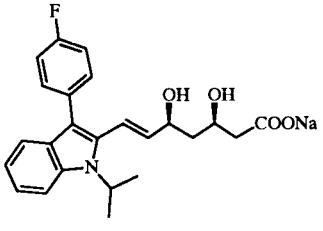
Received January 26, 1996
Revised April 22, 1996

Dedicated to the memory of Professor Nicholas Alexandrou

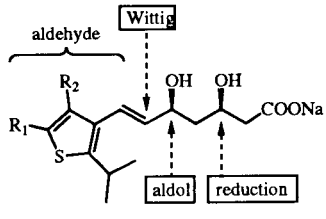
Highly functionalized thiophenes are prepared by two methods. The first uses a lithium-halogen exchange reaction on a trisubstituted 5-bromothiophene **25** to generate the corresponding 5-lithiothiophene **26** which is then reacted with either dimethylformamide or formaldehyde to give the 5-formyl **28** or 5-hydroxymethylthiophene derivative **31** in good yields. These are further transformed to other tetrasubstituted thiophenes. The second method assembles the thiophene ring from three components: a benzyl mercaptan, an aldehyde, and a vinylphosphonate **10**. Thus, the benzyl mercaptan is dilithiated then reacted with an appropriate aldehyde to afford a 2-mercapto-2-phenylethanol derivative **37**. Michael addition of **37** to **10** followed by oxidation of the hydroxyl group furnishes ketophosphonate **39**. An intramolecular Wittig-type reaction produces the thiophene skeleton.

J. Heterocyclic Chem., **33**, 687 (1996).

Lescol® (fluvastatin, **1**) is an extremely potent inhibitor of HMG-CoA reductase, the rate limiting enzyme in the biosynthesis of cholesterol [1]. In a continuing effort to explore the hydrophobic domain of the statin family we chose to investigate the thiophene ring as a potential replacement for the indole heterocycle.



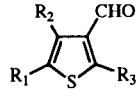
1



2

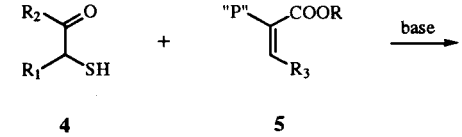
The side-chain of the target molecule of general formula **2** can be assembled by two carbon-carbon bond forming reactions. The first is a homologation of a suitably substituted thiophene-3-carboxaldehyde to an α,β-unsaturated aldehyde and a subsequent aldol reaction with an acetoacetate dianion would complete the carbon framework.

To implement this strategy, we needed access to a variety of fully substituted thiophene-3-carboxaldehydes **3** as a starting point for the synthesis of **2**. Herein, we wish to describe several methods for the preparation of highly substituted thiophenes with suitable functionality in the 3-position which can eventually be transformed to an aldehyde. Although many methods exist for the construction of the thiophene ring [2], few are applicable to produce highly substituted derivatives with the appropriate substitution pattern to fit our needs.

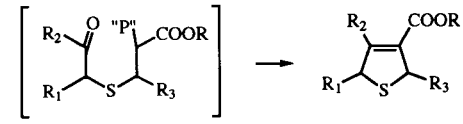


3

We required a synthesis which was flexible enough to accommodate the incorporation of either alkyl or aryl groups on the periphery of the thiophene nucleus in a variety of combinations. A strategy which has proved useful for the synthesis of 2,5-dihydrothiophenes involves the Michael addition of a α-mercaptocarbonyl compound **4** to vinylphosphonium salts or phosphonates **5** followed by a spontaneous intramolecular Wittig-type reaction of the resulting keto phosphorus intermediate **6** [3-6]. In several instances the dihydrothiophenes oxidize to the corresponding thiophenes when exposed to air, an ideal situation from our perspective.



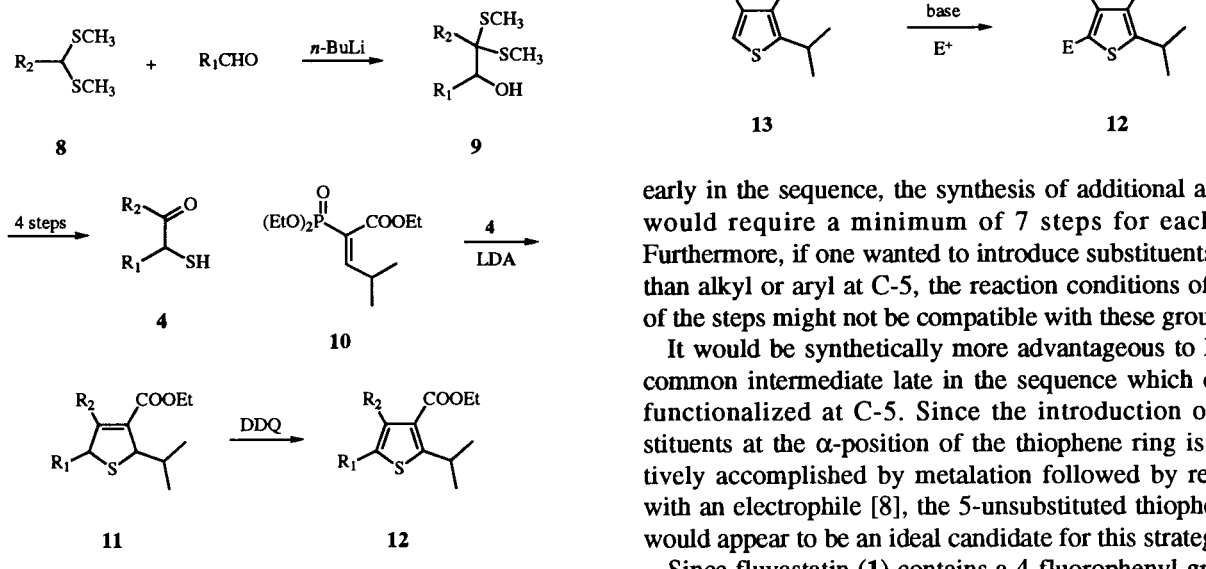
4 **5**



6 **7**

Previously, we have shown the feasibility of synthesizing 4-arylthiophene-3-carboxylates **12** (R_2 = C_6H_5 or 4-F-C_6H_4) containing a variety of alkyl and aryl substituents at C-5 [7]. The key α-mercapto ketone intermediate **4** was synthesized by a condensation of a benzaldehyde dimethylthioacetal **8** with an appropriate aldehyde which furnished **9**. A mercury-mediated hydrolysis of the thioacetal to a ketone followed by conversion of the

Scheme 1



hydroxyl group to thiol (OH → Br → SAc → SH) afforded **4**. A tandem Michael addition of **4** to vinyl phosphonate **10** and intramolecular Wittig reaction produced the dihydrothiophene **11** in one pot. Oxidation of **11** with DDQ gave the desired thiophene **12** (Scheme 1).

