

## Design, Synthesis, and Biological Evaluation of Aryloxyethyl Thiocyanate Derivatives against *Trypanosoma cruzi*

Eleonora Elhalem,<sup>†,‡</sup> Brian N. Bailey,<sup>§,‡</sup> Roberto Docampo,<sup>§</sup> István Ujváry,<sup>||</sup> Sergio H. Szajnman,<sup>†</sup> and Juan B. Rodriguez\*,<sup>†</sup>

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón 2, Ciudad Universitaria, RA-1428 Buenos Aires, Argentina, Laboratory of Molecular Parasitology, Department of Pathobiology, College of Veterinary Medicine, University of Illinois at Urbana–Champaign, 2001 South Lincoln Avenue, Urbana, Illinois 61802, and Institute of Chemistry, Chemical Research Center, Hungarian Academy of Sciences, H-1525 Budapest, P.O. Box 17, Hungary

Received April 8, 2002

As a continuation of our project aimed at the search for new and safe chemotherapeutic and chemoprophylactic agents against American trypanosomiasis (Chagas' disease), several drugs structurally related to 4-phenoxyphenoxyethyl thiocyanate (**4**) were designed, synthesized, and evaluated as antiproliferative agents against the parasite responsible for this disease, the hemoflagellated protozoan *Trypanosoma cruzi*. This thiocyanate derivative was previously shown to be an effective and potent agent against *T. cruzi* proliferation. Several drugs possessing thiocyanate groups proved to be effective growth inhibitors of *T. cruzi* growth. Among the designed compounds, it is important to point out the extremely potent activity shown by **11**, **23**, **38**, **53**, **90**, **99**, and **117** against the epimastigote forms of the parasite. All of them exhibited IC<sub>50</sub> values in the low micromolar range, and these values were comparable with those presented by our lead drug **4** and ketokonazole, a well-known antiparasitic agent. The activity displayed by the nitrogen-containing derivative **90** was very promising with IC<sub>50</sub> values of 3.3 μM. Several other thiocyanate derivatives also proved to be very potent inhibitors of the multiplication of *T. cruzi* epimastigotes, such as compounds **28**, **33**, **43**, **48**, **56**, **61**, **66**, **71**, **76**, and **124**. Compound **43** resulted in being a promising drug because it was also very effective against amastigotes, the clinically more relevant form of the parasite. This compound was 3-fold more potent than **4**, while **11** showed nearly the same activity as our lead drug against intracellular *T. cruzi*. It was very surprising that the experimental juvenoid **124**, although fairly devoid of activity against epimastigotes, was very effective against intracellular amastigotes growing in myoblasts. The rest of the designed compounds showed a broad degree of inhibitory action, from moderately active drugs to drugs almost devoid of antiparasitic activity. Compound **43** is an interesting example of an effective antichagasic agent that presents excellent prospectives not only as a lead drug but also to be used for further in vivo studies.

### Introduction

There is considerable interest in developing novel chemotherapeutic approaches against American trypanosomiasis (Chagas' disease) based on unique aspects of the structure and metabolism of the etiological agent for this disease, the protozoan *Trypanosoma cruzi*.<sup>1</sup> This disease is a significant cause of morbidity and mortality from southern United States to southern Argentina and is considered by the World Health Organization as one of the major parasitic diseases.<sup>2</sup> Despite the progresses made in *T. cruzi* biochemistry and physiology,<sup>3</sup> the chemotherapy of Chagas' disease remains deficient. It is based on old and fairly unspecific drugs such as nifurtimox (**1**) and benznidazole (**2**).<sup>4</sup> Although both of these drugs are able to cure at least 50% of recent infections, according to the disappearance of symptoms, and to give rise to negativization of parasitemia and serology, they suffer from serious drawbacks: (a) in

acute infections, effective therapy has not been consistent among distinct geographical areas, presumably because of selective drug sensitivity on different *T. cruzi* strains;<sup>5</sup> (b) both drugs produce serious side effects including vomiting, anorexia, peripheral neuropathy, allergic and dermatopathy; (c) long-term treatment is another disadvantage, since these agents have to be administered for extended periods. In addition, some concerns have been raised against gentian violet (**3**), the only drug available to prevent blood transmission of Chagas' disease, because it is carcinogenic in animals<sup>6</sup> (Chart 1). As with other kinetoplastid parasites, *T. cruzi* has a complex life cycle consisting of three main morphological forms: the dividing noninfective epimastigotes, the nondividing and highly infective trypomastigotes, and the intracellular and clinically more relevant form, amastigotes.<sup>7</sup>

Sterol biosynthesis proved to be an interesting target for the design of new drugs not only for fungi but also for different pathogenic parasites.<sup>8</sup> Sterol biosynthesis in parasites differs from that in mammalian hosts in that the final product is ergosterol rather than cholesterol.<sup>9</sup> Depletion of endogenous sterols produces growth

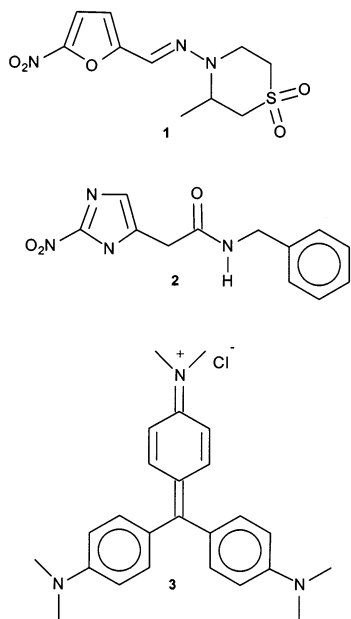
\* To whom correspondence should be addressed. Phone: (54 11) 4-576-3346. Fax: (54 11) 4-804-1692. E-mail: JBR@qo.fcen.uba.ar.

<sup>†</sup> Universidad de Buenos Aires.

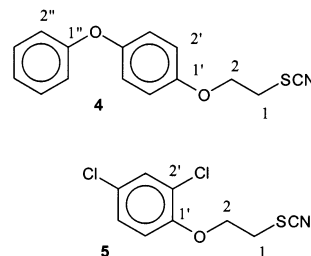
<sup>‡</sup> Both authors contributed equally to this work.

<sup>§</sup> University of Illinois at Urbana–Champaign.

<sup>||</sup> Hungarian Academy of Sciences.

**Chart 1.** Current Drugs for the Treatment of Chagas' Disease and Blood Sterilization

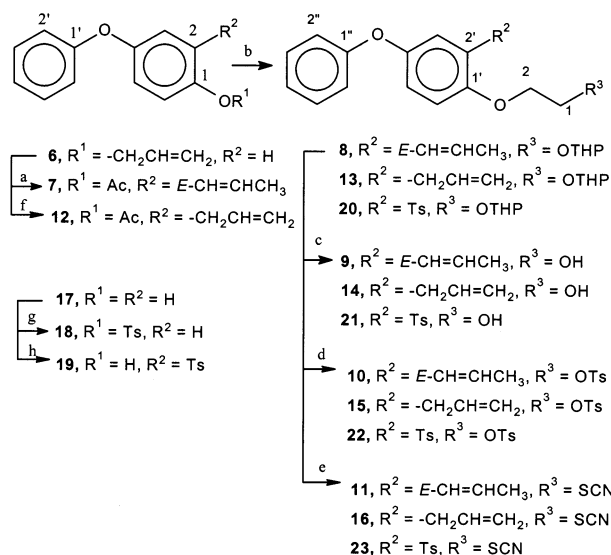
inhibition of the parasite; therefore, selective inhibition of a crucial enzyme responsible for sterol biosynthesis in the parasite will impair *T. cruzi* proliferation. The blockage of this metabolic pathway has been extensively studied, and some drugs, like triazole derivatives,<sup>9–13</sup> resulted in being potential chemotherapeutic agents against Chagas' disease. In addition, aryloxyethyl thiocyanate derivatives proved to be very effective and potent inhibitors of *T. cruzi* growth.<sup>14,15</sup> Some of them exhibited IC<sub>50</sub> values close to 1.0  $\mu$ M against epimastigotes and were efficient at the low nanomolar level against the intracellular form of the parasite.<sup>14</sup> 4-Phenoxyphenoxyethyl thiocyanate (**4**) is a representative member of this family of compounds and is now a lead drug for the present study together with 2,4-dichlorophenoxyethyl thiocyanate (**5**). The latter compound is a remarkable example of an effective inhibitor of *T. cruzi* proliferation in which the phenoxy terminal group is not present (Chart 2).<sup>15</sup> Under the same assay conditions, **4** was much more potent against amastigotes and epimastigotes than nifurtimox, one of the drugs currently in clinical use to control this disease.<sup>14</sup> We have established that the target of **4** is the sterol biosynthetic pathway. Parasites treated with **4** showed a significant decrease in the concentration of each biosynthetic precursor of ergosterol compared with controls. For example, at a concentration as low as 0.3  $\mu$ M, compound **4** was able to reduce the concentrations of ergosta-7,24-(24<sup>1</sup>)-dien-3 $\beta$ -ol, ergosta-5,7-dien-3 $\beta$ -ol, ergosta-5,7,24-(24<sup>1</sup>)-trien-3 $\beta$ -ol, 24-ethyl-5,7,22-cholestatrien-3 $\beta$ -ol, and ergosterol without squalene accumulation, indicating that the target enzyme was in the isoprenoid biosynthetic pathway.<sup>16</sup> Although farnesyl pyrophosphate synthase (FPPS) was thought to be the molecular target, even a concentration of 40  $\mu$ M drug **4** was not able to inhibit the *T. cruzi* recombinant FPPS activity.<sup>17,18</sup> According to these results, the more likely target was squalene synthase, the enzyme that catalyzes the reaction of two units of farnesyl pyrophosphate to produce squalene.

**Chart 2.** Chemical Structures of Two Representative Inhibitors of *T. cruzi* Proliferation Taken as Lead Drugs

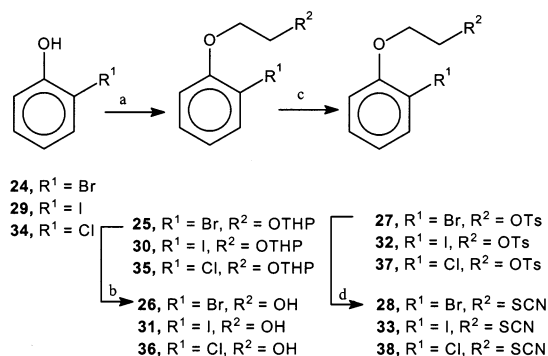
The increment in the inhibitory effectiveness produced by the presence of the thiocyanate unit is also observed with other sulfur-containing groups bonded at the same position, but to a lesser extent. The removal of this thiocyanate functionality by any oxygenated functional group produces a dramatic decrease in the biological activity, as indicated by the inhibitory action exhibited by their common synthetic intermediate, the corresponding tetrahydropyranyl ethers. In addition, we demonstrated that the 4-phenoxyphenoxy unit is very significant for molecular recognition because its presence results in inhibition of *T. cruzi* growth.<sup>14,15,19,20</sup> Bearing in mind that the pharmacophore corresponded to the phenoxyethyl unit and on the basis of the potent inhibitory action exhibited by sulfur-containing derivatives at C-1, we decided to design and prepare a new set of related compounds having this pharmacophore to be evaluated against *T. cruzi* growth.

## Chemistry

Compounds **11** and **16** were prepared starting from the known allyl ether **6**.<sup>20</sup> This compound was treated with acetyl chloride in the presence of aluminum chloride as catalyst in carbon disulfide at 0 °C and then at room temperature to produce the rearranged product **7** in 60% yield.<sup>21</sup> Acetate **7** was converted into **8** by treatment with 2-bromoethyl tetrahydro-2*H*-pyran-2-yl ether via a modified Williamson procedure.<sup>22</sup> Cleavage of the tetrahydropyranyl protecting group of **8** was conducted by treatment with pyridinium *p*-toluenesulfonate<sup>23</sup> to yield **9** in 80% yield, which on treatment with tosyl chloride gave rise to **10**. This compound was reacted with potassium thiocyanate in *N,N*-dimethylformamide at 100 °C to afford the respective thiocyanate **11** in 24% yield.<sup>24</sup> When the intramolecular alkylation of **6** was carried out, keeping the reaction temperature below 0 °C, no extension of conjugation was observed; instead, only the C-2' allyl derivative **12** was obtained in almost 40% yield. Acetate **12** was transformed into **13** in good yields following the same method for **7**, which after hydrolysis followed by treatment with tosyl chloride and further nucleophilic attack of potassium thiocyanate led to **16** in a similar overall yield. Compound **23** was synthesized starting from 4-phenoxyphenol (**17**), which was easily tosylated to afford **18** in excellent yield. The critical synthetic step for the preparation of **23** was a Fries photochemical reaction<sup>25</sup> that allowed the rearrangement of the tosyl group of **18** to form the corresponding sulfone at C-2' (**19**). Thus, **18** was irradiated with a medium-pressure mercury lamp at 254 nm to produce the rearranged product **19** in 65% yield. Once **19** was at hand, **23** was obtained by following an identical approach (Scheme 1).

Scheme 1<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) AlCl<sub>3</sub>, CS<sub>2</sub>, ClC(O)CH<sub>3</sub>, 0 °C, 4 h → room temp, 6 h, 60%; (b) KOH, DMSO, BrCH<sub>2</sub>CH<sub>2</sub>OTHP, room temp, 16 h, 50% for **8**, 83% for **13**, 42% for **20**; (c) PPTs, MeOH, room temp, 16 h, 81% for **9**, 76% for **14**, 68% for **21**; (d) ClTs, py, room temp, 4 h, 91% for **10**, 70% for **15**, 93% for **22**; (e) KSCN, DMF, 100 °C, 5 h, 24% for **11**, 47% for **16**, 83% for **23**; (f) AlCl<sub>3</sub>, CS<sub>2</sub>, ClC(O)CH<sub>3</sub>, -5 °C, 2 h, 39%; (g) ClTs, py, room temp, 5 h, 95%; (h) *hν* (λ<sub>exc</sub> = 254 nm), MeOH, room temp, 7 h, 65%.

Scheme 2<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) KOH, DMSO, BrCH<sub>2</sub>CH<sub>2</sub>OTHP, room temp, 16 h, 47% for **25**, 66% for **30**, 23% for **35**; (b) PPTs, MeOH, room temp, 16 h, 72% for **26**, 75% for **31**, 97% for **36**; (c) ClTs, py, room temp, 4 h, 72% for **27**, 97% for **32**, 62% for **37**; (d) KSCN, DMF, 100 °C, 5 h, 28% for **28**, 68% for **33**, 85% for **38**.

Starting from the corresponding ortho halophenols, 2-bromophenol (**24**), 2-iodophenol (**29**), and 2-chlorophenol (**34**), the desired thiocyanate derivatives **28**, **33**, and **38** were prepared via the respective tetrahydropyranyl derivatives **25**, **31**, **35**, respectively, as indicated in Scheme 2.

The preparation of the methylated derivatives of our lead **5** is illustrated in Schemes 3 and 4.

The key step for the preparation of **90** was the recently reported coupling reaction between an arylboronic acid and an appropriate aniline or phenol in the presence of cupric acetate and pyridine.<sup>27</sup> The straightforward approach to obtain the designed drug was the coupling between phenylboronic acid and *p*-anisidine (**77**) followed by methyl ether cleavage; the resulting phenol was the common intermediate for obtaining **90**, according to the general procedure. The coupling reaction to give **78** occurred with 56% yield, but all attempts

to remove the methyl protecting group of **78**, such as activation of aluminum chloride followed by nucleophilic attack of ethyl mercaptane<sup>28</sup> or by treatment with trimethylsilyl iodide,<sup>29</sup> were unsuccessful. Then, a more labile protecting group than the methyl ether was considered, the acetyl group being more appropriate. Thus, 4-nitrophenol was acetylated in excellent yield to give **81**, which was quantitatively hydrogenated<sup>30</sup> to give **82** and which was further hydrolyzed to afford the required phenol **83**. All attempts for O-alkylation of **83** failed even when treated with 1 equiv of bromoethyl tetrahydropyranyl ether; in this case, the di-O- and N-alkylated products were obtained together with unreacted starting material. Finally, **90** was successfully prepared by introducing the ethyl tetrahydropyranyl ether functionality at the beginning. Therefore, coupling of 4-nitrophenol with bromoethyl tetrahydropyranyl ether afforded **85** in low yields. Catalytic hydrogenation of **85** gave the required aniline **86**, which on reaction with phenyl boronic acid gave rise to **87** in 65% yield. Following the general procedure, **87** was converted into **90** (Scheme 5).