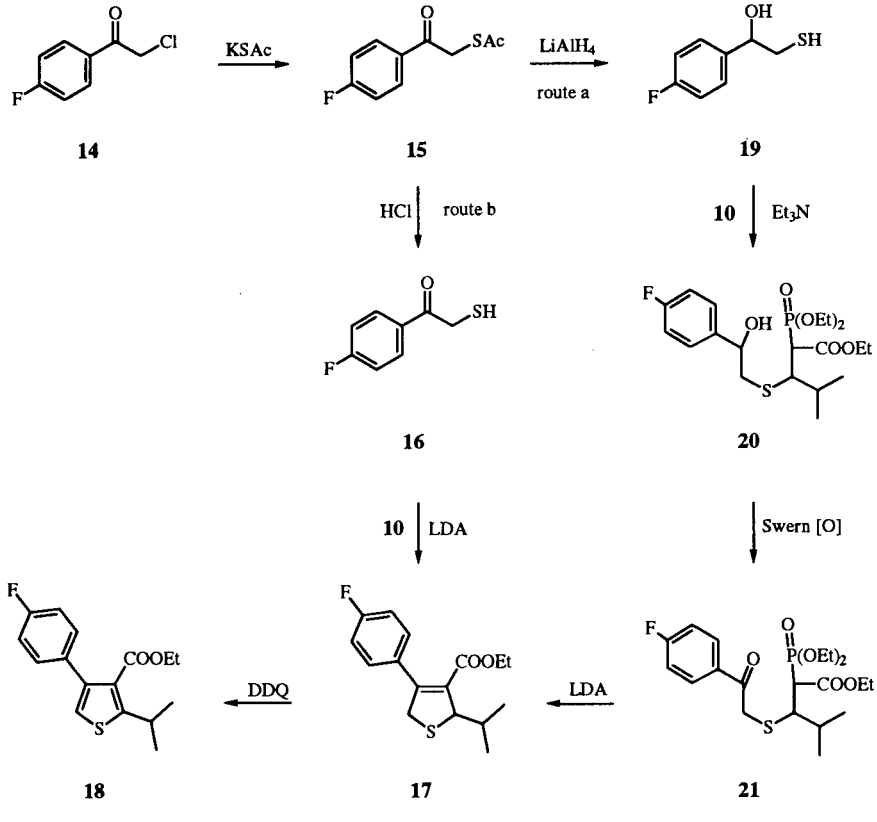
Counting the preparation of **8**, the synthesis of **12** was accomplished in 8 steps. Since the R_1 group is introduced early in the sequence, the synthesis of additional analogs would require a minimum of 7 steps for each one. Furthermore, if one wanted to introduce substituents other than alkyl or aryl at C-5, the reaction conditions of some of the steps might not be compatible with these groups.

It would be synthetically more advantageous to have a common intermediate late in the sequence which can be functionalized at C-5. Since the introduction of substituents at the α-position of the thiophene ring is effectively accomplished by metalation followed by reaction with an electrophile [8], the 5-unsubstituted thiophene **13** would appear to be an ideal candidate for this strategy.

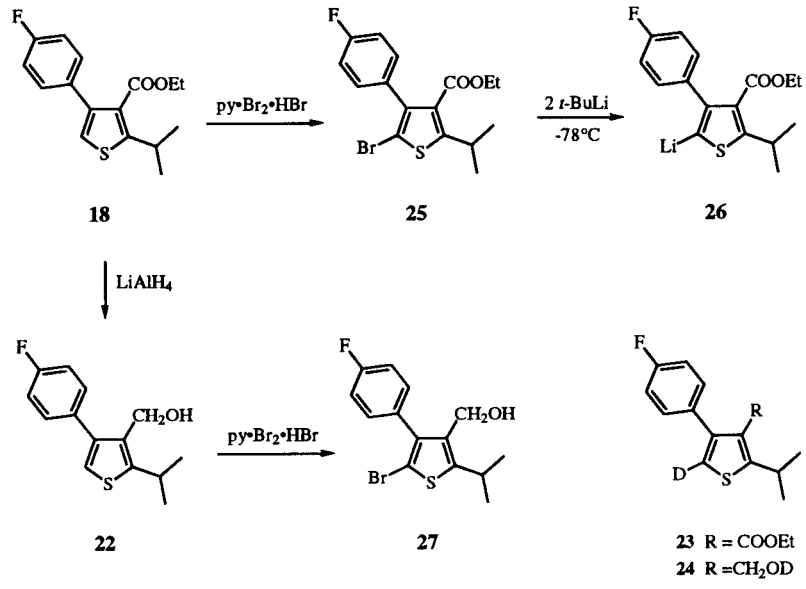
Since fluvastatin (**1**) contains a 4-fluorophenyl group at the 3-position of the indole ring, we initially chose to use that functionality as the R_2 substituent of the thiophene (compound **18**).

Synthetically, **18** is accessible from commercially available 2-chloro-4'-fluoroacetophenone (**14**) as illustrated in Scheme 2. Our initial approach to **18** relied on a tandem Michael-Wittig reaction of **16** with **10** using conditions

Scheme 2

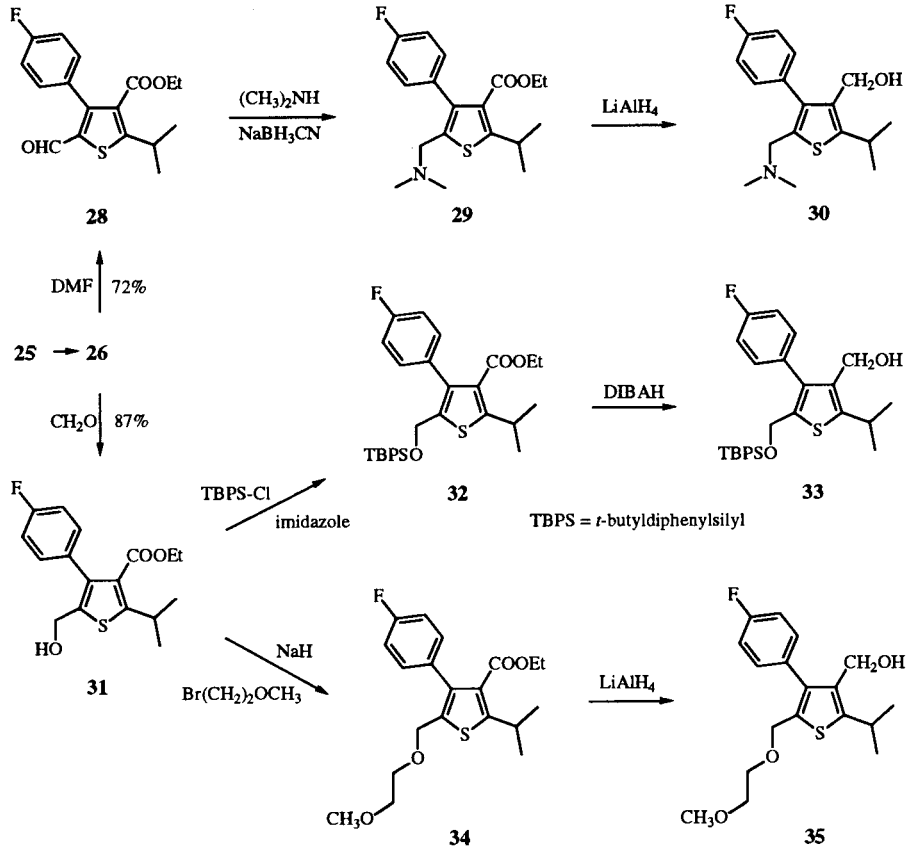


Scheme 3

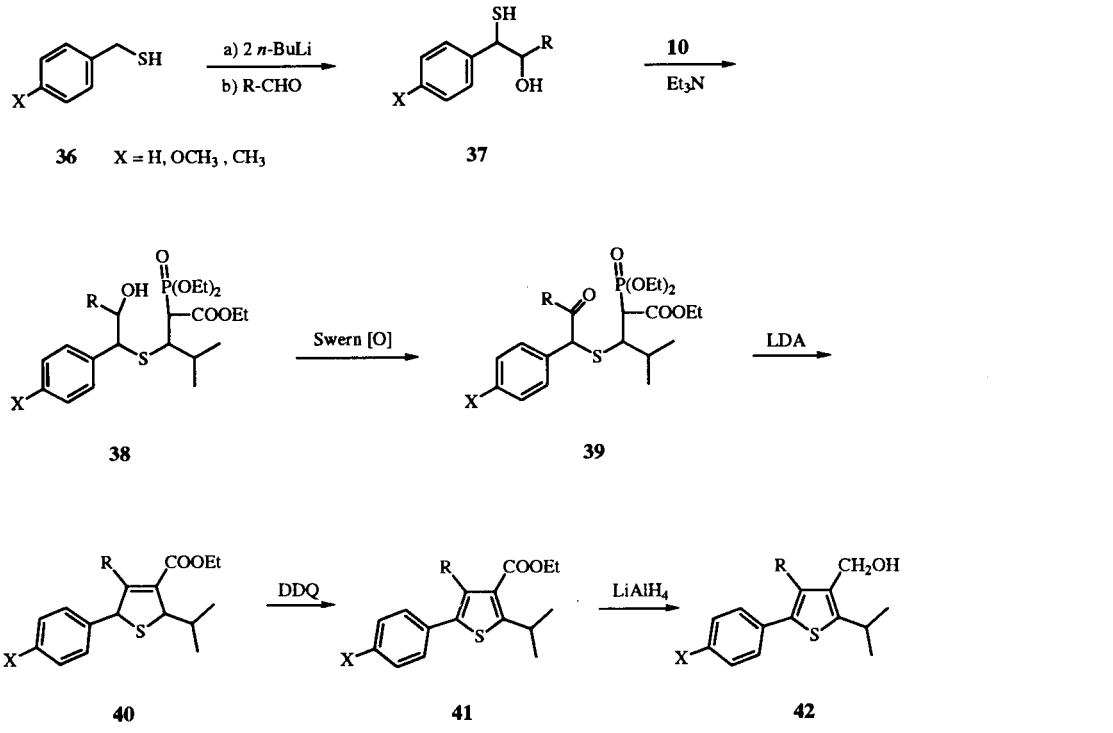


previously described [7] and although the transformation, which gives **17**, can be accomplished in reasonable yield, the limiting step in the sequence is the hydrolysis of the *S*-acetyl derivative **15** to thiol **16**. Due to the limited stability of **16** the reaction does not give consistent results and the quality of the ketothiol product is not reproducible. Consequently, the overall yield of the **15** → **18** sequence (3 steps) averages about 21%.

Scheme 4



Scheme 5



It was believed that the cause of the instability of **16** was the combination of its keto and thiol functionalities. Therefore, a derivative containing a latent carbonyl should circumvent the problem. Reduction of **15** with lithium aluminum hydride not only removes the acetyl group on sulfur but also reduces the keto group thus giving the mercaptoethanol derivative **19** in consistent yields.

Conversion of **19** to **17** is accomplished in 28% overall yield (Scheme 2). After aromatization of **17** with DDQ, thiophene **18** is isolated in 22% overall yield (5 steps from **15**).

The most expeditious route to **18** is a two-step sequence where the acetyl group of **15** is cleaved under basic conditions with lithium ethoxide. This *in situ* process generates the lithium thiolate of **16** which, when allowed to react with phosphonate **10**, produces the dihydrothiophene **17** directly. Depending on the scale, this reaction proceeds in 50-70% yield. Oxidation of **17** with DDQ provides the thiophene **18** in 40% overall yield from **15**.

Metalation of **18** was accomplished by bromination with pyridinium bromide perbromide [9] to furnish the desired 5-bromothiophene **25** in 94% yield followed by lithium-halogen exchange to give the lithiated species **26** (Scheme 3). Deuteration of **26** provides complete deuterium incorporation at the C-5 position of the thiophene **23**.

Direct metalation of **18** with a variety of bases at temperatures ranging between -78° and 0° fails. At higher temperatures, the base (*e.g.* *n*-butyllithium) adds to the ester group rather than deprotonate the 5-position of the thiophene. Optimum deprotonation of **22** with *n*-butyllithium in ether at 0° for 5 hours only results in 35% deuterium incorporation in **24**.

Consequently, treatment of **25** with two equivalents of *t*-butyllithium in tetrahydrofuran at -78° for 40 minutes followed by reaction of the lithiated species **26** with electrophiles such as formaldehyde and dimethylformamide produces fully substituted thiophenes in good yield (Scheme 4). This methodology allows the introduction of sensitive functionalities into the 5-position of the thiophene ring the preparation of which would be difficult if not impossible to achieve by our initial route outlined in Scheme 1.

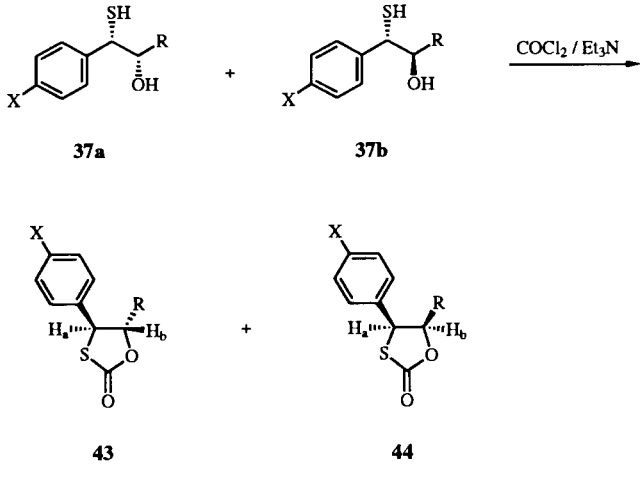
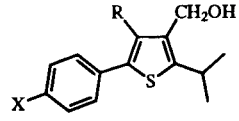
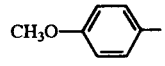
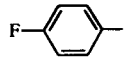
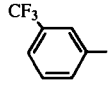
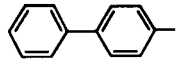
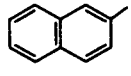
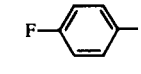
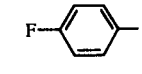