2-Hydroxycarbazole (**91**) was employed as a rigid template to prepare **99**. To avoid competition between O- and N-alkylation, a selective protection at N-9 was necessary. Then, **91** was treated with dihydropyran in the presence of pyridinium 4-toluenesulfonate to produce the O-protected carbazole derivative **92** in 89% yield. This compound treated with benzyl bromide gave **93** in almost quantitative yield that after tetrahydropyranyl cleavage afforded **94**. This compound was converted into **95**, which produced **96** after tetrahydropyranyl cleavage that was further tosylated to give **97**. At this point, the benzyl protecting group was removed to yield **98**, which reacted with potassium thiocyanate to form **99** (Scheme 6).

Compounds **101** and **103** were prepared by electrophilic attack of methyl iodide and benzyl bromide on the mercaptane derivative **100**<sup>31</sup> as depicted in Scheme 7. The sulfur-containing derivative **106** was prepared in moderate yield by an S<sub>N</sub>2 reaction between the known tosylate **105** and the potassium salt of thiophenol. Isocyanate **107** was prepared in 44% yield by nucleophilic attack of potassium cyanate on **105**, while the azido derivatives **108** and **110** were prepared by separate nucleophilic attacks of the azide ion on tosylate **105**<sup>14</sup> and epoxide **109**,<sup>20</sup> respectively (Scheme 7). The aziridine derivative **111** was prepared in 77% yield from the hydroxyazide **110** by treatment with triphenylphosphine<sup>33</sup> (Scheme 8).

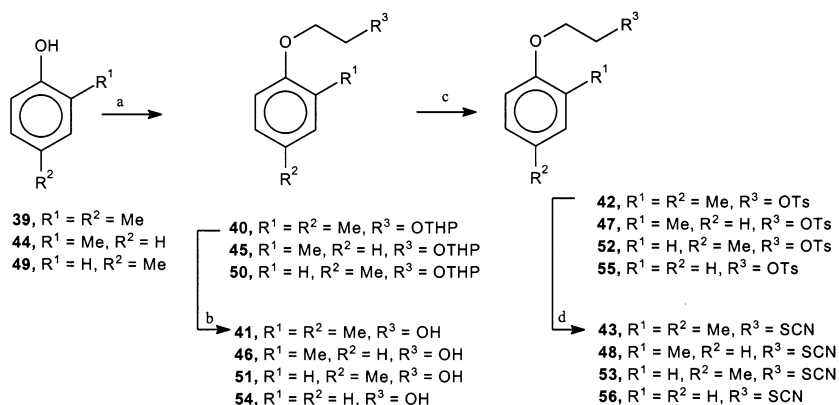
The preparation of **117** was carried out starting from the known 4-phenylsulfanylphenol **112**.<sup>14</sup> This compound was reacted with bromoethyl tetrahydropyranyl to produce **113** in 62% yield, which was further oxidized by treatment with 1 equiv of sodium metaperiodate<sup>34</sup> to afford the sulfoxide-containing drug **114**. Following the general method, **114** was transformed into **117** (Scheme 9).

Dithiolcarbamates **120–122** and thiourea **123** were prepared from the known amine **119**<sup>36</sup> as depicted in Scheme 10.

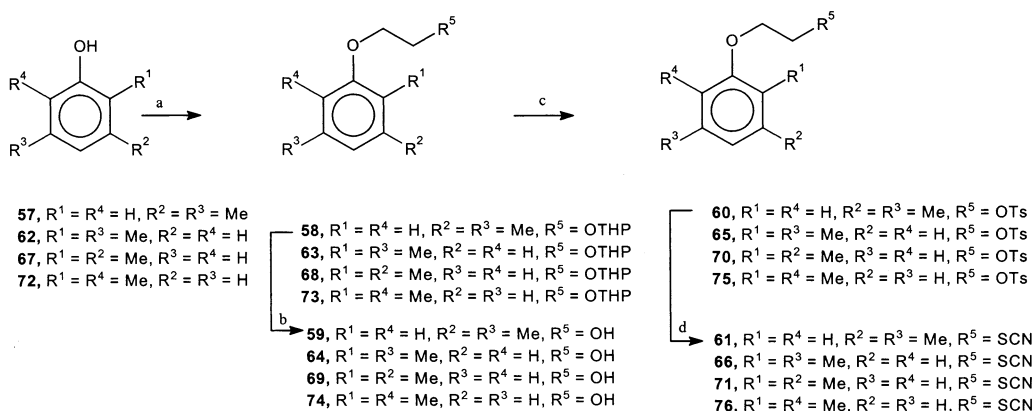
## Results and Discussion

The effect of a number of aryloxyethyl thiocyanate derivatives on the proliferation of the epimastigote form



Scheme 3<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) KOH, DMSO, BrCH<sub>2</sub>CH<sub>2</sub>OTHP, room temp, 16 h, 55% for **40**, 85% for **45**, 64% for **50**; (b) PPTs, MeOH, room temp, 16 h, 99% for **41**, 41% for **46**, 77% for **51**; (c) CITs, py, room temp, 4 h, 97% for **42**, 76% for **47**, 37% for **53**, 24% for **55**; (d) KSCN, DMF, 100 °C, 5 h, 77% for **43**, 52% for **48**, 58% for **53**, 61% for **56**.

Scheme 4<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) KOH, DMSO, BrCH<sub>2</sub>CH<sub>2</sub>OTHP, room temp, 16 h, 78% for **58**, 66% for **63**, 58% for **68**, 61% for **73**; (b) PPTs, MeOH, room temp, 16 h, 77% for **59**, 93% for **64**, 75% for **69**, 75% for **74**; (c) CITs, py, room temp, 4 h, 86% for **60**, 92% for **65**, 91% for **70**, 91% for **75**; (d) KSCN, DMF, 100 °C, 5 h, 86% for **61**, 83% for **66**, 52% for **71**, 85% for **76**.

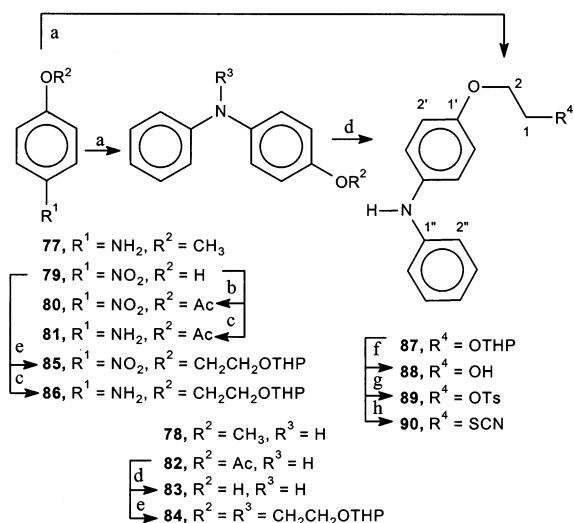
Table 1

compd	IC <sub>50</sub> , μM	compd	IC <sub>50</sub> , μM
<b>4</b>	2.2 <sup>14</sup>	<b>73</b>	>70.0
<b>8</b>	>60.0	<b>76</b>	13.3
<b>11</b>	6.8	<b>87</b>	31.4
<b>13</b>	>60	<b>90</b>	3.3
<b>16</b>	>60	<b>95</b>	>70.0
<b>20</b>	>70.0	<b>99</b>	10.3
<b>23</b>	4.7	<b>101</b>	>100.0
<b>28</b>	20.2	<b>103</b>	>60.0
<b>30</b>	>60.0	<b>106</b>	62.1
<b>33</b>	18.5	<b>107</b>	>70.0
<b>35</b>	>70.0	<b>108</b>	>70.0
<b>38</b>	11.4	<b>110</b>	>70.0
<b>40</b>	>70.0	<b>111</b>	41.5
<b>43</b>	18.8	<b>114</b>	>70.0
<b>45</b>	>70.0	<b>117</b>	7.7
<b>48</b>	16.4	<b>118</b>	15.9
<b>50</b>	>70.0	<b>120</b>	33.3
<b>53</b>	12.1	<b>121</b>	45.6
<b>56</b>	16.8	<b>122</b>	32.2
<b>58</b>	>70.0	<b>123</b>	40.3
<b>61</b>	19.3	<b>124</b>	>70.0
<b>63</b>	>70.0	<b>125</b>	>120
<b>66</b>	14.5	<b>126</b>	101.5
<b>68</b>	>70.0	ketoconazole	3.2
<b>71</b>	14.8		

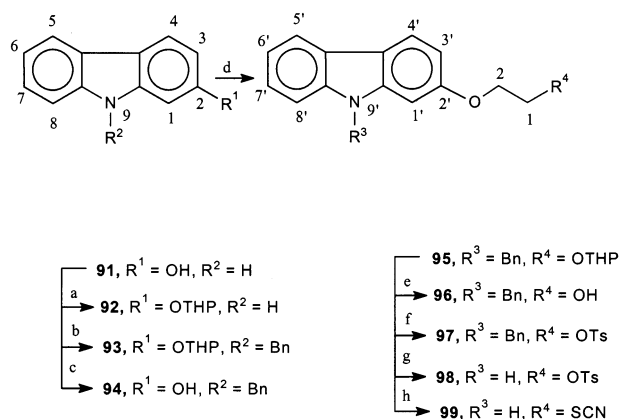
of *T. cruzi* is shown in Table 1. The well-known antifungal and antiparasitic agent ketoconazole and our lead drug **4** were employed as positive controls. Biological assays on the proliferation of the epimastigote form

of *T. cruzi* of this family of compounds were very encouraging.

**Replacement of the Hydrogen Atom at C-2' by a Bulky Group.** We have recently reported that minor structural modifications around the vicinity of the C-1 position had a marked effect on the biological activity.<sup>14,15</sup> In addition, we have found that the replacement of the ortho hydrogen atom at the C-2' position by a halogen atom in compound **4** modulated its efficacy in such a way that the inhibitory potency increased as the substituent size increased.<sup>14</sup> Therefore, it was of interest to introduce different alkyl or functional groups at C-2'. As a first variation, it was logical to replace the H-2' by alkyl groups. Two different alkyl groups were selected: a fairly unbending one like an *E*-prop-1-en-1-yl unit with concomitant expansion of conjugation and a flexible one like an allyl unit to form **11** and **16**, respectively. In addition, to study the influence of a bulky group on biological activity, we decided to incorporate a tosyl moiety at the C-2' position to produce drug **23**. Compounds **11**, **16**, and **23** resulted in a reduction of biological activity. Drugs **11** and **23** were 3- and 2-fold less potent than **4** under the same assay conditions, while the allyl derivative **16** was almost devoid of activity against epimastigotes. We had previously demonstrated that a major increase in biological activity

Scheme 5<sup>a</sup>

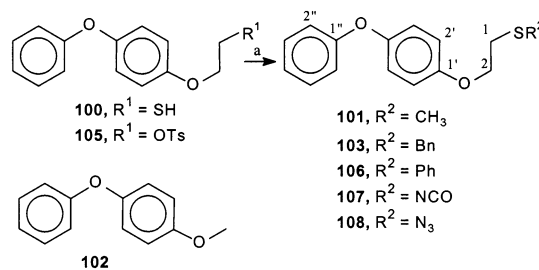
<sup>a</sup> Reagents and conditions: (a) PhB(OH)<sub>2</sub>, Cu(OAc)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, py, room temp, 72 h, 56% for **78**, 58% for **82**, 65% for **87**; (b) Ac<sub>2</sub>O/py, room temp, 16 h, 97%; (c) H<sub>2</sub>, Pd/C, 3 atm, 4 h, 100% for **81**, 100% for **86**; (d) K<sub>2</sub>CO<sub>3</sub>, MeOH/H<sub>2</sub>O, room temp, 4 h, 92%; (e) KOH, DMSO, BrCH<sub>2</sub>CH<sub>2</sub>OTHP, room temp, 16 h, 29% for **84**, 21% for **85**, 58% for **88**, 61% for **73**; (f) PPTs, MeOH, room temp, 16 h, 83%; (g) CITs, py, room temp, 4 h, 51%; (h) KSCN, DMF, 100 °C, 5 h, 52%.

Scheme 6<sup>a</sup>

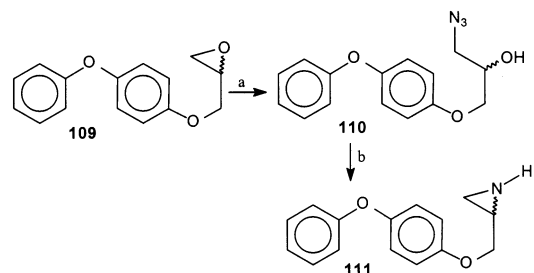
<sup>a</sup> Reagents and conditions: (a) DHP, CH<sub>2</sub>Cl<sub>2</sub>, room temp, 16 h, 89%; (b) 50% NaH, DMF, 0 °C, 2 h, 99%; (c) PPTs, MeOH, room temp, 16 h, 78%; (d) KOH, DMSO, BrCH<sub>2</sub>CH<sub>2</sub>OTHP, room temp, 16 h, 90%; (e) PPTs, MeOH, room temp, 16 h, 99%; (f) CITs, py, room temp, 4 h, 91%; (g) H<sub>2</sub>, Pd/C, 3 atm, 4 h, 100%; (h) KSCN, DMF, 100 °C, 5 h, 69%.

occurs when the thiocyanate moiety replaces the tetrahydropyranyl group.<sup>14</sup> Because these THP ether derivatives were the common synthetic precursors of thiocyanate-containing drugs, they were biologically evaluated to compare their relative potency with the thiocyanate derivatives.<sup>14,15</sup> Contrary to our previous observation on the biological action of THP ether derivatives, compounds **8**, **13**, and **20** exhibited marginal activity against *T. cruzi* epimastigotes.

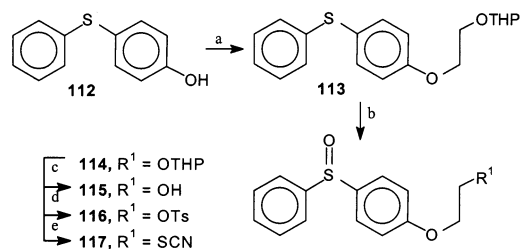
**Deleting the Chlorine Atom at C-4' in Lead Compound 5.** As mentioned before, the C-2' and C-4' substitution pattern is associated with high inhibitory action as is the case of drug **5**. Therefore, the influence of different groups at these two positions on their biological activity was investigated. Following this concept, first we decided to analyze the effect of the

Scheme 7<sup>a</sup>

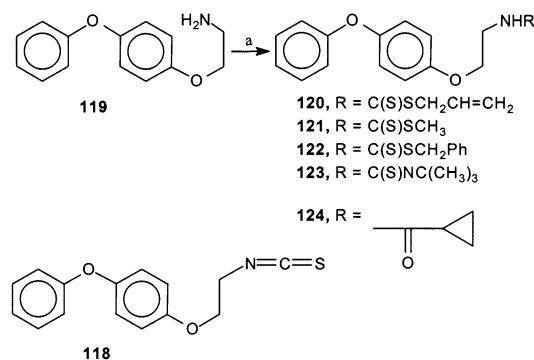
<sup>a</sup> Reagents and conditions: (a) KOH, DMSO, IMe, room temp, 4 h, 20% for **101**; ClBn, 63% for **103**; PhSH + **105**, 38% for **106**; **105** + KNCO, room temp, 16 h, 44%; **105** + NaN<sub>3</sub>, room temp, 16 h, 38%.