Table 1
Experimental Data For Compounds **42a-o**



42	X	R	Yield (%) [a]	Mp, (°C) crystallization solvent	Molecular formula	Analysis, % (Calcd./Found) C	H	S
a	H		27	128-128.5 cyclohexane	$C_{20}H_{20}OS$	77.88 77.85	6.54 6.71	10.40 10.20
b	H		28	120-121 cyclohexane	$C_{21}H_{22}O_2S$	74.30 74.64	6.83 6.55	9.44 9.66
c	H		29	97-98 cyclohexane	$C_{20}H_{19}OSF$	73.59 73.56	5.87 5.65	9.82 10.09
d	H		20	128-129 cyclohexane	$C_{20}H_{19}OSF$	73.59 73.42	5.87 5.91	9.82 9.97
e	H		32	140-143 hexane	$C_{20}H_{19}OSF$	73.59 73.35	5.87 5.86	9.82 9.54
f	H		22	159-161 cyclohexane	$C_{21}H_{19}OSF_3$	67.00 67.22	5.09 4.80	8.52 8.53
g	H		33	140-142 cyclohexane	$C_{26}H_{24}OS$	81.21 81.23	6.29 6.55	8.34 8.26
h	H		26	160-162 hexane	$C_{24}H_{22}OS$	80.41 80.56	6.18 6.58	8.94 9.18
i	H		29	oil				
j	H		32	156-158 hexane	$C_{20}H_{26}OS$	76.38 76.46	8.33 8.67	10.19 10.45
k	H		31	122-125 hexane	$C_{19}H_{24}OS$	75.91 76.09	8.05 7.93	10.67 10.66
l	H	*n*-C_8H_{17}	26	52-55 pentane	$C_{22}H_{32}OS$	76.69 76.38	9.36 9.08	9.30 9.18
m	H		7	oil				
n	OCH_3		8	105-106 cyclohexane	$C_{21}H_{21}O_2SF$	70.76 70.75	5.94 5.65	9.00 9.15
o	CH_3		30	161-161.5 cyclohexane	$C_{21}H_{21}OSF$	74.04 74.14	6.22 6.27	9.42 9.28

[a] Overall yield (six steps, **36** → **42**).

The synthesis of 5-arylthiophenes with a variety of substituents at the 4-position can be approached by a slightly different route (Scheme 5). The thiophene ring is assembled using three fragments: a benzyl mercaptan which supplies the C-5 aryl substituent and the S-1 sulfur atom, an aldehyde which supplies the C-4 carbon and its associated substituent, and Michael acceptor **10** which furnishes the remainder of the molecule.

Benzyl mercaptan can be doubly deprotonated on its sulfur and benzylic carbon atoms with *n*-butyllithium at

-5° [10]. This dilithiated species reacts with aldehydes to give 2-mercapto-2-phenylethanol derivatives **37** as inseparable mixtures of *syn* and *anti* isomers the ratio of which ranges from 3:1 to 5:1. The configuration was determined from the ^{1}H-nmr spectrum of the mixture of cyclic derivatives **43** and **44**. The *syn* isomer **37a** produces the *trans*-substituted heterocycle **43**. The two ring protons of the minor isomer **44** are seen as doublets centered at δ 5.96 (H_b) and 5.12 (H_a) with a *cis* coupling of 6.5 Hz. The protons of the major isomer **43** are also seen as doublets centered at δ 5.51 (H_b) and 4.98 (H_a) with a *trans* coupling of 9.5 Hz. The *syn*:*anti* isomer formation, however, is of no consequence since the stereocenters of **37** will eventually be destroyed.

Michael addition of **37** to phosphonate **10** gives adducts **38** in good yields. Since both reactants **37** and **10** are isomeric mixtures, the resulting product **38** (which contains 4 asymmetric centers) is produced as a complicated mixture of diastereomers. Consequently, the product was carried on to the next reaction without any purification. As the synthesis proceeds and the asymmetric centers are progressively destroyed, the reaction mixtures become less complicated and ultimately when the thiophene ring is aromatized the products **41** are nearly pure. The thiophenes can be purified at this stage, however, we routinely reduced the ester to alcohol **42** since almost all of these derivatives are crystalline and can be readily purified and thoroughly characterized. The overall yield of the 6-step sequence **36** → **42** averages approximately 30% (see Table 1) which translates to about 80% yield per step, a very efficient process.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on an Analect FX-6200 spectrometer. Nuclear magnetic resonance spectra were recorded on Jeol FX-90Q and Jeol FX-200 spectrometers using tetramethylsilane as an internal reference. The mass spectra were determined on a Finnegan 4600 spectrometer either in EI or CI modes.

All carbanion generating reactions were conducted under argon atmosphere using tetrahydrofuran which was freshly distilled over lithium aluminum hydride. No attempt has been made to optimize the yields of the described reactions. Compound **14** was purchased from Aldrich Chemical Co.

Ethyl 2-(Diethoxyphosphoryl)-4-methyl-2-pentenoate (**10**),

A mixture of 22.4 g (0.1 mole) of triethyl phosphonoacetate, 40.0 g (0.56 mole) of isobutyraldehyde, 3.0 ml of acetic acid, 0.6 g of piperidine and 200 ml of benzene was placed in a 1 liter flask equipped with a Dean-Stark trap. The solution was refluxed for 48 hours then the solvent was removed under reduced pressure. The residual oil was distilled at 0.5 mm to give 28.4 g (100%) of **10**, bp 107-108° (lit [12] bp 101-102° (0.25 mm)), as an 85:15 mixture of *Z* and *E*-isomers (determined by ^{1}H-nmr).

S-[2-(4-Fluorophenyl)-2-oxoethyl]Thioacetate (**15**)

A mixture of 40.0 g (0.232 mole) of **14** and 30.0 g (0.263 mole) of potassium thiolacetate in 500 ml of ethanol was stirred at room temperature for 24 hours. The ethanol was removed under reduced pressure and water was added to the residue. The mixture was extracted into methyl *t*-butyl ether and the organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure to afford 45 g (92%) of **15** as a yellow solid, mp 45-48°; ir (chloroform): 1683, 1598, 1500, 1268, 1224 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.08-7.87 (m, 2H), 7.25-6.96 (m, 2H), 4.31 (s, 2H), 2.39 (s, 3H).

Anal. Calcd. for $C_{10}H_9O_2SF$: C, 56.59; H, 4.27; S, 15.11. Found: C, 56.58; H, 4.48; S, 15.36.

1-(4-Fluorophenyl)-2-mercaptoethanone (**16**).

A mixture of 10.0 g (0.047 mole) of **15** and 16 ml of concentrated hydrochloric acid in 250 ml of tetrahydrofuran was stirred at 60° for 24 hours. The mixture was cooled then 8.0 g of sodium hydroxide pellets were added. The solvent was removed under reduced pressure and the residue was dissolved in ether. The organic solution was washed with water followed by saturated sodium chloride then was dried over magnesium sulfate. The solvent was removed under reduced pressure to give 8.8 g of crude **16**; ir (neat): 1678, 1596, 1500, 1230 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.15-6.88 (m, 5H), 3.82-3.50 (m, 2H). The material was used directly in the next reaction.

Ethyl 4-(4-Fluorophenyl)-2-(1-methylethyl)-2,5-dihydro-3-thiophenecarboxylate (**17**).

Method A.

To a solution of 6.0 g (0.059 mole) of diisopropylamine in 150 ml of tetrahydrofuran at 0° under an argon atmosphere was added 3.8 g (0.059 mole) of *n*-butyllithium (37 ml of a 1.6*M* solution in hexane). After 30 minutes, the solution was cooled to -78° then a solution of 8.0 g (0.047 mole) of **16** in 30 ml of tetrahydrofuran was added dropwise. The mixture was stirred at -78° for 1 hour then a solution of 14.0 g (0.05 mole) of **10** in 30 ml of tetrahydrofuran was added dropwise and the mixture was stirred at -78° for 1 hour then at room temperature for 2 hours. Saturated ammonium chloride solution was added to the reaction and the mixture was extracted with ether. The organic phase was dried over magnesium sulfate and the solvent was removed to give 11.0 g (80%) of crude **17** as an oil. This material was used as is in the next reaction.

Method B.

To a solution of 13.0 g (0.128 mole) of diisopropylamine in 750 ml of tetrahydrofuran at 0° under an argon atmosphere was added 8.5 g (0.133 mole) of *n*-butyllithium (83 ml of a 1.6*M* solution in hexane). After 5 minutes a solution of 56.0 g (0.125 mole) of crude **21** in 100 ml of tetrahydrofuran was added dropwise. After stirring at 0° for 4 hours, the reaction was quenched with saturated ammonium chloride solution then was extracted with methyl *t*-butyl ether. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to give 46 g of crude product. The oil was chromatographed on a Waters Prep 500 apparatus using methylene chloride to elute 17.2 g (47%) of pure **17**; ir (film): 1718, 1602, 1510, 1229 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.33-6.88 (m, 4H), 4.70

(m, 1H), 4.04 (q, 2H), 3.95 (m, 2H), 2.28 (m, 1H), 1.02 (d, 6H), 0.96 (t, 3H).

Anal. Calcd. for $C_{16}H_{19}O_2SF$: C, 65.28; H, 6.50; S, 10.89. Found: C, 65.32; H, 6.67; S, 11.01.

Method C.

To a solution of 1.5 g (0.032 mole) of ethanol in 75 ml of tetrahydrofuran at -60° was added dropwise 2.1 g (0.0328 mole) of *n*-butyllithium. After stirring at -60° for 20 minutes, a solution of 6.0 g (0.028 mole) of **15** in 50 ml of tetrahydrofuran was added dropwise. The mixture was stirred at -60° for 6 hours then a solution of 8.5 g (0.030 mole) of **10** in 40 ml of tetrahydrofuran was added dropwise. The mixture was stirred at -60° for 1 hour then was allowed to warm to room temperature over night. The mixture was poured into water and was extracted into methyl *t*-butyl ether (1x) and methylene chloride (1x). The organic phases were combined and dried over sodium sulfate. The solvent was removed under reduced pressure to give 10.0 g of **17**. This was used without further purification in the next reaction.

Conversion of **15** to **18** by Route b.

Ethyl 4-(4-Fluorophenyl)-2-(1-methylethyl)-3-thiophenecarboxylate (**18**) *via* **17** From Method A.

A mixture of 11.0 g (0.037 mole) of crude **17** and 10.0 g (0.044 mole) of DDQ in 400 ml of methylene chloride was stirred at room temperature for 18 hours. The mixture was washed with 10% aqueous sodium bicarbonate solution and the organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting oil was chromatographed on a column of silica gel using hexane/ethyl acetate to elute the product, 1.7 g of **18** (21% overall yield form **15**).

Via **17** From Method C.

A mixture of 10.0 g (0.034 mole) of crude **17** and 7.0 g (0.031 mole) of DDQ in 280 ml of methylene chloride was stirred at room temperature for 18 hours. The mixture was washed with 10% aqueous sodium bicarbonate solution and the organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting oil was chromatographed on a column of silica gel using methylene chloride to elute the product, 3.3 g of **18** (40% overall yield from **15**).

Conversion of **15** to **18** by Route a.

Intermediate**19**.

A solution of 270 ml of lithium aluminum hydride (1.0*M* in tetrahydrofuran) was diluted with 400 ml of dry tetrahydrofuran. To this solution was added dropwise a solution of 45.0 g (0.212 mole) of **15** in 300 ml of tetrahydrofuran at such a rate that the temperature was kept below 50°. After the addition was complete the mixture was stirred at room temperature for 1 hour. A saturated solution of sodium sulfate was added dropwise until a thick precipitate formed. The mixture was diluted with methyl *t*-butyl ether and the solids were filtered through Celite. The solvent was removed from the filtrate under reduced pressure to give 24.0 g of nearly pure **19**. This material was used without further purification in the next step; ir (chloroform): 3680, 3608, 3430, 1601, 1503, 1223 cm^{-1}.

Intermediate **20**.

A mixture of 24.0 g of the preceding crude **19**, 39.0 g (0.139 mole) of **10**, and 15.0 g (0.148 mole) of triethylamine in 500 ml of tetrahydrofuran was stirred at room temperature for 24 hours. The mixture was poured into water and extracted into methyl *t*-butyl ether. The organic phase was dried over sodium sulfate and the solvent removed under reduced pressure to give 59.5 g of **20** as an oil. This was used without further purification in the next step; ir (neat): 3380, 1723, 1600, 1502 cm^{-1}.

Intermediate **21**.

To a solution of 20.0 g (0.157 mole) of oxalyl chloride in 900 ml of methylene chloride at -78° was added dropwise a solution of 24.0 g (0.308 mole) of dimethyl sulfoxide in 50 ml of methylene chloride. After stirring at -78° for 5 minutes, a solution of 59.5 g of the preceding crude **20** in 250 ml of methylene chloride was added dropwise. The mixture was stirred at -78° for 1 hour then 50.0 g of triethylamine was added dropwise. The mixture was allowed to warm to room temperature then was washed with water. The solvent was removed under reduced pressure and the resulting oil was dissolved in methyl *t*-butyl ether. The solution was washed with water and the organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure to give 56.0 g of **21** as an oil. This material was used without further purification in the next step; ir (neat): 1728, 1675, 1597, cm^{-1}.

Ethyl 4-(4-Fluorophenyl)-2-(1-methylethyl)-3-thiophenecarboxylate (**18**).

A mixture of 9.0 g (0.031 mole) of pure **17** (from **21** in Method B) and 8.0 g (0.035 mole) of DDQ in 300 ml of methylene chloride was stirred at room temperature for 18 hours. The mixture was washed with 10% aqueous sodium bicarbonate solution and the organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting oil was chromatographed on a Waters Prep 500 apparatus using methylene chloride to elute the product, 7.0 g (78%) of **18** as an oil (22% overall yield from **15**); ir (neat): 1718, 1517 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.33-6.82 (m, 5H), 4.10 (q, 2H), 3.78 (m, 1H), 1.36 (d, J = 6.75 Hz, 6H), 1.04 (t, 3H).

Anal. Calcd. for $C_{16}H_{17}O_2SF$: C, 65.73; H, 5.86. Found: C, 65.92; H, 6.33.

4-(4-Fluorophenyl)-2-(1-methylethyl)-3-thiophenemethanol (**22**).

To a solution of 4.5 g (0.015 mole) of **18** in 100 ml of tetrahydrofuran was added dropwise 15 ml of a 1.0*M* solution of lithium aluminum hydride in tetrahydrofuran. After stirring at room temperature for 1 hour, a saturated aqueous solution of sodium sulfate was carefully added dropwise until a precipitate formed. The solids were filtered through Celite and the solvent was removed from the filtrate under reduced pressure to give 3.5 g (90%) of **22**. An analytical sample was crystallized from cyclohexane, mp 113-115°; ir (chloroform): 3622, 1601, 1510, 1227 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.59-6.90 (m, 5H), 4.53 (s, broad, 2H), 3.49 (m, 1H), 1.39 (d, J = 6.75 Hz, 6H), OH proton not seen.