Scheme 8<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) NaN<sub>3</sub>, Me<sub>2</sub>CO/H<sub>2</sub>O, room temp, 48 h, 82%; (b) Ph<sub>3</sub>P, THF, room temp, 2 h, 72%.

Scheme 9<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) KOH, DMSO, BrCH<sub>2</sub>CH<sub>2</sub>OTHP, room temp, 16 h, 62%; (b) NaIO<sub>4</sub>, MeOH/H<sub>2</sub>O, room temp, 48 h, 80%; (c) PPTs, MeOH, room temp, 16 h, 91%; (d) CITs, py, room temp, 4 h, 45%; (e) KSCN, DMF, 100 °C, 5 h, 70%.

Scheme 10<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) (i) NaOH, S<sub>2</sub>C, EtOH/H<sub>2</sub>O, 0 °C, 4 h, (ii) BrCH<sub>2</sub>CH=CH<sub>2</sub>, room temp, 4 h, 71% for **120**; (ii) IMe, room temp, 4 h, 80% for **121**; (ii) ClBn, room temp, 4 h, 72% for **122**; (b) <sup>t</sup>BuNCS, NEt<sub>3</sub>, benzene, room temp, 24 h, 62%.

chlorine at C-4' by replacing this halogen atom by a hydrogen atom. Then, to study the influence of the halogen size at C-2' on biological activity, bromine, iodine, or chlorine was introduced at this position. All the 2-halophenoxyethyl thiocyanate derivatives showed

potent inhibitory action, especially the C-2' chlorine derivative **38**, with IC<sub>50</sub> values close to 10 μM. Compound **38** resulted in being 10-fold less potent than **5**, which had an IC<sub>50</sub> value of 1.0 μM.<sup>15</sup> These results indicate that the presence of a chlorine atom at C-4' is very important for biological activity. The bromine and iodine derivatives, compounds **28** and **33**, were also potent inhibitors of *T. cruzi* growth but to a lesser extent than **38**, both of these compounds being nearly 2-fold less effective than the chlorine derivative **38**. The THP precursors **30** and **35** were much less potent than the corresponding final products. At 60 μM, **30** produced a 20% growth inhibition, while at 80 μM, **35** produced a 22% growth inhibition.

**Replacing the Chlorine Atoms of 5 by Methyl Groups.** Another interesting structural variation was the replacement of both chlorine atoms in **5** by two methyl groups to produce **43**. This compound was an extremely effective antiproliferative agent with an IC<sub>50</sub> close to 20 μM. Removal of one methyl group at either C-1' or C-4' or both methyl groups to form compounds **48**, **53**, or **56**, respectively, also resulted in very potent growth inhibitors. Only **53** was slightly more potent than **43** with an IC<sub>50</sub> value of 12 μM, but its synthetic precursor **50** was barely active against epimastigotes. This compound, at a concentration of 85 μM, only produced 11% growth inhibition. Therefore, it can be concluded that the phenoxyethyl thiocyanate is the pharmacophore group responsible for the antiparasitic activity. Compound **43** was also very effective against the intracellular form of *T. cruzi* and is even significantly more potent than **4** and **5**, as detailed below.

**Testing of Different Dimethylphenoxyethyl Thiocyanates.** The good prospective of **43** prompted us to optimize this new lead structure. Consequently, a comprehensive SAR study was conducted on this compound. Similar to the structural variations made in halogen derivatives, we decided to analyze the influence of each methyl group on biological action as well as the optimized position of all possible dimethylated isomers of **43**. Thus, the methyl at C-4' was deleted to form **48**; the methyl group at C-2' was eliminated to afford **53**; both methyl groups were removed to produce **56**. In addition, the following dimethylated phenoxyethyl thiocyanates were considered: 3,5-dimethyl, 2,5-dimethyl, 2,3-dimethyl, and 2,6-dimethyl derivatives (compounds **61**, **66**, **71**, and **76**, respectively). All of them exhibited more or less the same potency as **43** regardless of the relative positions between the methyl groups. Thus, **61**, **66**, **71**, and **76** exhibited IC<sub>50</sub> values of 19.3, 14.5, 14.8, and 13.3 μM, respectively. We have found that tetrahydropyranyl precursors of potent thiocyanate-containing drugs were moderately active against *T. cruzi* growth, while THP intermediates of moderately effective thiocyanate-bearing compounds were almost devoid of inhibitory action against this parasite.<sup>14,15</sup> To complete our SAR studies, these THP derivatives were considered as inhibitors rather than simple thiocyanate precursors. At a concentration of 80 μM, only **63** was somewhat active, showing 15% growth inhibition, while **58** and **68** were devoid of antiparasitic activity.

**Replacement of the Oxygen Atom between the Phenyl Groups by a Nitrogen Atom.** Although our lead drug **4** was able to substantially reduce parasitemia

in an experimental model of Chagas disease employing Swiss mice, this effect was not as pronounced as that observed for benznidazole used as a positive control.<sup>26</sup> The lack of complete effectiveness of this drug, even administered intraperitoneally, might be attributed to a low plasma concentration of the drug. It was thought that a more water-soluble analogue would solve this problem. Therefore, a nitrogen atom replacing the oxygen atom between both phenyl groups would improve water solubility. The estimated log *P* value of 3.76 for this new analogue compared with the corresponding one of 4.51 for **4** enforced this idea. Certainly, **90** was very effective against the epimastigote forms of *T. cruzi* with an IC<sub>50</sub> value of 3.3 μM, indicating that this compound was as effective as the ergosterol biosynthesis inhibitor ketoconazole and **4** with IC<sub>50</sub> values of 3.2 and 2.2 μM, respectively. Interestingly, the activity shown by **90** correlated quite well with those exhibited by the tetrahydropyranyl precursor **87** with an IC<sub>50</sub> of around 30 μM, suggesting that this nitrogen atom plays an important role for molecular recognition. The conformationally constrained analogue of **90** (compound **99**) also was a very potent inhibitor of *T. cruzi* multiplication with an IC<sub>50</sub> value of 10 μM, but its THP precursor **95** presented reduced biological activity.

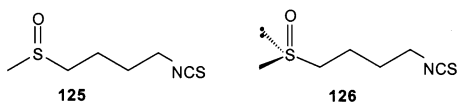
**Elimination of the Electrophilic Center Keeping a Sulfur Atom at the Polar End.** With this structural variation, compound **106** resulted in being moderately active (IC<sub>50</sub> = 62.1 μM), while **103** at a concentration of 60 μM showed 41% of growth inhibition. On the other hand, at a concentration of 100 μM, compound **101** was only able to inhibit growth by 18%. These results strengthen the idea that covalent binding takes place in order for enzyme inhibition to occur.

**Introduction of an Electrophilic Center Other Than a Thiocyanate Group at the Polar End.** We figured out that the presence of a sulfur atom at C-1 was very important for molecular recognition even when the thiocyanate moiety was not present.<sup>31</sup> On the other hand, because the thiocyanate group is an electrophilic center responsible for biological action by covalently binding with a specific amino acid residue, it was of interest to study both the influence of this electrophilic center erasing it and keeping the sulfur atom, and also the replacement of the whole thiocyanate moiety by other electrophilic groups. Therefore, methyl, benzyl, and phenyl groups to give drugs **101**, **103**, and **106**, respectively, replaced the cyanide (CN) unit, while isocyanate, azide, and aziridine groups substituted the thiocyanate moiety to yield **107**, **108**, **110**, and **111**, respectively. The lack of biological action of drug **107** was surprising because it was anticipated that this 4-phenoxyphenoxyethyl derivative with an electrophilic isocyanate would behave as a good inhibitor. The same arguments can be applied to azide-containing drugs such as **108** and **110**. Both of these drugs were poorly active against *T. cruzi* cell growth, exhibiting 28% and 26% growth inhibition at concentrations of 80 and 70 μM, respectively. The aziridine-containing compound **111** resulted in being only moderately potent with an IC<sub>50</sub> of 41.5 μM.

**Replacement of the Oxygen Atom between the Phenyl Groups by a Sulfoxide Moiety.** The replacement of the bridge oxygen atom by a sulfoxide group



**Chart 3.** Chemical Structures of Synthetic and Natural Sulforaphane, the Cancer Chemopreventive Agent Isolated from Broccoli<sup>a</sup>



<sup>a</sup> The naturally occurring sulforaphane has an *R* configuration.

brought about a very potent antiparasitic drug (**117**) with an  $IC_{50}$  value in the low micromolar range ( $7.7 \mu M$ ). This interesting structural variation opens new perspectives in antiparasitic drug design.

**Preparation of Analogues of 4-Phenoxyphenoxyethyl Isothiocyanate.** We have recently described that juvenile hormone analogues act as inhibitors of *T. cruzi* growth even in the event that these drugs presented juvenoid activity on several nonrelated bug species such as *Tenebrio molitor*, *Galleria mellonella*, *Dysdercus cingulatos*, and *Pyrrhocoris apterus* instead of Chagas' disease vectors such as *Rhodnius prolixus* or *Triatoma infestans*.<sup>35</sup> 2-(4-Phenoxyphenoxy)ethyl isothiocyanate (**118**) is an interesting example of a sulfur-containing derivative and is a position isomer of our lead drug **4**.<sup>36</sup> This isothiocyanate has the nitrogen atom of this functionality bonded at C-1, and the electrophilic carbon is at almost the same distance as that in **4**. Preliminary biological evaluation of this drug had indicated low efficacy against epimastigotes but high potency against the intracellular form of the parasite. To confirm that this electrophilic center was very important for molecular recognition, a series of closely related nitrogen- and sulfur-containing drugs were prepared keeping a nitrogen atom at C-1. Therefore, compounds **120**–**123** were envisioned for this purpose, three of them bearing a dithiolcarbamate as the polar extreme (compounds **120**, **121**, and **122**), and the other one having a thiourea moiety at the same position. In addition and in order to confirm the critical role of the sulfur atom for molecular recognition, the experimental insect juvenile hormone analogue *N*-[(4-phenoxyphenoxy)ethyl]cyclopropanecarboxamide (**124**) was also tested (Scheme 10).<sup>37</sup> Moreover, sulforaphane<sup>38</sup> is a naturally occurring anticarcinogenic agent isolated from broccoli that presents the isothiocyanate moiety bonded at one end of an aliphatic chain; that is, there is no aryloxyethyl unit in its structure (Chart 3). For the above reasons, it was quite desirable to test this compound in order to confirm that the electrophilicity of the isothiocyanate group was not responsible for the cellular activity against *T. cruzi*. Similar to **4**, this compound was a potent inhibitor of *T. cruzi* proliferation but to a lesser extent, with an  $IC_{50}$  value close to  $15 \mu M$ . The rest of the 4-phenoxyphenoxyethylamine derivatives were around 2-fold less effective than **118** despite the substituent at the sulfur atom. The experimental juvenoid **124** was not a very potent compound. At a concentration of  $70 \mu M$ , it was able to reduce growth by 31%.

The synthetic and naturally occurring sulforaphane, compounds **125** and **126**, respectively, were evaluated against epimastigotes. Both of these drugs were devoid of antiparasitic activity. These results reinforce the idea that the 4-phenoxyphenoxy skeleton plays a critical role in molecular recognition. In fact, **125** and **126** both have

**Table 2**

compd	$IC_{50}$ , $\mu M$	compd	$IC_{50}$ , $\mu M$
<b>4</b>	16.0	<b>90</b>	41.1
<b>8</b>	> 70.0	<b>117</b>	58.8
<b>11</b>	14.0	<b>118</b>	46.7
<b>16</b>	> 70.0	<b>120</b>	> 70.0
<b>30</b>	29.0	<b>121</b>	27.4
<b>33</b>	> 70.0	<b>122</b>	> 70.0
<b>35</b>	72.7	<b>123</b>	24.2
<b>43</b>	5.0	<b>124</b>	6.7
<b>76</b>	> 70.0		

an isothiocyanate group bonded at their polar ends, exhibiting no cellular activity toward *T. cruzi* cells.

The more promising drugs (compounds **11**, **30**, **43**, **90**, and **118**) and others not so potent were assayed against amastigotes, the form of the parasite that is more clinically relevant. Compound **4** was used as a positive control. The dimethyl derivative **43** was a very effective agent against the intracellular form of the parasite. This compound was 3-fold more potent than **4**, while **11** exhibited practically the same potency as **4** against amastigotes. Unexpectedly, the tetrahydropyranyl derivative **30** was a relatively effective inhibitor of *T. cruzi* (amastigotes), being 2-fold less potent than **4**. Compound **90** and the sulfoxide derivative **117** were potent inhibitors of *T. cruzi* (amastigotes) but to a lesser extent than our lead drug **4** with  $IC_{50}$  values of 41.1 and  $58.8 \mu M$ , respectively. The experimental juvenoid **124** was a very effective agent as an inhibitor of intracellular *T. cruzi* growing in myoblasts ( $IC_{50}$  value of  $6.7 \mu M$ ), while **121** and **123** were moderately effective antiparasitic agents. It is worthy to point out that **124** was practically inactive against epimastigotes. The rest of the designed drugs exhibited a wide level of biological activity against amastigotes, from more or less active compounds to roughly free of antiparasitic activity. The results are presented in Table 2. These drugs exhibited no toxicity to the host cells, as assessed by phase contrast microscopy observation of detachment, vacuolation, and rounding of the cells. In conclusion, drug **43** is an encouraging model of an effective antiparasitic agent, which is an excellent prospective not only as a lead drug but also to be used for further in vivo studies. Efforts in these aspects are currently being pursued in our laboratory.

### Experimental Section

The glassware used in air- and moisture-sensitive reactions were flame-dried under a dry argon atmosphere. Unless otherwise noted, chemicals were commercially available and used without further purification. Solvents were distilled before use. Benzene and tetrahydrofuran were distilled from sodium/benzophenone ketyl, and methylene chloride was distilled from phosphorus pentoxide and stored over freshly activated 4 Å molecular sieves. Anhydrous *N,N*-dimethylformamide was used as supplied from Aldrich.

Nuclear magnetic resonance spectra were recorded using Bruker AC 200 MHz and Bruker AM 500 MHz spectrometers. Chemical shifts are reported in parts per million ( $\delta$ ) relative to tetramethylsilane. The <sup>1</sup>H NMR spectra are referenced with respect to the residual CHCl<sub>3</sub> proton of the CDCl<sub>3</sub> solvent at 7.26 ppm. Coupling constants are reported in hertz. <sup>13</sup>C NMR spectra were fully decoupled and are referenced to the middle peak of the CDCl<sub>3</sub> solvent at 77.0 ppm. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet).

Melting points were determined using a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded using Nicolet Magna 550 and Nicolet Magna 750 spectrometers.

Low-resolution mass spectra were obtained on VG TRIO 2 and VG ZAB2-SEQ instruments in electron-impact mode at 70 eV (direct inlet). High-resolution mass spectrometry (HRMS) were conducted on a VG ZAB BEqQ spectrometer.

Column chromatography was performed with E. Merck silica gel (Kieselgel 60, 230–400 mesh). Analytical thin-layer chromatography was performed employing 0.2 mm coated commercial silica gel plates (E. Merck, DC-Aluminum sheets, Kieselgel 60 F<sub>254</sub>) and was visualized by 254 nm UV, iodine vapor, or immersion into an ethanolic solution of 5% H<sub>2</sub>SO<sub>4</sub>.

Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia, and to a lesser extent by the microanalytical laboratory of the Chemical Research Center of the HAS. The results were within ±0.4% of the theoretical values except where otherwise stated.