Anal. Calcd. for $C_{14}H_{15}OSF$: C, 67.17; H, 6.04; S, 12.81. Found: C, 67.54; H, 6.43; S, 12.48.

Ethyl 5-Bromo-4-(4-fluorophenyl)-2-(1-methylethyl)-3-thiophenecarboxylate (**25**).

To a solution of 3.3 g (0.011 mole) of **18** in 20 ml of pyridine at 0° was added 6.5 g (0.02 mole) of pyridinium bromide perbromide. After stirring at 0° for 3 hours, the mixture was poured into water. The mixture was extracted into methyl *t*-butyl ether

and the organic phase was washed with 2*N* hydrochloric acid (3x). The aqueous phase was extracted with methylene chloride and the combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting oil was purified by filtration through a pad of silica gel using methylene chloride to elute the product, 4.06 g (94% yield) of **25** as an oil; ir (neat): 1710, 1508, 1245, 756 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.37-6.95 (m, 4H), 4.03 (q, 2H), 3.84 (m, 1H), 1.35 (d, J = 6.75 Hz, 6H), 0.96 (t, 3H); ms: m/z 371 (100, MH^+), 293 (79).

Anal. Calcd. for $C_{16}H_{16}O_2SFBr$: C, 51.76; H, 4.34; S, 8.64. Found: C, 51.80; H, 4.42; S, 8.77.

5-Bromo-4-(4-fluorophenyl)-2-(1-methylethyl)-3-thiophenemethanol (**27**).

To a solution of 100 mg (0.4 mmole) of **22** in 20 ml of pyridine at 0° was added 150 mg (0.47 mmole) of pyridinium bromide perbromide. After stirring at 0° for 2 hours an additional 70 mg of pyridinium bromide perbromide was added and stirring was continued for an additional one hour. The mixture was poured into water and was extracted into methyl *t*-butyl ether. The organic phase was washed with water (3x), 2*N* hydrochloric acid (1x), and saturated sodium chloride (1x) then was dried over sodium sulfate. The solvent was removed under reduced pressure to give 124 mg (94%) of **27** as a solid, mp 105-108°; ir (potassium bromide): 3280, 1602, 1517, 1459, 1230, 1018, 838 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.49-7.03 (m, 5H), 4.42 (s, broad, 2H), 3.50 (m, 1H), 1.38 (d, J = 6.75 Hz, 6H); ms: 330 (35, MH^+), 328 (34), 313 (98), 311 (100), 250 (16), 233 (61).

Anal. Calcd. for $C_{14}H_{14}OSFBr$: C, 51.07; H, 4.29; S, 9.74. Found: C, 51.46; H, 4.26; S, 9.84.

Ethyl 4-(4-Fluorophenyl)-5-formyl-2-(1-methylethyl)-3-thiophenecarboxylate (**28**).

To a solution of 4.8 g (0.013 mole) of **25** in 50 ml of tetrahydrofuran at -78° (under an argon atmosphere) was added dropwise 2.02 g (0.031 mole) of *t*-butyllithium (18.6 ml of a 1.7*M* solution in pentane). After the mixture was stirred at -78° for one hour, a solution of 4.8 g (0.066 mole) of dimethylformamide in 10 ml of tetrahydrofuran was added. The solution was stirred at -78° for one hour then was quenched with saturated ammonium chloride solution. The mixture was extracted into ether and the organic layer was washed with water. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was flash chromatographed using hexane/ethyl acetate (3:1) to elute the product, 3.9 g (72%) of **28** as an oil; ir (neat): 1718, 1663, 1502, 1370, 1200 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 9.50 (s, 1H, CHO), 7.43-6.97 (m, 4H), 4.10 (q, 2H), 3.87 (m, 1H), 1.43 (d, J = 6.75 Hz, 6H), 1.02 (t, 3H); ms: 337 (100, NH_4^+ adduct ion), 321 (17, MH^+). The material was used as is in the following reaction.

Ethyl 5-Dimethylaminomethyl-4-(4-fluorophenyl)-2-(1-methylethyl)-3-thiophenecarboxylate (**29**).

A mixture of 3.9 g (0.012 mole) of **28**, 6.0 ml of 40% aqueous dimethylamine, 1.5 g (0.024 mole) of sodium cyanoborohydride, and 4.0 ml of concentrated hydrochloric acid in 100 ml of tetrahydrofuran (*p*H 6) was stirred at room temperature for 4 hours. Concentrated hydrochloric acid was added until *p*H 2 then the mixture was extracted with ether. The *p*H of the aqueous layer was adjusted to 10 by addition of potassium hydroxide then the mixture was extracted with ether. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to give 1.8 g (42%) of **29**, mp 58°; ir (potassium bromide): 1690, 1500, 1203 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.27-6.93 (m, 4H), 4.04 (q, 2H), 3.92 (m, 1H), 3.41 (s, 2H), 2.27 (s, 6H), 1.38 (d, J = 6.75 Hz, 6H), 0.99 (t, 3H); ms: 350 (89, MH^+), 336 (32), 323 (94), 305 (100). The material was used directly in the next reaction.

Evaporation of the above ether wash results in the recovery of 2.0 g of unreacted **28** which can then be recycled. The yield of the reaction based on consumed starting material is 87%.

5-Dimethylaminomethyl-4-(4-fluorophenyl)-2-(1-methylethyl)-3-thiophenemethanol (**30**).

To a solution of 1.7 g (4.8 mmoles) of **29** in 30 ml of tetrahydrofuran was added 7.5 ml of a 1*M* solution of lithium aluminum hydride in tetrahydrofuran. After the mixture was stirred at room temperature for 4 hours, ether and concentrated ammonium hydroxide were added slowly. The resulting precipitate was filtered and the filtrate was evaporated. The residue was passed through a plug of silica gel and the solvent removed under reduced pressure to give 1.4 g (92%) of **30**, mp 102-104°; ir (potassium bromide): 3350, 1508, 1450, 1220, 1017, 840, 755 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.39-7.00 (m, 4H), 4.36 (s, 2H), 3.43 (m, 1H), 3.42 (s, 2H), 2.24 (s, 6H), 1.40 (d, J = 6.75 Hz, 6H), OH proton not seen.

Anal. Calcd. for $C_{17}H_{22}NOSF$: C, 66.42; H, 7.21; F, 10.43. Found: C, 66.31; H, 7.35; F, 10.53.

Ethyl 4-(4-Fluorophenyl)-5-hydroxymethyl-2-(1-methylethyl)-3-thiophenecarboxylate (**31**).