**2-(E-[Prop-1-en-1-yl])-4-phenoxyphenyl Acetate (7).** To a suspension of aluminum trichloride (888 mg, 6.7 mmol) in carbon disulfide (20 mL) cooled to 0 °C was added allyl ether **6** (1.502 g, 6.7 mmol) followed by addition of acetyl chloride (450 μL, 6.7 mmol) dropwise with vigorous stirring. The reaction mixture was stirred at 0 °C for 4 h and at room temperature for an additional 6 h. Then, the mixture was poured into crushed ice. Concentrated hydrochloric acid (5 mL) was added, and the mixture was extracted with methylene chloride (3 × 20 mL). The combined organic layers were washed with water (3 × 50 mL) and dried (MgSO<sub>4</sub>), and the solvent was evaporated. The residue was purified by column chromatography (silica gel), eluting with a mixture of hexanes/EtOAc (49:1) to give 333 mg (60% yield) of pure acetate **7** as a colorless oil: *R*<sub>f</sub> = 0.53 (hexanes/EtOAc, 17:3).

**2-(E-[Prop-1-en-1-yl])-4-phenoxyphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (8).** A solution of **7** (330 mg, 1.2 mmol) in dimethyl sulfoxide (3 mL) was treated with potassium hydroxide (300 mg, 5.4 mmol). The mixture was stirred at room temperature for 5 min. Then, bromoethyl tetrahydropyranyl ether (389 mg, 1.86 mmol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between water (50 mL) and methylene chloride (50 mL). The aqueous phase was extracted with methylene chloride (2 × 30 mL). The combined organic layers were washed with a saturated solution of sodium chloride (5 × 50 mL) and were dried (MgSO<sub>4</sub>), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexanes/EtOAc (95:5) to yield 220 mg (50% yield) of pure compound **8** as a colorless oil: *R*<sub>f</sub> = 0.30 (hexanes/EtOAc, 9:1); IR (film, cm<sup>-1</sup>) 2943, 2874, 1638, 1589, 1489, 1221, 1036, 692; MS (*m/z*, relative intensity) 354 (M<sup>+</sup>, 10), 314 (7), 270 (14), 226 (33), 186 (31), 129 (100). Anal. (C<sub>22</sub>H<sub>26</sub>O<sub>4</sub>) C, H.

**2-(E-[Prop-1-en-1-yl])-4-phenoxyphenoxyethanol (9).** To a solution of compound **8** (187 mg, 0.5 mmol) in methanol (30 mL) was added pyridinium *p*-toluenesulfonate (0.5 mg). The reaction mixture was stirred at room temperature overnight. The mixture was partitioned between water (70 mL) and methylene chloride (70 mL). The aqueous phase was extracted with methylene chloride (2 × 30 mL), the combined organic layers were washed with brine (2 × 50 mL) and dried (MgSO<sub>4</sub>), and the solvent was evaporated. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (4:1) to afford 110 mg (81% yield) of pure alcohol **9** as a colorless oil: MS (*m/z*, relative intensity) 270 (M<sup>+</sup>, 100), 230 (24), 226 (65), 186 (36), 132 (39).

**2-(E-[Prop-1-en-1-yl])-4-phenoxyphenoxyethyl 4-Toluenesulfonate (10).** A solution of alcohol **9** (120 mg, 0.44 mmol) in pyridine (3 mL) was treated with *p*-toluenesulfonyl chloride (250 mg, 1.3 mmol), and the mixture was stirred at room temperature for 4 h. Then, 5% HCl (50 mL) was added and the reaction mixture was stirred for an additional hour. The mixture was extracted with methylene chloride (50 mL), and the organic layer was washed with 5% HCl (3 × 50 mL) and H<sub>2</sub>O (3 × 50 mL). The organic phase was dried (MgSO<sub>4</sub>), and the solvent was evaporated to afford 170 mg (91% yield) of pure compound **10** as a colorless oil that was used in the next step without further purification: *R*<sub>f</sub> = 0.36 (hexanes/EtOAc,

4:1); MS (*m/z*, relative intensity) 424 (M<sup>+</sup>, 7), 304 (18), 288 (42), 199 (48), 132 (88), 77 (85), 43 (100); IR (film, cm<sup>-1</sup>) 3042, 2926, 2876, 1722, 1686, 1597, 1483, 1177, 1097, 1022, 930.

**2-(E-[Prop-1-en-1-yl])-4-phenoxyphenoxyethyl Thiocyanate (11).** To a solution of tosylate **10** (170 mg, 0.4 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was added potassium thiocyanate (300 mg, 3.1 mmol). The reaction mixture was heated at 100 °C for 5 h. The mixture was allowed to cool to room temperature, and water (50 mL) was added. The aqueous phase was extracted with methylene chloride (2 × 50 mL), and the combined organic layers were washed with an aqueous saturated solution of sodium chloride (5 × 50 mL) and water (2 × 50 mL). The solvent was dried (MgSO<sub>4</sub>) and evaporated. The residue was purified by column chromatography (silica gel) using hexanes/EtOAc (24:1) as eluent to afford 30 mg (24% yield) of pure compound **11** as a colorless oil: *R*<sub>f</sub> = 0.33 (hexanes/EtOAc, 4:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.89 (dd, *J* = 7.0, 1.6 Hz, 3 H, *Me*), 3.37 (t, *J* = 5.9 Hz, 2 H, H-1), 4.29 (t, *J* = 5.9 Hz, 2 H, H-2), 6.17 (dq, *J* = 15.7, 6.6 Hz, 1 H, CHCH<sub>3</sub>), 6.70 (dq, *J* = 15.9, 1.6 Hz, 1 H, PhCH), 6.78–7.34 (m, 8 H, aromatic protons); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 18.8 (*Me*), 33.5 (C-1), 67.1 (C-2), 114.0 (C-6'), 117.6 (C-2''), 117.8 (C-3'), 118.6 (C-4'), 122.6 (C-4''), 124.5 (CHCH<sub>3</sub>), 128.0 (PhCH), 129.3 (C-2'), 129.6 (C-3'), 150.6 (C-4'), 151.3 (C-1'), 158.1 (C-1''); MS (*m/z*, relative intensity) 311 (M<sup>+</sup>, 44), 271 (7), 225 (9), 185 (12), 132 (100). Anal. (C<sub>18</sub>H<sub>17</sub>O<sub>2</sub>NS) C, H, N, S.

**4-(Phenoxy)-2-(prop-2-en-1-yl)phenyl Acetate (12).** To a suspension of aluminum trichloride (260 mg, 2.0 mmol) in carbon disulfide (10 mL) cooled at -5 °C was added allyl ether **6** (431 mg, 1.9 mmol) followed by addition of acetyl chloride (140 μL, 2.1 mmol) dropwise with vigorous stirring. The reaction mixture was stirred at -5 °C for 2 h. Then, the mixture was poured into crushed ice. Concentrated hydrochloric acid (5 mL) was added, and the mixture was extracted with methylene chloride (3 × 20 mL). The combined organic layers were washed with water (3 × 50 mL) and dried (MgSO<sub>4</sub>), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane/CH<sub>2</sub>Cl<sub>2</sub> (4:1) as eluent to afford 201 mg (39% yield) of pure acetate **12** as a colorless oil: *R*<sub>f</sub> = 0.43 (CH<sub>2</sub>Cl<sub>2</sub>/hexane, 3:2); IR (film, cm<sup>-1</sup>) 3094, 3030, 2982, 1771, 1587, 1491, 1370, 1226, 1186, 1017, 921, 841, 761, 705; MS (*m/z*, relative intensity) 268 (M<sup>+</sup>, 32), 226 (100).

**4-Phenoxy(prop-2-en-1-yl)phenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (13).** A solution of acetate **12** (880 mg, 3.3 mmol) in methyl sulfoxide (3 mL) was treated with bromoethyl tetrahydropyranyl ether (1.028 g, 5.0 mmol) as described for **8**. The product was purified by column chromatography eluting with hexanes/EtOAc (9:1) to afford 970 mg (83% yield) of pure compound **13** as a colorless oil: *R*<sub>f</sub> = 0.45 (hexanes/EtOAc, 4:1); IR (film, cm<sup>-1</sup>) 3074, 2941, 2874, 1589, 1489, 1221, 1036, 754, 692. Anal. (C<sub>22</sub>H<sub>26</sub>O<sub>4</sub>) C, H.

**4-Phenoxy(prop-2-en-1-yl)phenoxyethanol (14).** A solution of compound **13** (935 mg, 2.6 mmol) in methanol (20 mL) was treated with pyridinium *p*-toluenesulfonate (30 mg). The mixture was treated as described for the preparation of compound **9**. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (9:1) to afford 532 mg (76% yield) of pure alcohol **14** as a colorless oil: *R*<sub>f</sub> = 0.23 (hexanes/EtOAc, 7:3).

**4-Phenoxy(prop-2-en-1-yl)phenoxyethyl 4-Toluenesulfonate (15).** A solution of alcohol **14** (192 mg, 0.71 mmol) in pyridine (3 mL) was treated with tosyl chloride (500 mg, 2.6 mmol) as described for the preparation of **10**. After the usual workup, 210 mg (70% yield) of pure tosylate **15** were obtained as a colorless oil that was used in the next step without further purification: *R*<sub>f</sub> = 0.53 (hexanes/EtOAc, 7:3); MS (*m/z*, relative intensity) 424 (M<sup>+</sup>, 8), 380 (5), 288 (17), 270 (30), 226 (100), 199 (29), 155 (20), 132 (53), 131 (55)

**4-Phenoxy-2-(prop-2-en-1-yl)phenoxyethyl Thiocyanate (16).** Tosylate **15** (180 mg, 0.42 mmol) was treated with 570 mg of potassium thiocyanate as described for **11**. After the usual workup, the product was purified by column chromatography (silica gel), employing a mixture of hexanes/EtOAc



(19:1) as eluent to afford 61 mg (47% yield) of pure compound **16** as a colorless oil:  $R_f = 0.55$  (hexanes/EtOAc, 7:3); IR (film,  $\text{cm}^{-1}$ ) 3074, 2926, 2872, 2156, 1589, 1489, 1219, 1032, 758, 692;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.33 (d,  $J = 6.2$  Hz, 2 H,  $\text{PhCH}_2$ ), 3.36 (t,  $J = 5.9$  Hz, 2 H, H-1), 4.30 (t,  $J = 5.9$  Hz, 2 H, H-2), 5.05 (m, 2 H,  $\text{CHCH}_2$ ), 5.95 (ddt,  $J = 16.1, 9.5, 6.6$  Hz, 1 H,  $\text{CHCH}_2$ ), 6.78–7.34 (m, 8 H, aromatic protons);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  33.6 (C-1), 34.1 ( $\text{CHCH}_2$ ), 66.4 (C-2), 112.7 (C-6), 116.0 (C-5), 117.8 (C-2'), 117.9 ( $\text{PhCH}_2$ ), 121.7 (C-3'), 122.6 (C-4'), 129.6 (C-3''), 130.9 (C-2'), 136.2 ( $\text{CHCH}_2$ ), 150.9 (C-4'), 151.7 (C-1'), 158.2 (C-1''); MS ( $m/z$ , relative intensity) 311 ( $\text{M}^+$ , 100), 271 (21), 225 (18), 185 (21), 132 (81). Anal. ( $\text{C}_{18}\text{H}_{17}\text{O}_2\text{NS}$ ) C, H, N, S.

**4-Phenoxyphenyl 4-Toluenesulfonate (18).** A solution of 4-phenoxyphenol (**17**, 2.000 g, 10.8 mmol) was treated with tosyl chloride as described for **10**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc as eluent to afford 3.50 g (95% yield) of pure **18** as a pale-yellow solid:  $R_f = 0.37$  (hexanes/EtOAc, 4:1); IR (KBr,  $\text{cm}^{-1}$ ) 3065, 1595, 1499, 1377, 1260, 1180, 1094, 866.

**4-Phenoxy-2-(4-toluenesulfonyl)phenol (19).** A solution of tosylate **18** (1.25 g, 4.4 mmol) was irradiated with a medium-pressure Hg lamp (TQ 150, Hanau) in a quartz vessel ( $\lambda_{\text{exc}}$ : 254 nm) at room temperature for 7 h. The solvent was evaporated, and the residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (19:1) to yield 972 mg (65% yield) of pure **19** as a white solid: mp 50–52 °C;  $R_f = 0.24$  (hexanes/EtOAc, 4:1); IR (KBr,  $\text{cm}^{-1}$ ) 3444, 3059, 1604, 1497, 1213, 1127, 1086, 829, 714, 606, 525; MS ( $m/z$ , relative intensity) 340 ( $\text{M}^+$ , 77), 184 (73), 57 (88), 43 (100).

**4-Phenoxy-2-(4-toluenesulfonyl)phenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (20).** Compound **19** (635 mg, 2.2 mmol) was treated with bromoethyl tetrahydropyranyl ether as described for **8**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (19:1) to give 440 mg (42% yield) of pure compound **20** as a colorless oil: HRMS calcd for ( $\text{C}_{26}\text{H}_{28}\text{O}_6\text{S}$ ) 468.1607, found 468.1610.

**4-Phenoxy-2-(4-toluenesulfonyl)phenoxyethanol (21).** The tetrahydropyranyl group of **20** (220 mg, 0.5 mmol) was cleaved as described for **9**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (3:1) to give 130 mg (68% yield) of pure compound **21** as a white solid: mp 90 °C; MS ( $m/z$ , relative intensity) 384 ( $\text{M}^+$ , 37), 340 (71), 184 (100).

**4-Phenoxy-2-(4-toluenesulfonyl)phenoxyethyl 4-Toluenesulfonate (22).** Alcohol **21** (140 mg, 0.36 mmol) was tosylated as described for **10**. After the usual workup, 180 mg (93% yield) of pure **22** was obtained as a white solid: mp 138–140 °C;  $R_f = 0.21$  (hexanes/EtOAc, 7:3); IR (KBr,  $\text{cm}^{-1}$ ) 3067, 2986, 2949, 2874, 1597, 1485, 1381, 1315, 1265, 1213, 1180, 1153, 1094, 1026, 920, 773, 662; MS ( $m/z$ , relative intensity) 538 ( $\text{M}^+$ , 8), 199 (94), 91 (72), 44 (100).

**4-Phenoxy-2-(4-toluenesulfonyl)phenoxyethyl Thiocyanate (23).** Tosylate **22** (90 mg, 0.17 mmol) was treated with potassium thiocyanate (500 mg, 5.1 mmol) as described for **11**. The product was purified by column chromatography (silica gel), employing a mixture of toluene/EtOAc (19:1) as eluent to afford 60 mg (83% yield) of pure **23** as a white solid: mp 118–120 °C;  $R_f = 0.25$  (hexanes/EtOAc, 7:3);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.42 (s, 3 H, Me), 3.23 (t,  $J = 6.0$  Hz, 2 H, H-1), 4.28 (t,  $J = 6.0$  Hz, 2 H, H-2), 6.90–7.39 (m, 9 H, aromatic protons), 7.78 (d,  $J = 8.0$  Hz, 2 H, H-2''), 7.83 (d,  $J = 2.9$  Hz, 1 H, H-3');  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  21.6 (Me), 32.6 (C-1), 68.1 (C-2), 116.2 (C-2'), 118.5 (C-6'), 120.5 (C-3'), 123.8 (C-4'), 125.6 (C-5'), 128.0 (C-2''), 129.4 (C-3''), 130.0 (C-3''), 131.4 (C-2'), 138.3 (C-1''), 144.4 (C-4''), 151.1 (C-4), 151.6 (C-1), 156.9 (C-1''); MS ( $m/z$ , relative intensity) 425 ( $\text{M}^+$ , 43), 340 (33), 232 (11), 184 (66), 139 (82), 119 (100). HRMS calcd for ( $\text{C}_{22}\text{H}_{19}\text{O}_4\text{NS}_2$ ) 425.0756, found 425.0749.

**2-Bromophenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (25).** 2-Bromophenol (**24**, 865 mg, 5.0 mmol) reacted with bromoethyl tetrahydropyranyl ether as described for **8**. The product was purified by column chromatography (silica gel), employing hexanes/EtOAc (19:1) as eluent to give 711 mg (47%

yield) of pure **25** as a colorless oil:  $R_f = 0.62$  (hexanes/EtOAc, 7:3); IR (film,  $\text{cm}^{-1}$ ) 3065, 2943, 2874, 1587, 1481, 1140, 1032, 872, 748, 667; MS ( $m/z$ , relative intensity) 302 ( $\text{M}^+$ , 5), 300 ( $\text{M}^+$ , 5), 129 (47), 85 (100). Anal. ( $\text{C}_{13}\text{H}_{17}\text{O}_3\text{Br}$ ) C, H, Br.

**2-Bromophenoxyethylanol (26).** A solution of **25** (628 mg, 2.1 mmol) was treated as described for the preparation of **9**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (9:1) as eluent to afford 326 mg (72% yield) of pure **26** as a colorless oil:  $R_f = 0.21$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3383, 3065, 2939, 2876, 1587, 1479, 1248, 1126, 1078, 1055, 1032, 920, 748, 665; MS ( $m/z$ , relative intensity) 218 ( $\text{M}^+$ , 93), 216 ( $\text{M}^+$ , 100), 174 (53), 172 (56).

**2-Bromophenoxyethyl 4-Toluenesulfonate (27).** Alcohol **26** (320 mg, 1.5 mmol) was treated with tosyl chloride (600 mg, 3.1 mmol) as described for **10**. The product was purified by column chromatography (silica gel) using hexanes/EtOAc (19:1) as eluent to give 402 mg (72% yield) of pure **27** as a colorless oil:  $R_f = 0.19$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3105, 3059, 2945, 1585, 1485, 1366, 1254, 1175, 937, 669; MS ( $m/z$ , relative intensity) 372 ( $\text{M}^+$ , 1), 370 ( $\text{M}^+$ , 1), 199 (31), 174 (18), 172 (21), 155 (35), 91 (100).

**2-Bromophenoxyethyl Thiocyanate (28).** A solution of **27** (358 mg, 0.97 mmol) in dimethylformamide (3 mL) was treated with potassium thiocyanate (500 mg, 5.2 mmol) as described for **11**. After the usual treatment, the product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (19:1) to give 70 mg (28% yield) of pure thiocyanate **28** as a colorless oil:  $R_f = 0.32$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3065, 2928, 2878, 2156, 1585, 1496, 1279, 1248, 1126, 1032, 750, 665;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.39 (t,  $J = 5.9$  Hz, 2 H, H-1), 4.36 (t,  $J = 5.9$  Hz, 2 H, H-2), 6.91 (m, 2 H, aromatic protons), 7.28 (dt,  $J = 7.6, 1.4$  Hz, 1 H, H-5'), 7.56 (dd,  $J = 7.7, 1.4$  Hz, 1 H, H-3');  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  33.2 (C-1), 67.1 (C-2), 111.6 (SCN), 112.7 (C-2'), 114.2 (C-6'), 123.2 (C-4'), 128.6 (C-5'), 133.7 (C-3'), 154.3 (C-1'); MS ( $m/z$ , relative intensity) 259 ( $\text{M}^+$ , 13), 257 ( $\text{M}^+$ , 13), 178 (9), 86 (100). Anal. ( $\text{C}_9\text{H}_8\text{ONSBr}$ ) C, H, N, S.

**2-Iodophenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (30).** 2-Iodophenol (**29**, 910 mg, 4.1 mmol) was treated with bromoethyl tetrahydropyranyl ether as described for **8**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (19:1) to afford 940 mg (66% yield) of pure **30** as a colorless oil:  $R_f = 0.61$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 2941, 2870, 1582, 1497, 1439, 1277, 1248, 1138, 1034, 750;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.53–1.81 (m, 6 H, H-3'', H-4'', H-5''), 3.55 (m, 1 H, H-6''a), 3.91 (m, 2 H, H-1), 4.04 (m, 1 H, H-6''b), 4.20 (t,  $J = 4.8$  Hz, 2 H, H-2), 4.82 (distorted t,  $J = 3.3$  Hz, 1 H, H-2''), 6.71 (dt,  $J = 7.7, 1.2$  Hz, 1 H, H-4'), 6.85 (dd,  $J = 8.0, 1.1$  Hz, 1 H, H-6'), 7.28 (dt,  $J = 7.7, 1.5$  Hz, 1 H, H-5'), 7.77 (dd,  $J = 7.7, 1.4$  Hz, 1 H, H-3');  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  19.2 (C-4''), 25.4 (C-5''), 30.5 (C-3''), 62.0 (C-6''), 66.6 (C-1), 70.4 (C-2), 86.7 (C-2'), 99.0 (C-2''), 112.4 (C-6'), 122.6 (C-4'), 129.3 (C-5'), 139.4 (C-3'), 157.5 (C-1'); MS ( $m/z$ , relative intensity) 348 ( $\text{M}^+$ , 6), 246 (3), 220 (4), 129 (37), 85 (100); HRMS calcd for ( $\text{C}_{13}\text{H}_{17}\text{O}_3\text{I}$ ) 348.0222, found 348.0218.

**2-Iodophenoxyethanol (31).** Compound **30** (900 mg, 2.6 mmol) was treated with pyridinium 4-toluenesulfonate as described for the preparation of **9**. The product was purified by column chromatography (silica gel) using a mixture of hexanes/EtOAc (17:3) as eluent to give 514 mg (75% yield) of pure **31** as a colorless oil:  $R_f = 0.28$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3383, 2937, 1582, 1474, 1439, 1277, 1248, 1051, 1018, 920, 748, 650; MS ( $m/z$ , relative intensity) 264 ( $\text{M}^+$ , 45), 220 (100).

**2-Iodophenoxyethyl 4-Toluenesulfonate (32).** Alcohol **31** (460 mg, 1.7 mmol) was treated with tosyl chloride as described for **10**. Evaporation of the solvent yielded 691 mg (97% yield) of pure **32** as a colorless oil that was used as such in the next step:  $R_f = 0.32$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3063, 2953, 2876, 1597, 1495, 1439, 1360, 1250, 1177, 1040, 932, 750; MS ( $m/z$ , relative intensity) 418 ( $\text{M}^+$ , 11), 199 (71), 155 (38), 91 (100).

**2-Iodophenoxyethyl Thiocyanate (33).** Tosylate **32** (309 mg, 0.74 mmol) was treated with potassium thiocyanate as

described for **11**. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (19:1) to afford 153 mg (68% yield) of pure thiocyanate **33** as a colorless oil:  $R_f = 0.30$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3061, 2939, 2876, 2154, 1580, 1489, 1277, 1246, 1018, 750;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.39 (t,  $J = 5.8$  Hz, 2 H, H-1), 4.34 (t,  $J = 5.9$  Hz, 2 H, H-2), 6.81 (m, 2 H, aromatic protons), 7.32 (dt,  $J = 7.6$ , 1.4 Hz, 1 H, H-5'), 7.79 (dd,  $J = 7.7$ , 1.4 Hz, 1 H, H-3');  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  33.3 (C-1), 67.0 (C-2), 86.7 (C-2'), 112.8 (C-6'), 123.8 (C-4'), 129.6 (C-5'), 139.7 (C-3'), 156.5 (C-1'); MS ( $m/z$ , relative intensity) 305 ( $\text{M}^+$ , 23), 220 (9), 178 (13), 86 (100). Anal. ( $\text{C}_9\text{H}_8\text{IONS}$ ) C, H, N, S.

**2-Chlorophenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (35)**. Compound **35** was prepared from 2-chlorophenol (**34**, 1.005 g, 7.77 mmol) according to the method of preparation for **8**. The residue was purified by column chromatography (silica gel), employing hexanes/EtOAc (19:1) as eluent to afford 462 mg (23% yield) of pure **35** as a colorless oil:  $R_f = 0.19$  (hexanes/EtOAc, 4:1); MS ( $m/z$ , relative intensity) 258 ( $\text{M}^+$ , 0.8), 256 ( $\text{M}^+$ , 2.3), 172 (4), 129 (24), 128 (24), 85 (100). Anal. ( $\text{C}_{13}\text{H}_{17}\text{O}_3\text{Cl}$ ) C, H, Cl.

**2-Chlorophenoxyethanol (36)**. Ether **35** (341 mg, 1.3 mmol) was reacted with pyridinium 4-toluenesulfonate according to the procedure of **9** and was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (9:1) to give 217 mg (97% yield) of pure **36** as a colorless oil:  $R_f = 0.14$  (hexanes/EtOAc, 4:1); MS ( $m/z$ , relative intensity) 174 ( $\text{M}^+$ , 12), 172 ( $\text{M}^+$ , 39), 130 (33), 128 (100).

**2-Chlorophenoxyethyl 4-Toluenesulfonate (37)**. Alcohol **36** (137 mg, 0.78 mmol) was treated with tosyl chloride as described for the preparation of **10**. Purification by column chromatography, eluting with hexanes/EtOAc (9:1), gave 159 mg (62% yield) of pure **37** as a colorless oil:  $R_f = 0.25$  (hexanes/EtOAc, 4:1); MS ( $m/z$ , relative intensity) 328 ( $\text{M}^+$ , 4), 326 ( $\text{M}^+$ , 11), 199 (72), 155 (48), 91 (100).

**2-Chlorophenoxyethyl Thiocyanate (38)**. Compound **37** (111 mg, 0.34 mmol) was reacted with potassium thiocyanate as described for **11**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (19:1) to afford 62 mg (85% yield) of pure thiocyanate **38** as a colorless oil:  $R_f = 0.37$  (hexanes/EtOAc, 4:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.38 (t,  $J = 6.1$  Hz, 2 H, H-1), 4.29 (t,  $J = 6.1$  Hz, 2 H, H-2), 6.98 (m, 2 H, aromatic protons), 7.24 (m, 1 H, aromatic proton), 7.38 (dd,  $J = 8.0$ , 1.5 Hz, 1 H, H-3');  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  33.2 (C-1), 67.2 (C-2), 111.6 (SCN), 114.5 (C-6'), 122.8 (C-4'), 123.6 (C-2'), 127.8 (C-5'), 130.6 (C-3'), 153.5 (C-1'); MS ( $m/z$ , relative intensity) 215 ( $\text{M}^+$ , 4), 213 ( $\text{M}^+$ , 12), 128 (11), 86 (100); HRMS calcd for ( $\text{C}_9\text{H}_8\text{ONS}$ ) 213.0015, found 213.0018.

**2,4-Dimethylphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (40)**. 2,4-Dimethylphenol (**39**, 630 mg, 5.2 mmol) reacted with bromoethyl tetrahydropyranyl ether in a similar way as described for the preparation of **8**. The product was purified by column chromatography (silica gel), employing hexanes/EtOAc (19:1) as eluent to produce 710 mg (55% yield) of pure compound **40** as a colorless oil:  $R_f = 0.76$  (hexanes/EtOAc, 7:3); IR (film,  $\text{cm}^{-1}$ ) 2943, 2872, 1506, 1456, 1256, 1136, 1036, 802; MS ( $m/z$ , relative intensity) 250 ( $\text{M}^+$ , 10), 166 (13), 129 (60), 122 (59), 107 (28), 85 (100). Anal. ( $\text{C}_{15}\text{H}_{22}\text{O}_3$ ) C, H.

**2,4-Dimethylphenoxyethanol (41)**. Compound **40** (282 mg, 1.1 mmol) was treated as described for the preparation of **9**. The usual workup and evaporation of the solvent afforded 185.8 mg (99% yield) of pure alcohol **41** as a colorless oil.

**2,4-Dimethylphenoxyethyl 4-Toluenesulfonate (42)**. Alcohol **41** (171.5 mg, 1.03 mmol) was treated with tosyl chloride (250 mg, 1.3 mmol) as described for **10**. The product was purified by column chromatography (silica gel) using hexanes/EtOAc (19:1) as eluent to afford 312 mg (97% yield) of pure **42** as a colorless oil:  $R_f = 0.56$  (hexanes/EtOAc, 7:3); IR (film,  $\text{cm}^{-1}$ ) 2922, 2874, 1599, 1506, 1360, 1190, 1034, 926, 816, 569.

**2,4-Dimethylphenoxyethyl Thiocyanate (43)**. Compound **42** (145 mg, 0.45 mmol) was treated with potassium thiocyanate as described for **11**. The residue was purified by column chromatography (silica gel), eluting with hexanes/

EtOAc (19:1) to afford 72 mg (77% yield) of pure thiocyanate **43** as a colorless oil:  $R_f = 0.49$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 2938, 2874, 2154, 1604, 1505, 1456, 1396, 1296, 1220, 1134, 1070, 1035, 870, 806;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.12 (s, 3 H, *Me*), 2.26 (s, 3 H, *Me*), 3.33 (t,  $J = 5.8$  Hz, 2 H, H-1), 4.26 (t,  $J = 5.8$  Hz, 2 H, H-1), 6.69 (d,  $J = 8.0$  Hz, 1 H, H-6'), 6.94 (d,  $J = 8.0$  Hz, 1 H, H-5'), 6.96 (s, 1 H, H-3');  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.0 (*Me*), 20.4 (*Me*), 33.7 (C-1), 66.0 (C-2), 111.4 (C-6'), 127.0 (C-2'), 130.8 (C-4'), 131.8 (C-3'), 153.8 (C-1'); MS ( $m/z$ , relative intensity) 207 ( $\text{M}^+$ , 81), 147 (19), 121 (100). Anal. ( $\text{C}_{11}\text{H}_{13}\text{ONS}$ ) C, H, N, S.

**2-Methylphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (45)**. 2-Methylphenol (**44**, 1.00 g, 9.25 mmol) was treated with bromoethyl tetrahydropyranyl ether according to the general procedure. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (49:1) to afford 1.854 g (85% yield) of pure compound **45** as a colorless oil:  $R_f = 0.33$  (hexanes/EtOAc, 9:1); IR (film,  $\text{cm}^{-1}$ ) 2943, 2874, 1603, 1497, 1248, 1124, 1036, 750; MS ( $m/z$ , relative intensity) 236 ( $\text{M}^+$ , 9), 152 (6), 129 (34), 108 (17), 85 (100).

**2-Methylphenoxyethanol (46)**. Compound **45** (1.70 g, 7.2 mmol) was treated as described for **9**. The product was purified by column chromatography (silica gel), employing a mixture of hexanes/EtOAc (97:3) as eluent to give 450 mg (41% yield) of pure alcohol **46** as a colorless oil:  $R_f = 0.23$  (hexanes/EtOAc, 7:3); MS ( $m/z$ , relative intensity) 152 ( $\text{M}^+$ , 38), 108 (100).

**2-Methylphenoxyethyl 4-Toluenesulfonate (47)**. Alcohol **46** (390 mg, 2.6 mmol) was treated with tosyl chloride (975 mg, 5.1 mmol) as described for **10**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (49:1) to yield 603 mg (76% yield) of pure **47** as a white solid: mp 68–70 °C;  $R_f = 0.44$  (hexanes/EtOAc, 4:1); MS ( $m/z$ , relative intensity) 306 ( $\text{M}^+$ , 11), 199 (49), 155 (28), 91 (100).

**2-Methylphenoxyethyl Thiocyanate (48)**. Tosylate **47** (540 mg, 1.8 mmol) was treated with potassium thiocyanate as described for the preparation of **11**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (99:1) to afford 180 mg (52% yield) of pure **48** as a colorless oil:  $R_f = 0.63$  (hexanes/EtOAc, 9:1); IR (film,  $\text{cm}^{-1}$ ) 3062, 3026, 2918, 2870, 2156, 1591, 1495, 1462, 1244, 1123, 1032, 752;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.25 (s, 3 H, *Me*), 3.37 (t,  $J = 5.8$  Hz, 2 H, H-1), 4.31 (t,  $J = 5.8$  Hz, 2 H, H-2), 6.78–7.18 (m, 4 H, aromatic protons);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.1 (*Me*), 33.7 (C-1), 65.8 (C-2), 111.2 (C-6'), 121.5 (C-4'), 126.9 (C-5'), 127.2 (C-2'), 131.0 (C-3'), 155.9 (C-1'); MS ( $m/z$ , relative intensity) 193 ( $\text{M}^+$ , 41), 133 (32), 107 (50), 86 (100). Anal. ( $\text{C}_{10}\text{H}_{11}\text{NOS}$ ) C, H, N, S.