To a solution of 3.4 g (9.2 mmoles) of **25** in 35 ml of tetrahydrofuran at -78° (under an argon atmosphere) was added 1.2 g (18.7 mmole) of *t*-butyllithium (11 ml of a 1.7*M* solution in pentane) dropwise. The solution was stirred at -78° for 30 minutes then the temperature was raised to -25° at which point excess formaldehyde (generated from cracking paraformaldehyde) was introduced over a period of one hour. The mixture was quenched with saturated ammonium chloride and was extracted into methyl *t*-butyl ether. The organic phase was dried over sodium sulfate and the solvent removed under reduced pressure to give 3.0 g (100%) of **31** as an oil; ir (neat): 3420, 1710, 1510 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.33-6.92 (m, 5H), 4.54 (s, 2H), 4.03 (q, 2H), 3.78 (m, 1H), 1.36 (d, J = 6.75 Hz, 6H), 0.93 (t, 3H).

Anal. Calcd. for $C_{17}H_{19}O_3SF$: C, 63.33; H, 5.94; S, 9.94. Found: C, 63.33; H, 6.32; S, 9.53.

Ethyl 5-(Diphenyl-*t*-butylsilyloxymethyl)-4-(4-fluorophenyl)-2-(1-methylethyl)-3-thiophenecarboxylate (**32**).

To a solution of 2.2 g (6.8 mmoles) of **31** and 1.9 g (6.9 mmoles) of *t*-butyldiphenylsilyl chloride in 15 ml of dimethylformamide at 0° was added 1.0 g (14.7 mmoles) of imidazole. After the mixture was stirred at 0° for 2 hours, it was poured into water and was extracted with methyl *t*-butyl ether. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to give 4.2 g (100%) of **32** as an oil. The material was used directly without further purification in the next reaction; ir (neat): 1710, 1680 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.68-6.82 (m, 14H), 4.57 (s, 2H), 4.04 (q, 2H), 3.82 (m, 1H), 1.38 (d, J = 6.75 Hz, 6H), 1.03 (s, 9H), 0.93 (t, 3H).

5-(Diphenyl-*t*-butylsilyloxymethyl)-4-(4-fluorophenyl)-2-(1-methylethyl)-3-thiophenemethanol (**33**).

To a solution of 4.0 g (7 mmoles) of **32** in 75 ml of tetrahydrofuran at 0° was added dropwise 30 ml of a 1.0*M* solution of diisobutylaluminum hydride in tetrahydrofuran. After the solution was stirred at 0° for 6 hours, it was poured into cold 1*N* hydrochloric acid. The mixture was extracted with methyl *t*-butyl ether (1x) and methylene chloride (1x). The organic solutions were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and the residual oil was flash chromatographed using hexane/ethyl acetate (3:1) to elute the product, 2.1 g (57%) of **33** as an oil; ir (neat): 3350 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.70-6.92 (m, 14H), 4.63 (s, 2H), 3.49 (m, 1H), 1.43 (d, J = 6.75 Hz, 6H), 1.03 (s, 9H).

Anal. Calcd. for $C_{31}H_{35}O_2SFSi$: C, 71.77; H, 6.80. Found: C, 71.71; H, 7.02.

Ethyl 4-(4-Fluorophenyl)-5-(2-methoxyethoxymethyl)-2-(1-methylethyl)-3-thiophenecarboxylate (**34**).

To a suspension of 300 mg of sodium hydride (60% in mineral oil) in 8 ml of dimethylformamide was added dropwise a solution of 2.0 g (6 mmoles) of **31** in 10 ml of dimethylformamide. After the mixture was stirred at room temperature for 30 minutes, 1.1 g (8 mmoles) of 2-bromoethyl methyl ether was added and the mixture was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure and the residual oil was flash chromatographed using hexane/ethyl acetate (7:3) to elute the product, 1.8 g (76%) of **34** as an oil; ir (neat): 1700, 1400, 1348, 1263, 1175 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.32-6.91 (m, 4H), 4.41 (s, 2H), 4.02 (q, 2H), 3.86 (m, 1H), 3.52 (s, 3H), 3.37 (s, 4H), 1.33 (d, J = 6.75 Hz, 6H), 0.95 (t, 3H). The material was used as is in the next reaction.

4-(4-Fluorophenyl)-5-(2-methoxyethoxymethyl)-2-(1-methylethyl)-3-thiophenemethanol (**35**).

To a solution of 5 ml of a 1*M* solution of lithium aluminum hydride in 25 ml of tetrahydrofuran at -78° was added dropwise a solution of 1.8 g (4.7 mmoles) of **34** in 5 ml of tetrahydrofuran. The mixture was allowed to warm to room temperature then was stirred for 2 hours. A saturated solution of sodium sulfate was added dropwise to the mixture until a thick precipitate formed. The mixture was diluted with methyl *t*-butyl ether and the insoluble inorganic salts were filtered through Celite. The solvent was removed under reduced pressure and the residual oil was flash chromatographed using hexane/ethyl acetate (3:1) to elute the product, 1.2 g (75%) of **35** as a waxy solid, mp 52-55°; ir (chloroform): 1503, 1222, 1080 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.46-6.97 (m, 4H), 4.47 (s, 2H), 4.40 (d, J = 5.6 Hz, 2H), 4.14 (m, 1H), 3.56 (s, broad, 5H), 3.38 (s, 2H), 1.38 (d, J = 6.75 Hz, 6H), OH proton not seen.

Anal. Calcd. for $C_{18}H_{23}O_3SF$: C, 63.88; H, 6.85; S, 9.47. Found: C, 63.90; H, 6.73; S, 9.50.

General Procedure for the Preparation of Mercapto Alcohols **37**.

To a solution of 0.1 mole of **36** in 150 ml of tetrahydrofuran at 0° was added dropwise 0.22 mole of *n*-butyllithium (1.6*M* solution in hexane). After the mixture was stirred at 0° for 4 hours, the resulting orange suspension was cooled to -78° then a solution of 0.1 mole of the appropriate aldehyde in 100 ml of tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to -20° at which point a pale yellow solution formed. After stirring at this temperature for 30 minutes, saturated ammonium chloride was added. The organic phase was separated and the aqueous portion was extracted with methylene chloride. The organic solutions were combined and dried over sodium sulfate then the solvent was removed under reduced pressure to give the product **37** as an oil.

General Procedure for the Michael Addition of **37** to **10**.

To a solution of 0.1 mole of **37** and 0.1 mole of **10** in 300 ml of tetrahydrofuran was added 0.11 mole of triethylamine. After stirring the mixture at room temperature for 4 hours, water was added. The mixture was extracted with methyl *t*-butyl ether (1x) then methylene chloride (1x). The organic solutions were combined and dried over sodium sulfate then the solvent was removed under reduced pressure to give the product **38** as an oil.

General Procedure for the Oxidation of **38** to **39**.

To a solution of 0.096 mole of oxalyl chloride in 1 liter of methylene chloride at -65° was added dropwise a solution of 0.19 mole of dimethyl sulfoxide in 40 ml of methylene chloride. After the mixture was stirred at -65° for 5 minutes, a solution of 0.08 mole of **38** in 200 ml of methylene chloride was added dropwise. Stirring was continued at -65° for 1 hour then 0.4 mole of triethylamine was added. The temperature of the reaction was allowed to rise to room temperature then the mixture was washed with water. The solvent was removed under reduced pressure and methyl *t*-butyl ether was added to the residue. The mixture was washed with water then the organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure to give the product **39** as an oil.

General Procedure for the Preparation of Dihydrothiophenes **40**.