**4-Methylphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (50)**. 4-Methylphenol (**49**, 1.00 g, 9.25 mmol) was treated with bromoethyl tetrahydropyranyl ether according to the general procedure. The product was purified by column chromatography (silica gel) using hexanes/EtOAc (97:3) as eluent to afford 1.392 g (64% yield) of pure compound **49** as a colorless oil:  $R_f = 0.48$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3030, 2941, 2872, 1615, 1510, 1456, 1248, 1140, 816, 741;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.3 (C-4'), 20.4 (*Me*), 25.4 (C-5'), 30.5 (C-3'), 62.1 (C-6'), 65.9 (C-1), 67.5 (C-2), 98.9 (C-2'), 114.6 (C-2), 129.8 (C-3', C-4'), 156.8 (C-1'); MS ( $m/z$ , relative intensity) 236 ( $\text{M}^+$ , 12), 129 (59), 108 (36), 85 (100). Anal. ( $\text{C}_{14}\text{H}_{20}\text{O}_3$ ) C, H.

**4-Methylphenoxyethanol (51)**. Compound **50** (1.12 g, 4.6 mmol) was treated as described for **9**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (97:3) to yield 498 mg (77% yield) of pure **51** as a white solid: mp 40–42 °C;  $R_f = 0.33$  (hexanes/EtOAc, 7:3); MS ( $m/z$ , relative intensity) 152 ( $\text{M}^+$ , 34), 108 (100).

**4-Methylphenoxyethyl 4-Toluenesulfonate (52)**. Compound **51** (430 mg, 2.8 mmol) was treated with tosyl chloride according to the general method. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (99:1) to produce 321 mg (37% yield) of pure compound **52**:  $R_f = 0.54$  (hexanes/EtOAc, 7:3); MS ( $m/z$ , relative intensity) 306 ( $\text{M}^+$ , 12), 199 (62), 155 (35), 91 (100).

**4-Methylphenoxyethyl Thiocyanate (53)**. Compound **52** (320 mg, 1.05 mmol) reacted with potassium thiocyanate



according to the general procedure. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (49:1) to afford 116 mg (58% yield) of pure **53** as a colorless oil:  $R_f = 0.45$  (hexanes/EtOAc, 4:1);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.30 (s, 3 H, *Me*), 3.32 (t,  $J = 5.8$  Hz, 2 H, H-1), 4.29 (t,  $J = 5.8$  Hz, 2 H, H-2), 6.82 (d,  $J = 8.4$  Hz, 2 H, H-2'), 7.10 (d,  $J = 8.4$  Hz, 2 H, H-3');  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  20.5 (*Me*), 33.4 (C-1), 66.0 (C-2), 114.7 (C-2'), 130.1 (C-3'), 131.2 (C-4'), 155.7 (C-1'); MS ( $m/z$ , relative intensity) 193 ( $\text{M}^+$ , 47), 149 (28), 107 (70), 57 (93), 43 (100). Anal. ( $\text{C}_{10}\text{H}_{11}\text{NOS}$ ) C, H, N, S.

**Phenoxyethyl 4-Toluenesulfonate (55)**. Phenoxyethanol (**54**, 1.30 g, 10 mmol) was treated with tosyl chloride following the general methodology. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (7:3) to give 712 mg (24% yield) of pure **55** as a white solid: mp 78 °C;  $R_f = 0.43$  (hexanes/EtOAc, 7:3); MS ( $m/z$ , relative intensity) 292 ( $\text{M}^+$ , 11), 199 (49), 155 (28), 120 (16), 91 (100).

**Phenoxyethyl Thiocyanate (56)**. Compound **55** (620 mg, 2.1 mmol) was treated with potassium thiocyanate as described for **11**. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (99:1) to afford 230 mg (61% yield) of pure compound **56** as a colorless oil:  $R_f = 0.38$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3042, 2934, 2874, 2156, 1601, 1497, 1235, 1173, 1036, 756, 692, 511;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.30 (t,  $J = 5.9$  Hz, 2 H, H-1), 4.28 (t,  $J = 5.9$  Hz, 2 H, H-2), 6.89–7.34 (m, 5 H, aromatic protons);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  33.3 (C-1), 65.7 (C-2), 114.7 (C-3'), 121.7 (C-4'), 129.6 (C-3'), 157.7 (C-1'); MS ( $m/z$ , relative intensity) 179 ( $\text{M}^+$ , 58), 107 (30), 86 (100). Anal. ( $\text{C}_9\text{H}_9\text{NOS}$ ) C, H, N, S.

**3,5-Dimethylphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (58)**. 3,5-Dimethylphenol (**57**, 1.00 g, 8.2 mmol) was treated with bromoethyl tetrahydropyranyl ether according to the general method. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (199:1) to afford 1.60 g (78% yield) of pure **58** as a colorless oil:  $R_f = 0.51$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 2941, 2872, 1595, 1472, 1323, 1296, 1140, 1076, 1036, 829, 689; MS ( $m/z$ , relative intensity) 250 ( $\text{M}^+$ , 14), 150 (14), 129 (29), 122 (75), 85 (100). Anal. ( $\text{C}_{15}\text{H}_{22}\text{O}_3$ ) C, H.

**3,5-Dimethylphenoxyethanol (59)**. Compound **58** (1.20 g, 4.8 mmol) was treated with pyridinium 4-toluenesulfonate as described for **9**. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (49:1) to afford 612 mg (77% yield) of pure **59** as a white solid: mp 43–44 °C;  $R_f = 0.26$  (hexanes/EtOAc, 7:3).

**3,5-Dimethylphenoxyethyl 4-Toluenesulfonate (60)**. Alcohol **59** (480 mg, 2.89 mmol) was treated with tosyl chloride to produce 791 mg (86% yield) of pure **60** as a white solid. The product was used as such in the next step: mp 85–86 °C;  $R_f = 0.54$  (hexanes/EtOAc, 7:3).

**3,5-Dimethylphenoxyethyl Thiocyanate (61)**. Tosylate **60** (700 mg, 2.2 mmol) was treated with potassium thiocyanate according to the general method. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (99:1) to afford 393 mg (86% yield) of pure **61** as a colorless oil:  $R_f = 0.43$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 2920, 2872, 2156, 1590, 1472, 1323, 1296, 1171, 1080, 831;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.29 (s, 6 H, *Me*), 3.31 (t,  $J = 5.8$  Hz, 2 H, H-1), 4.28 (t,  $J = 5.8$  Hz, 2 H, H-2), 6.55 (br s, 2 H, H-2', H-6'), 6.65 (br s, 1 H, H-4');  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  21.4 (*Me*), 33.4 (C-1), 65.7 (C-2), 112.5 (C-2'), 123.6 (C-4'), 139.5 (C-3'), 157.9 (C-1'). Anal. ( $\text{C}_{11}\text{H}_{13}\text{NOS}$ ) C, H, N, S.

**2,5-Dimethylphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (63)**. 2,5-Dimethylphenol (**62**, 1.00 g, 8.2 mmol) was treated with bromoethyl tetrahydropyranyl ether according to the general procedure. The residue was purified by column chromatography (silica gel) employing hexanes/EtOAc (99:1) as eluent to give 1.353 g (66% yield) of pure **63** as a colorless oil:  $R_f = 0.43$  (hexanes/EtOAc, 9:1); IR (film,  $\text{cm}^{-1}$ ) 2943, 2874, 1585, 1508, 1456, 1265, 1130, 1036, 872, 804; MS ( $m/z$ , relative intensity) 250 ( $\text{M}^+$ , 13), 166 (10), 129 (44), 122 (35), 85 (100); HRMS calcd for ( $\text{C}_{15}\text{H}_{22}\text{O}_3$ ) 250.1569, found 250.1568.

**2,5-Dimethylphenoxyethanol (64)**. Compound **63** (1.11 g, 4.4 mmol) was treated with pyridinium 4-toluenesulfonate

as described for **9**. The residue was purified by column chromatography (silica gel) employing hexanes/EtOAc (19:1) as eluent to produce 682 mg (93% yield) of pure **64** as a white solid: mp 44–45 °C;  $R_f = 0.38$  (hexanes/EtOAc, 7:3).

**2,5-Dimethylphenoxyethyl 4-Toluenesulfonate (65)**. Alcohol **64** (500 mg, 3.0 mmol) was treated with tosyl chloride to afford 880 mg (92% yield) of pure **65** as a white solid. The product was used as such in the next step: mp 80–82 °C;  $R_f = 0.60$  (hexanes/EtOAc, 7:3).

**2,5-Dimethylphenoxyethyl Thiocyanate (66)**. Compound **65** (600 mg, 1.9 mmol) was reacted with potassium thiocyanate. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (99:1) to afford 328 mg (83% yield) of pure thiocyanate **66** as a colorless oil:  $R_f = 0.44$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 2922, 2870, 2156, 1616, 1585, 1508, 1414, 1261, 1132, 1036, 808;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.20 (s, 3 H, *Me*), 2.32 (s, 3 H, *Me*), 3.36 (t,  $J = 5.9$  Hz, 2 H, H-1), 4.29 (t,  $J = 5.9$  Hz, 2 H, H-2), 6.62 (br s, 1 H, H-6'), 6.72 (d,  $J = 7.8$  Hz, 1 H, H-3'), 7.02 (d,  $J = 7.9$  Hz, 1 H, H-4');  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  15.7 (*Me* at C-2), 21.3 (*Me* at C-5), 33.7 (C-1), 65.8 (C-2), 112.4 (C-6'), 124.0 (C-2', C-4'), 130.8 (C-3'), 136.7 (C-5'), 155.8 (C-1'). Anal. ( $\text{C}_{11}\text{H}_{13}\text{NOS}$ ) C, H.

**2,3-Dimethylphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (68)**. 2,3-Dimethylphenol (**67**, 1.02 g, 8.2 mmol) was treated with bromoethyl tetrahydropyranyl ether according to the general protocol. The residue was purified by column chromatography (silica gel) employing a mixture of hexanes/EtOAc as eluent to give 1.195 g (58% yield) of pure **68** as a colorless oil:  $R_f = 0.64$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 2941, 2872, 1472, 1261, 1100, 1078, 1035, 768. Anal. ( $\text{C}_{15}\text{H}_{22}\text{O}_3$ ) C, H.

**2,3-Dimethylphenoxyethanol (69)**. Compound **68** (1.20 g, 4.8 mmol) was treated with pyridinium 4-toluenesulfonate as described for **9**. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (9:1) to afford 608 mg (75% yield) of pure compound **69** as a white solid: mp 73–74 °C;  $R_f = 0.35$  (hexanes/EtOAc, 7:3).

**2,3-Dimethylphenoxyethyl 4-Toluenesulfonate (70)**. Alcohol **69** (401 mg, 2.4 mmol) was treated with tosyl chloride according to the general procedure. After the usual workup, the product was used in the next step without further purification in 91% yield as a colorless oil:  $R_f = 0.58$  (hexanes/EtOAc, 7:3).

**2,3-Dimethylphenoxyethyl Thiocyanate (71)**. Tosylate **70** (600 mg, 1.9 mmol) was reacted with potassium thiocyanate according to the general method. The residue was purified by column chromatography (silica gel) employing a mixture of hexanes/EtOAc (99:1) as eluent to give 203 mg (52% yield) of pure **71** as a colorless oil:  $R_f = 0.39$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3032, 2924, 2870, 2156, 1510, 1240, 1034, 818, 511;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.17 (s, 3 H, *Me*), 2.28 (s, 3 H, *Me*), 3.37 (t,  $J = 5.8$  Hz, 2 H, H-1), 4.29 (t,  $J = 5.8$  Hz, 2 H, H-2), 6.69 (d,  $J = 8.0$  Hz, 1 H, H-6'), 6.83 (d,  $J = 7.7$  Hz, 1 H, H-4'), 7.05 (t,  $J = 7.9$  Hz, 1 H, H-5');  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  11.6 (*Me*), 20.0 (*Me*), 33.8 (C-1), 66.1 (C-2), 109.3 (C-6'), 123.4 (C-4'), 125.7 (C-2'), 125.9 (C-5'), 138.4 (C-3'), 155.7 (C-1'). Anal. ( $\text{C}_{11}\text{H}_{13}\text{NOS}$ ) C, H, N, S.

**2,6-Dimethylphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (73)**. 2,6-Dimethylphenol (**72**, 980 mg, 8.0 mmol) was treated with bromoethyl tetrahydropyranyl ether as described for **8**. After the usual treatment, the residue was purified by column chromatography (silica gel), eluting with hexane/0.1% EtOAc to give 1.21 g (61% yield) of ether **73** as a colorless oil:  $R_f = 0.55$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3020, 2943, 2872, 1477, 1203, 1140, 1036, 872, 768; HRMS calcd for ( $\text{C}_{15}\text{H}_{22}\text{O}_3$ ) 250.1569, found 250.1563.

**2,6-Dimethylphenoxyethanol (74)**. Ether **73** (1.02 g, 4.0 mmol) was treated with *p*-toluenesulfonic acid. The residue was purified by column chromatography, eluting with hexanes/EtOAc (49:1) to afford 496 mg (75% yield) of pure **74** as a white solid: mp 68–70 °C;  $R_f = 0.44$  (hexanes/EtOAc, 7:3).

**2,6-Dimethylphenoxyethyl 4-Toluenesulfonate (75)**. Alcohol **74** (402 mg, 2.4 mmol) was treated with tosyl chloride. After the usual treatment, 697 mg (91% yield) of pure **75** was



obtained as a colorless oil, which was used as such in the next step:  $R_f = 0.50$  (hexanes/EtOAc, 7:3).

**2,6-Dimethylphenoxyethyl Thiocyanate (76).** Compound **75** (690 mg, 2.1 mmol) was treated with potassium thiocyanate as described for **11**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (49:1) to afford 370 mg (85% yield) of pure **76** as a colorless oil:  $R_f = 0.40$  (hexanes/EtOAc); IR (film,  $\text{cm}^{-1}$ ) 3022, 2951, 2924, 2872, 2156, 1476, 1263, 1200, 1092, 1022, 874, 772;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.30 (s, 6 H, Me), 3.35 (t,  $J = 5.8$  Hz, 2 H, H-1), 4.11 (t,  $J = 5.8$  Hz, 2 H, H-2), 7.00 (m, 3 H, aromatic protons);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.2 (Me), 34.2 (C-1), 69.0 (C-2), 124.5 (C-4'), 129.1 (C-3'), 130.6 (C-2'), 154.7 (C-1'). Anal. ( $\text{C}_{11}\text{H}_{13}\text{NOS}$ ) C, H, N, S.

**4-(Phenylamino)phenyl Methyl Ether (78).** To a solution of *p*-anisidine (compound **77**, 2.00 g, 16.2 mmol) and phenylboronic acid (4.00 g, 32.8 mmol) in anhydrous methylene chloride (50 mL) was added cupric acetate (6.00 g, 33.0 mmol) and pyridine (4.0 mL) with vigorous stirring under an argon atmosphere. The reaction mixture was stirred at room temperature for 72 h. Then, the crude reaction mixture was adsorbed on silica gel and purified by column chromatography, eluting with hexanes/EtOAc (19:1) to afford 1.82 g (56% yield) of pure **78** as a yellow solid: mp 101–103 °C;  $R_f = 0.42$  (hexanes/EtOAc, 4:1).

**4-Nitrophenyl Acetate (80).** A solution of 4-nitrophenol (**79**, 4.601 g, 33.1 mmol) in pyridine (5 mL) was treated with acetic anhydride (5 mL). The mixture was stirred at room temperature for 16 h. Then, 5% hydrochloric acid (20 mL) was added, and the mixture was stirred for 1 h. The aqueous phase was extracted with methylene chloride (2  $\times$  50 mL). The combined organic layers were washed with 5% HCl (3  $\times$  50 mL) and water (2  $\times$  50 mL). The solvent was dried ( $\text{MgSO}_4$ ) and evaporated to afford 5.808 g (97% yield) of pure acetate **80** as a brown solid that was used in the next step without further purification: mp 71–73 °C.

**4-Aminophenyl Acetate (81).** A solution of **80** (5.010 g, 32.1 mmol) in ethyl acetate (50 mL) in the presence of 5% palladium on charcoal (50 mg) was treated with hydrogen at 3 atm. The reaction mixture was stirred at room temperature for 4 h. The mixture was filtered off, and the solvent was evaporated to produce 4.788 g (100% yield) of pure **81** as a brown solid.

**4-(Phenylamino)phenyl Acetate (82).** Compound **81** (1.00 g, 6.6 mmol) was treated with phenylboronic acid (1.60 g, 13.2 mmol) as described for **78**. The residue was purified by column chromatography (silica gel) employing a mixture of hexanes/EtOAc (19:1) as eluent to give 869 mg (58% yield) of pure compound **82** as a yellow solid: mp 77–78 °C.

**4-(Phenylamino)phenol (83).** To compound **82** (350 mg, 1.5 mmol) in methanol (10 mL) potassium carbonate (anhydrous powder, 465 mg) was added with stirring followed by enough water to effect nearly complete solution. After 4 h at room temperature, the reaction mixture was extracted with methylene chloride (3  $\times$  25 mL). The combined organic layers were washed with water (2  $\times$  50 mL) and dried ( $\text{MgSO}_4$ ), and the solvent was evaporated. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc as eluent to produce 256 mg (92% yield) of pure phenol **83** as a colorless oil.

**Phenyl-[4-[2-(tetrahydropyran-2-yloxy)ethoxy]phenyl]-[2-(tetrahydropyran-2-yloxy)ethylamine (84).** Phenol **83** (500 mg, 2.7 mmol) was treated with bromoethyl tetrahydropyran-2-yl ether (2.7 mmol) as described for **8**. The residue was purified by column chromatography (silica gel) employing hexanes/EtOAc (93:7) as eluent to give 350 mg (29% yield) of pure **84** as a colorless oil:  $R_f = 0.22$  (hexanes/EtOAc, 4:1); MS ( $m/z$ , relative intensity) 441 ( $\text{M}^+$ , 56), 326 (100), 198 (26), 85 (52).

**4-Nitrophenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (85).** 4-Nitrophenol (**79**, 4.634 g, 33.3 mmol) was treated with bromoethyl tetrahydropyran-2-yl ether as described for **8**. The product was purified by column chromatography (silica gel),

eluting with hexanes/EtOAc (17:3) to afford 1.90 g (21% yield) of pure **85** as a colorless oil:  $R_f = 0.44$  (hexanes/EtOAc, 7:3).

**4-Aminophenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (86).** Compound **85** (1.90 g, 7.1 mmol) was hydrogenated following the procedure employed for the preparation of **81**. After the usual workup, the solvent was evaporated to afford 1.68 g (100% yield) of pure aniline **86** as a brown solid that was used as such in the next step:  $R_f = 0.44$  (hexanes/EtOAc, 7:3).

**4-(Phenylamino)phenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (87).** Compound **86** (2.00 g, 8.5 mmol) was treated with phenyl boronic acid (2.10 g, 17.0 mmol), anhydrous cupric acetate (3.10 g, 17.0 mmol), and pyridine (4.2 mL, 25.5 mmol) according to the method of preparation of compound **78**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (9:1) to give 1.72 g (65% yield) of pure compound **87** as a colorless oil:  $R_f = 0.37$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3375, 3049, 3030, 2941, 2872, 1601, 1510, 1236, 1034, 746, 694; MS ( $m/z$ , relative intensity) 313 ( $\text{M}^+$ , 19), 185 (67), 129 (67), 85 (100). Anal. ( $\text{C}_{19}\text{H}_{23}\text{NO}_3$ ) C, H, N.

**4-(Phenylamino)phenoxyethanol (88).** Compound **87** (350 mg, 1.1 mmol) was treated as described for **9**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (3:1) to produce 210 mg (83% yield) of pure alcohol **88** as a white solid: mp 82–85 °C;  $R_f = 0.07$  (hexanes/EtOAc, 4:1); MS ( $m/z$ , relative intensity) 229 ( $\text{M}^+$ , 59), 185 (63), 184 (100).

**4-(Phenylamino)phenoxyethyl 4-Toluenesulfonate (89).** Alcohol **88** (510 mg, 2.2 mmol) was treated with tosyl chloride as described for **10**. After the usual workup, the product was purified by column chromatography (silica gel) employing hexanes/EtOAc (9:1) as eluent to afford 430 mg (51% yield) of pure **89** as a white solid: mp 127–129 °C;  $R_f = 0.45$  (hexanes/EtOAc, 7:3); MS ( $m/z$ , relative intensity) 383 ( $\text{M}^+$ , 42), 199 (69), 184 (100), 167 (13), 155 (29), 91 (74).

**4-(Phenylamino)phenoxyethyl Thiocyanate (90).** Tosylate **89** (330 mg, 0.86 mmol) was treated with potassium thiocyanate (500 mg) as described for **11**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc as eluent to give 140 mg (52% yield) of pure compound **90** as a colorless oil:  $R_f = 0.20$  (hexanes/EtOAc, 4:1); IR (film,  $\text{cm}^{-1}$ ) 3385, 3049, 3030, 2933, 2870, 2154, 2116, 1597, 1508, 1499, 1319, 1229, 1070, 1030, 826, 748, 694;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.30 (t,  $J = 5.9$  Hz, 2 H, H-1), 4.27 (t,  $J = 5.9$  Hz, 2 H, H-2), 5.53 (s, 1 H, NH), 6.86 (d,  $J = 9.1$  Hz, 2 H, H-3'), 6.91–6.96 (m, 2 H, aromatic protons), 7.06 (d,  $J = 8.9$  Hz, 2 H, H-2'), 7.17–7.27 (m, 3 H, aromatic protons);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  33.4 (C-1), 66.5 (C-2), 115.8 (C-2'), 116.2 (C-2''), 120.0 (C-4'), 121.4 (C-3'), 129.3 (C-3''), 137.1 (C-4'), 144.5 (C-1'), 153.1 (C-1'); MS ( $m/z$ , relative intensity) 270 ( $\text{M}^+$ , 41), 184 (100). Anal. ( $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$ ) C, H, N, S.

**2-(Tetrahydro-2H-pyran-2-yloxy)-9H-carbazole (92).** To a solution of 2-hydroxycarbazole (**91**, 270 mg, 1.5 mmol) in methylene chloride (20 mL) was added dihydropyran (1.0 mL) and pyridinium 4-toluenesulfonate (30 mg). The mixture was stirred at room temperature for 16 h. The product was purified by column chromatography (silica gel) employing a mixture of hexanes/EtOAc (19:1) as eluent to give 204 mg (89% yield) of pure **92** as a white solid: mp 191–193 °C;  $R_f = 0.15$  (hexanes/EtOAc, 4:1); MS ( $m/z$ , relative intensity) 267 ( $\text{M}^+$ , 20), 209 (5), 183 (100), 85 (66).

**9-Benzyl-2-(tetrahydro-2H-pyran-2-yloxy)-9H-carbazole (93).** A solution of compound **92** (174 mg, 0.65 mmol) in anhydrous *N,N*-dimethylformamide (3.0 mL) was treated with 50% sodium hydride (80 mg, 1.6 mmol). The mixture was stirred at 0 °C for 5 min, and then benzyl bromide (86  $\mu\text{L}$ , 124 mg, 0.72 mmol) was added. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with an aqueous saturated solution of ammonium chloride (50 mL). The mixture was extracted with methylene chloride (3  $\times$  30 mL), and the combined organic layers were washed with brine (5  $\times$  100 mL) and dried ( $\text{MgSO}_4$ ), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing a mixture of hexanes/EtOAc (49:1) to give 230 mg

(99% yield) of pure **93** as a white solid: mp 121–123 °C; MS ( $m/z$ , relative intensity) 357 ( $M^+$ , 17), 273 (44), 182 (83), 154 (23), 127 (11), 91 (100).

**9-Benzyl-9H-carbazol-2-ol (94).** The tetrahydropyranyl group of compound **93** (200 mg, 0.56 mmol) was cleaved as described for **8**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (7:3) to afford 120 mg (78% yield) of pure compound **94** as a white solid: mp 240–242 °C; MS ( $m/z$ , relative intensity) 273 ( $M^+$ , 38), 182 (70), 154 (45), 127 (12), 91 (100).

**9-Benzyl-2-[2-(Tetrahydro-2H-pyran-2-yloxy)ethoxy]-9H-carbazole (95).** Compound **94** (110 mg, 0.40 mmol) was reacted with bromoethyl tetrahydropyranyl ether as described for **8**. The product was purified by column chromatography (silica gel), eluting with toluene/EtOAc (9:1) to afford 144 mg (90% yield) of pure **95** as a white solid: mp 78–80 °C; HRMS calcd for ( $C_{26}H_{27}O_3N$ ) 401.1991, found 401.2003.

**2-(9-Benzyl-9H-carbazol-2-yloxy)ethanol (96).** Compound **95** (130 mg, 0.32 mmol) was treated with pyridinium 4-toluenesulfonate as described for **9**. The product was purified by column chromatography (silica gel), eluting with toluene/EtOAc (4:1) to afford 101 mg (99% yield) of pure **96** as a white solid: mp 84–85 °C;  $R_f$  = 0.20 (hexanes/EtOAc, 7:3); MS ( $m/z$ , relative intensity) 317 ( $M^+$ , 44), 286 (7), 226 (100), 196 (28), 167 (33), 91 (57).

**4-Toluenesulfonic Acid 2-(9-Benzyl-9H-carbazol-2-yloxy)ethyl Ester (97).** Alcohol **96** (90 mg, 0.28 mmol) was treated with tosyl chloride as described for **10**. The product was purified by column chromatography (silica gel) employing hexanes/EtOAc (9:1) as eluent to afford 120 mg (91% yield) of pure **97** as a white solid:  $R_f$  = 0.44 (hexanes/EtOAc, 7:3); MS ( $m/z$ , relative intensity) 471 ( $M^+$ , 28), 380 (44), 286 (10), 224 (21), 167 (27), 91 (100).

**4-Toluenesulfonic Acid 2-(9H-Carbazol-2-yloxy)ethyl Ester (98).** Compound **97** (85 mg, 0.18 mmol) was hydrogenated and quenched as described for **81**. Evaporation of the solvent afforded 68 mg (100% yield) of pure **98** as a yellow solid.

**2-(2-Thiocyanate-ethoxy)-9H-carbazole (99).** Compound **98** (50 mg, 0.13 mmol) was treated with potassium thiocyanate as described for **11**. The product was purified by column chromatography (silica gel) employing hexanes/EtOAc (4:1) as eluent to afford 23 mg (69% yield) of pure **99** as a white solid:  $R_f$  = 0.25 (hexanes/EtOAc, 7:3);  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.31 (t,  $J$  = 7.1 Hz, 2 H, H-1), 4.65 (t,  $J$  = 7.1 Hz, 2 H, H-2), 6.79 (dd,  $J$  = 8.2, 2.0 Hz, 1 H, H-3'), 6.89 (d,  $J$  = 1.8 Hz, 1 H, H-1'), 7.23–7.42 (m, 3 H, aromatic protons), 7.91 (d,  $J$  = 8.0 Hz, 1 H), 7.98 (d,  $J$  = 7.7 Hz, 1 H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  31.7 (C-1), 42.4 (C-2), 94.7 (C-1'), 108.3 (C-3'), 110.4 (C-8'), 117.9 (C-4'a), 119.4 (C-5'), 119.5 (C-7'), 120.8 (C-6'), 123.6 (C-5'a), 124.9 (C-4'), 139.9 (C-8a), 141.4 (C-1'a), 155.3 (C-2'); MS ( $m/z$ , relative intensity) 268 ( $M^+$ , 36), 196 (100); HRMS calcd for ( $C_{15}H_{12}ON_2S$ ) 268.0670; found 268.0678.

**4-Phenoxyphenyl Methylthioethyl Ether (101).** A solution of mercaptane derivative **100** (150 mg, 0.61 mmol) in dimethyl sulfoxide (3.0 mL) was treated with potassium hydroxide (80 mg, 1.44 mmol) and methyl iodide (102 mg, 0.72 mmol). The mixture was stirred at room temperature for 4 h. The reaction was quenched as described for **8**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (19:1) to give 98 mg of undesired methyl ether **102** and 32 mg (20% yield) of pure **101** as a colorless oil. Compound **101**:  $R_f$  = 0.60 (hexanes/EtOAc, 4:1); IR (film,  $cm^{-1}$ ) 3063, 2920, 2872, 1589, 1506, 1489, 1219, 1024, 843, 758, 692;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  2.22 (s, 3 H,  $SCH_3$ ), 2.88 (t,  $J$  = 6.7 Hz, H, H-2), 4.14 (t,  $J$  = 6.8 Hz, H, H-1), 6.86–7.33 (m, 9 H, aromatic protons); MS ( $m/z$ , relative intensity) 260 ( $M^+$ , 10), 185 (100); HRMS calcd for ( $C_{15}H_{16}O_2S$ ) 260.0871, found 260.0870. Compound **102**: MS ( $m/z$ , relative intensity) 200 ( $M^+$ , 46), 185 (31), 75 (100).

**4-Phenoxyphenyl Phenylmethylthioethyl Ether (103).** A solution of compound **100** (157 mg, 0.64 mmol) in dimethyl sulfoxide (3.0 mL) was treated with potassium hydroxide (214 mg, 3.8 mmol). The mixture was stirred for 5 min, and then

benzyl chloride (101 mg, 0.8 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. The reaction was quenched as described for the preparation of **8**. The product was purified by column chromatography using hexanes/EtOAc (97:3) as eluent to give 135 mg (63% yield) of pure **103** as a colorless oil:  $R_f$  = 0.69 (hexanes/EtOAc, 4:1); IR (film,  $cm^{-1}$ ) 3034, 2920, 2868, 1589, 1504, 1489, 1296, 1221, 1196, 1072, 1022, 843, 756, 692;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  2.80 (t,  $J$  = 6.6 Hz, 2 H, H-2), 3.82 (s, 2 H,  $PhCH_2$ ), 4.06 (t,  $J$  = 6.6 Hz, 2 H, H-1), 6.80–7.34 (m, 14 H, aromatic protons);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  30.2 (C-2), 36.8 ( $PhCH_2$ ), 68.3 (C-1), 115.7 (C-2''), 117.7 (C-2'), 120.7 (C-3'), 122.5 (C-4''), 127.1 (C-4'''), 128.6 (C-3'''), 129.0 (C-2'''), 129.6 (C-3'), 138.2 (C-1'''), 150.5 (C-4'), 154.7 (C-1'), 158.4 (C-1''); MS ( $m/z$ , relative intensity) 336 ( $M^+$ , 2), 151 (43), 91 (100). Anal. ( $C_{21}H_{20}O_2S$ ) C, H, S.

**4-Phenoxyphenyl Phenylthioethyl Ether (106).** A solution of thiophenol (compound **104**, 114 mg, 1.04 mmol) in dimethyl sulfoxide (3.0 mL) was treated with potassium hydroxide (200 mg, 3.6 mmol), and the mixture was stirred for 10 min. Then, tosylate **105** (200 mg, 0.52 mmol) was added, and the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched as described for **8**. The product was purified by column chromatography (silica gel) employing hexanes/EtOAc (49:1) as eluent to afford 123 mg (38% yield) of pure compound **106** as a white solid: mp 52–54 °C;  $R_f$  = 0.67 (hexanes/EtOAc, 4:1); IR (KBr,  $cm^{-1}$ ) 3055, 2961, 2926, 2872, 1589, 1520, 1242, 1070, 1016, 835, 731, 689;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.28 (t,  $J$  = 6.9 Hz, 2 H, H-1), 4.12 (t,  $J$  = 6.9 Hz, 2 H, H-2), 6.76–7.43 (m, 14 H, aromatic protons);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  33.0 (C-1), 67.3 (C-2), 115.8 (C-2''), 117.7 (C-2'), 122.5 (C-4''), 126.5 (C-2'''), 129.0 (C-4'''), 129.6 (C-3'''), 129.9 (C-3'''), 135.5 (C-1'''), 150.6 (C-4'), 154.7 (C-1'), 158.3 (C-1''); MS ( $m/z$ , relative intensity) 322 ( $M^+$ , 6), 137 (100), 109 (48), 77 (34). Anal. ( $C_{15}H_{22}S$ ) C, H, S.