To a solution of 0.08 mole of diisopropylamine in 500 ml of tetrahydrofuran at 0° under an argon atmosphere was added slowly 0.082 mole of *n*-butyllithium (1.6*M* in hexane). The solution was stirred at 0° for 5 minutes then a solution of 0.08 mole of **39** in 100 ml of tetrahydrofuran was added rapidly. The temperature of the mixture was allowed to warm to room temperature and stirring was continued for 1 hour. Saturated ammonium chloride was added and the mixture was extracted with methyl *t*-butyl ether (2x). The organic solution was dried over sodium sulfate and the solvent was removed under reduced pressure to give the product **40**.

General Procedure for the Oxidation of Dihydrothiophenes **40** to Thiophenes **41**.

To a suspension of 0.11 mole of DDQ in 1 liter of methylene chloride was added slowly to a solution of 0.1 mole of **40** in 125 ml of methylene chloride. The mixture was stirred at room temperature for 24 hours. Any insoluble material was filtered from the mixture and the filtrate was washed with aqueous sodium bicarbonate solution. The organic solution was dried over sodium sulfate and the solvent was removed under reduced pressure to give the crude product as an oil. The oil was dissolved in a minimum volume of methylene chloride then was passed through a plug of silica gel using methylene chloride to elute the pure product **41**.

General Procedure for the Reduction of **41** to **42**.

To a solution of 0.1 mole of lithium aluminum hydride in 500 ml of tetrahydrofuran was added dropwise a solution of 0.1 mole of **41** in 100 ml of tetrahydrofuran. After the mixture was stirred

at room temperature for 5 hours, 15 ml of a saturated aqueous sodium sulfate solution was added dropwise (carefully - a vigorous reaction occurs). To the resulting thick precipitate was added 300 ml of methyl *t*-butyl ether. The solids were filtered and washed well with additional methyl *t*-butyl ether. The solvent was removed under reduced pressure to give essentially pure **42**. Spectral data are given below and other information is presented in Table 1.

Spectral Data for Compounds **42**.

Compound **42a** had ir (chloroform): ν 3635, 1610, 1001 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.37-7.21 (m, 6H), 7.11 (s, 5H), 4.46 (s, 2H), 3.52 (m, 1H), 1.42 (d, J = 6.75 Hz, 6H).

Compound**42b** had ir (potassium bromide): ν 3550, 1620, 1530, 1298, 1260 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.45-7.01 (m, 10H), 4.44 (s, 2H), 3.82 (s, 3H), 3.51 (m, 1H), 1.42 (d, J = 6.75 Hz, 6H).

Compound **42c** had ir (neat): ν 3460, 1450, 1251, 1020 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.40-6.90 (m, 9H), 4.42 (s, 2H), 3.48 (m, 1H), 1.52 (s, broad, 1H), 1.41 (d, J = 6.75 Hz, 6H).

Compound **42d** had ir (potassium bromide): ν 3415, 1580, 1448, 1218, 1004, 750, 692 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.38-6.85 (m, 9H), 4.40 (s, 2H), 3.50 (m, 1H), 1.56 (s, broad, 1H), 1.42 (d, J = 6.75 Hz, 6H).

Compound **42e** had ir (potassium bromide): ν 3618, 3440, 1600, 1504, 1231, 997, 836 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.40-6.84 (m, 4H), 7.11 (s, 5H), 4.42 (s, 2H), 3.50 (m, 1H), 1.43 (d, J = 6.75 Hz, 6H), 1.27 (s, broad, 1H).

Compound **42f** had ir (chloroform): ν 3620, 1323, 1170, 1128 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.59-7.00 (m, 9H), 4.41 (s, broad, 2H), 3.49 (m, 1H), 1.39 (d, J = 6.75 Hz, 6H), 1.37 (s, broad, 1H).

Compound **42g** had ir (chloroform): ν 3620, 1490, 1216 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.71-7.21 (m, 9H), 7.17 (s, 5H), 4.49 (s, broad, 2H), 3.52 (m, 1H), 1.58 (s, broad, 1H), 1.44 (d, J = 6.75 Hz, 6H).

Compound **42h** had ir (potassium bromide): ν 3527, 1500, 1460, 1016, 750 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.88-7.61 (m, 4H), 7.52-6.97 (m, 8H), 4.43 (s, broad, 2H), 3.52 (m, 1H), 1.43 (d, J = 6.75 Hz, 6H).

Compound **42i** had ir (film): ν 3430, 1602, 1255 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.37-6.88 (m, 3H), 7.17 (s, 5H), 4.48 (s, 2H), 3.48 (m, 1H), 1.54 (s, broad, 1H), 1.41 (d, J = 6.75 Hz, 6H).

Compound **42j** had ir (potassium bromide): ν 3460, 1448, 1006 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.32 (s, 5H), 4.47 (d, J = 4.5 Hz, 2H), 3.45 (m, 1H), 2.80 (m, broad, 1H), 1.69 (m, broad, 10H), 1.38 (d, J = 6.75 Hz, 6H), 1.23 (s, broad, 1H).

Compound **42k** had ir (chloroform): ν 3619, 1460, 1382, 995 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.35 (s, 5H), 4.64 (s, broad, 2H), 3.48 (m, 1H), 3.32 (m, 1H), 2.00-1.50 (m, 8H), 1.39 (d, J = 6.75 Hz, 6H).

Compound **42l** had ir (potassium bromide): ν 3460, 1600, 1460, 998 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.40-7.15 (m, 5H), 4.53 (d, J = 4.6 Hz, 2H), 3.40 (m, 1H), 2.67-2.45 (m, 2H), 1.50 (s, broad, 1H), 1.38 (d, J = 6.75 Hz, 6H), 1.20 (s, broad, 12H), 0.82 (t, broad, 3H).

Compound **42m** had ir (neat): ν 3390, 1442 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.51-7.04 (m, 6H), 6.08 (m, 1H), 4.46 (s, 2H), 3.40 (m, 1H), 1.82 (m, 6H), 1.35 (d, J = 6.75 Hz, 6H).

Compound **42n** had ir (film): ν 3400, 1607, 1518, 1247, 1015, 832 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.31-7.19 (m, 5H), 7.05 (d, J = 9 Hz, 2H), 6.72 (d, J = 9 Hz, 2H), 4.43 (d, J = 4.5 Hz, 2H), 3.76 (s, 3H), 3.49 (m, 1H), 1.42 (d, J = 6.75 Hz, 6H).

Compound **42o** had ir (chloroform): ν 3605, 1601, 1510, 1235 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.33-6.85 (m, 4H), 6.97 (s, 4H), 4.39 (s, broad, 2H), 3.49 (m, 1H), 2.27 (s, 3H), 1.58 (s, broad, 1H), 1.41 (d, J = 6.75 Hz, 6H).

General Procedure for the Preparation of **43** and **44**.

To a solution of 0.87 mmole of **37** and 1.0 mmole of triethylamine in 15 ml of tetrahydrofuran was added dropwise 0.87 mmole of phosgene (12.5% in toluene). The mixture was stirred at room temperature for 4 hours then was poured into cold water and extracted with methylene chloride (2x). The organic phases were combined and dried over sodium sulfate and the solvent was removed under reduced pressure to afford a mixture of **43** and **44**.

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