**4-Phenoxyphenoxyethyl Isocyanate (107).** To a solution of compound **105** (230 mg, 0.6 mmol) in dimethyl sulfoxide (2.0 mL) was added potassium cyanate (950 mg, 11.7 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was worked up as described for **8**. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (4:1) to give 67 mg (44% yield) of pure isocyanate **107** as a white solid: mp 134–136 °C; IR (KBr,  $cm^{-1}$ ) 3053, 2938, 2870, 1632, 1585, 1501, 1242, 1061, 841, 750, 691, 627;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.62 (m, 2 H, H-1), 4.02 (t,  $J$  = 4.9 Hz, 2 H, H-2), 6.83–7.32 (m, 9 H, aromatic protons);  $^{13}C$  NMR ( $CDCl_3$ , 125 MHz)  $\delta$  40.2 (C-1), 68.2 (C-2), 115.6 (C-2''), 117.8 (C-2'), 120.7 (C-3'), 122.6 (C-4'), 129.6 (C-3'''), 150.7 (C-4'), 154.7 (C-1'), 158.1 (C-1''), 158.3 (NCO);  $^{40}MS$  ( $m/z$ , relative intensity) 255 ( $M^+$ , 10), 186 (39), 77 (34), 44 (100); HRMS calcd for ( $C_{15}H_{13}O_3N$ ) 255.0895, found 255.0898.

**4-Phenoxyphenoxyethyl Azide (108).** A solution of **105** (168 mg, 0.59 mmol) in dimethyl sulfoxide (3.0 mL) was treated with sodium azide (500 mg, 7.7 mmol). The mixture was stirred at room temperature for 14 h. The reaction was worked up as described for **8**. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (7:3) to afford 57 mg (38% yield) of pure **110** as a colorless oil:  $R_f$  = 0.50 (hexanes/EtOAc, 7:3); IR (film,  $cm^{-1}$ ) 3042, 2932, 2874, 2120, 1591, 1504, 1287, 1223, 1063, 920, 872, 845, 760;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.60 (t,  $J$  = 4.9 Hz, 2 H, H-1), 4.14 (t,  $J$  = 4.9 Hz, 2 H, H-2), 6.88–7.34 (m, 9 H, aromatic protons);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  50.2 (C-1), 67.5 (C-2), 115.8 (C-2''), 117.8 (C-2'), 120.7 (C-3'), 122.6 (C-4'), 129.6 (C-3'''), 150.8 (C-4'), 154.4 (C-1'), 158.3 (C-1''). Anal. Calcd for  $C_{14}H_{13}O_2N_3$ : C, 65.87; H, 5.13; N, 16.46. Found: C, 66.42; H, 5.44; N, 15.89.

**(±)-2-Azido-3-[4-phenoxyphenoxy]propanol (110).** A solution of sodium azide (247 mg, 3.8 mmol) in acetone/water (7:5, 10 mL) was treated with epoxide **109** (200 mg, 0.83 mmol). The mixture was stirred at room temperature for 48 h. The acetone was evaporated, and the mixture was partitioned between water (50 mL) and methylene chloride (50 mL). The aqueous phase was extracted with methylene chloride (2 × 30 mL). The combined organic layers were washed with water (2 × 50 mL) and dried ( $MgSO_4$ ), and the solvent was evapo-



rated. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (9:1) as eluent to afford 194 mg (82% yield) of pure compound **110** as a colorless oil: IR (film,  $\text{cm}^{-1}$ ) 3421, 3042, 2928, 2874, 2104, 1589, 1504, 1489, 1221, 1045, 843, 692;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.47 (s, 1 H, OH), 3.55 (m, 2 H, H-1), 4.02 (m, 2 H, H-3), 4.16 (m, 1 H, H-2), 6.87–7.34 (m, 9 H, aromatic protons);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  53.4 (C-2), 69.3 (C-1), 69.7 (C-3), 115.7 (C-2''), 117.8 (C-2'), 120.7 (C-3'), 122.7 (C-4''), 129.6 (C-3''), 151.0 (C-4'), 154.4 (C-1'), 158.2 (C-1''); MS ( $m/z$ , relative intensity) 285 ( $\text{M}^+$ , 48), 228 (7), 186 (73), 77 (100); HRMS calcd for ( $\text{C}_{15}\text{H}_{15}\text{O}_3\text{N}_3$ ) 285.1113, found 285.1121.

**4-Phenoxyphoxymethyl Aziridine (111).** A solution of azido alcohol **110** (100 mg, 0.35 mmol) in anhydrous tetrahydrofuran (10.0 mL) was treated with triphenylphosphine (92 mg, 0.35 mmol) under an argon atmosphere. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the residue was absorbed on silica gel and purified by column chromatography (silica gel) using hexanes/EtOAc (7:3) as eluent to afford 64 mg (72% yield) of pure compound **111** as a white solid: mp 88–90 °C; IR (KBr,  $\text{cm}^{-1}$ ) 3360, 3294, 1589, 1508, 1292, 1242, 1194, 814, 741, 691;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.99 (m, 4 H, H-1, H-2, NH), 3.96 (m, 2 H, H-3), 6.87–7.32 (m, 9 H, aromatic protons);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{-OD}/\text{CDCl}_3$ )  $\delta$  43.8 (C-1), 69.8 (C-2), 70.4 (C-3), 115.4 (C-2''), 117.5 (C-2'), 120.5 (C-3'), 122.4 (C-4''), 129.4 (C-3''), 150.4 (C-4'), 154.7 (C-1'), 158.1 (C-1''); HRMS calcd for ( $\text{C}_{15}\text{H}_{15}\text{O}_2\text{N}$ ) 241.1103, found 241.1098.

**4-Phenylsulfanylphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (113).** 4-Phenylsulfanylphenol (**112**, 454 mg, 2.2 mmol) was treated with bromoethyl tetrahydropyranyl ether following the general method. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (49:1) to produce 462 mg (62% yield) of pure **113** as a colorless oil:  $R_f$  = 0.63 (hexanes/EtOAc, 7:3); MS ( $m/z$ , relative intensity) 330 ( $\text{M}^+$ , 49), 202 (43), 129 (100).

**4-Phenylsulfanylphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (114).** A solution of **113** (412 mg, 1.2 mmol) in methanol/water (20 mL, 7:3) was treated with sodium metaperiodate (301 mg, 1.3 mmol). The reaction mixture was stirred at room temperature for 48 h. Then, the mixture was partitioned between brine (60 mL) and methylene chloride (50 mL). The aqueous layer was extracted with methylene chloride (2  $\times$  30 mL). The combined organic layers were washed with water (2  $\times$  50 mL) and dried ( $\text{MgSO}_4$ ), and the solvent was evaporated. The product was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (9:1) to afford 334 mg (80% yield) of pure **114** as a colorless oil:  $R_f$  = 0.13 (hexanes/EtOAc, 7:3); IR (film,  $\text{cm}^{-1}$ ) 3059, 2943, 2872, 1593, 1495, 1304, 1254, 1036, 831, 750, 691; MS ( $m/z$ , relative intensity) 346 ( $\text{M}^+$ , 14), 303 (11), 255 (34), 169 (28), 129 (39), 86 (100). Anal. ( $\text{C}_{19}\text{H}_{22}\text{O}_4\text{S}$ ) C, H, S.

**4-Phenylsulfanylphenoxyethanol (115).** Compound **114** (320 mg, 0.88 mmol) was treated with 4-toluenesulfonic acid. After the usual workup, 210 mg (91% yield) of pure alcohol **115** was obtained as a colorless oil. This product was used as such in the next step:  $R_f$  = 0.12 (hexanes/EtOAc, 1:1).

**4-Phenylsulfanylphenoxyethyl 4-Toluenesulfonate (116).** Alcohol **115** (200 mg, 0.76 mmol) was treated with tosyl chloride and purified by column chromatography (silica gel), eluting with hexanes/EtOAc (4:1) as eluent to give 138 mg (45% yield) of pure tosylate **116** as a colorless oil:  $R_f$  = 0.38 (hexanes/EtOAc, 1:1).

**4-Phenylsulfanylphenoxyethyl Thiocyanate (117).** Compound **116** (113 mg, 0.27 mmol) was treated with potassium thiocyanate. Purification by column chromatography (silica gel), eluting with hexanes/EtOAc (7:3), afforded 58 mg (70% yield) of pure **117** as a colorless oil: IR (film,  $\text{cm}^{-1}$ ) 3059, 2997, 2931, 2878, 2154, 1593, 1593, 1495, 1249, 1173, 1042, 831, 750, 691;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.32 (d,  $J$  = 5.8 Hz, 2 H, H-1), 4.32 (d,  $J$  = 5.8 Hz, 2 H, H-2), 6.98 (d,  $J$  = 8.8 Hz, 2 H, H-), 7.46 (m, 3 H, aromatic protons), 7.60 (m, 4 H, aromatic protons);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  33.0 (C-1), 66.0 (C-2), 115.4 (C-2'), 124.6 (C-2''), 127.2 (C-3'), 129.3 (C-3''), 130.9 (C-4''), 160.1 (C-1'); MS

( $m/z$ , relative intensity) 303 ( $\text{M}^+$ , 14), 255 (36), 194 (13), 169 (24), 86 (100). Anal. ( $\text{C}_{15}\text{H}_{13}\text{O}_2\text{NS}_2$ ) C, H, N, S.

**Allyl-*N*-[2-(4-phenoxyphenoxy)ethyl] Dithiocarbamate (120).** To a mixture of 2-(4-phenoxyphenoxy)ethylamine hydrochloride (**119**, 266 mg, 1.0 mmol), water (5 mL), ethanol (2 mL), and sodium hydroxide (80 mg, 2.0 mmol) cooled at 0 °C was added carbon disulfide (66  $\mu\text{L}$ , 1.1 mmol), and the reaction mixture was stirred vigorously at 0 °C for 4 h. Then freshly distilled allyl bromide (96  $\mu\text{L}$ , 1.1 mmol) was added and the mixture was allowed to warm to room temperature while being stirred for 4 h. The reaction mixture was then diluted with water (10 mL) and extracted with chloroform (3  $\times$  20 mL). The combined organic layers were washed sequentially with 5% hydrochloric acid (25 mL), an aqueous saturated solution of sodium hydrogen carbonate (25 mL), and water (2  $\times$  25 mL). The solvent was dried ( $\text{MgSO}_4$ ) and evaporated. The residue was purified by column chromatography (silica gel), eluting with hexanes/EtOAc (19:1) to afford 245 mg (71% yield) of the title product **120** as a colorless oil:  $R_f$  = 0.36 (hexanes/EtOAc, 4:1); IR ( $\text{CHCl}_3$  film,  $\text{cm}^{-1}$ ) 695, 770, 840, 870, 920, 975, 1055, 1220, 1380, 1490, 1505, 1590, 1645, 2920, 3030, 3300;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.92 (d,  $J$  = 6.8 Hz, 2 H, H-1''), 4.16 (m, 4 H, H-1, H-2), 5.17 (d,  $J$  = 9.9 Hz, 1 H, H-3''', *cis* to H-2''), 5.33 (d,  $J$  = 16.8 Hz, 1 H, H-3''', *trans* to H-2''), 5.90 (m, 1 H), 6.93 (AB,  $J$  = 9.2 Hz, 4 H, aromatic protons), 6.93–7.33 (m, 5 H, aromatic protons), 7.45 (bs, 1 H, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  38.5 ( $\text{SCH}_2$ ), 46.3 (C-1), 66.0 (C-2), 115.6 (C-2''), 117.8 (C-2'), 118.6 ( $\text{CHCH}_2$ ), 120.8 (C-3'), 122.7 (C-4'), 129.6 (C-3''), 132.7 ( $\text{CHCH}_2$ ), 151.0 (C-4'), 154.4 (C-1'), 158.2 (C-1''), 198.2 (CS); MS ( $m/z$ , relative intensity) 345 ( $\text{M}^+$ , 0.9), 271 (84), 212 (19), 199 (13), 186 (48), 160 (100), 86 (39), 77 (52), 41 (27). Anal. ( $\text{C}_{18}\text{H}_{19}\text{NO}_2\text{S}_2$ ) C, H, N, S.

**Methyl-*N*-[2-(4-phenoxyphenoxy)ethyl] Dithiocarbamate (121).** This compound was prepared in 80% yield using the procedure as described above for **120** employing methyl iodide as alkylating agent:  $R_f$  = 0.63 (hexanes/EtOAc, 7:3); IR (film,  $\text{cm}^{-1}$ ) 695, 845, 870, 875, 1055, 1220, 1490, 1500, 1590, 2915, 3030, 3300;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.65 (s, 3 H, Me), 4.14 (m, 4 H, H-1, H-2), 6.93 (AB,  $J$  = 9.1 Hz, 4 H, aromatic protons), 6.93–7.32 (m, 5 H, aromatic protons), 7.80 (bs, 1 H, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.3 ( $\text{SCH}_3$ ), 46.3 (C-1), 66.1 (C-2), 115.6 (C-2''), 117.8 (C-2'), 120.8 (C-3'), 122.7 (C-4''), 129.7 (C-3''), 151.0 (C-4'), 154.4 (C-1'), 158.2 (C-1''), 200.0 (CS); MS ( $m/z$ , relative intensity) 319 ( $\text{M}^+$ , 0.5), 271 (100), 212 (7), 199 (13), 186 (48), 134 (78), 77 (50). Anal. ( $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{S}_2$ ) C, H, N, S.

**Benzyl-*N*-[2-(4-phenoxyphenoxy)ethyl] Dithiocarbamate (122).** This compound was prepared in 72% yield using the same procedure as described above for **120** employing benzyl chloride as alkylating agent:  $R_f$  = 0.68 (hexanes/EtOAc, 7:3); mp 67–68 °C; IR ( $\text{CHCl}_3$  film,  $\text{cm}^{-1}$ ) 695, 770, 840, 975, 1060, 1220, 1380, 1490, 1500, 2915, 3035, 3300;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.16 (m, 4 H, H-1, H-2), 4.56 (s, 2 H,  $\text{PhCH}_2$ ), 6.93–7.37 (m, 14 H, aromatic protons), 7.80 (bs, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  38.8 ( $\text{PhCH}_2$ ), 46.4 (C-1), 66.0 (C-2), 115.6 (C-2''), 117.8 (C-2'), 118.6, 120.8 (C-3'), 122.6 (C-4''), 127.6 (C-4'''), 128.6 (C-3'''), 129.6 (C-3''), 130.8 (C-2'''), 151.0 (C-4'), 154.4 (C-1'), 158.2 (C-1''); MS ( $m/z$ , relative intensity) 395 ( $\text{M}^+$ , 0.2), 271 (100), 210 (17), 199 (12), 186 (40), 124 (28), 91 (83), 77 (46). Anal. ( $\text{C}_{22}\text{H}_{21}\text{NO}_2\text{S}_2$ ) C, H, N, S.

***N*-(1-*tert*-Butyl)-*N*-[2-(4-phenoxyphenoxy)ethyl] Thiourea (123).** To a mixture of 2-(4-phenoxyphenoxy)ethylamine hydrochloride (200 mg, 0.75 mmol) and anhydrous benzene (1.5 mL) cooled at  $\sim$ 5 °C was added triethylamine (140  $\mu\text{L}$ , 1.0 mmol) followed by *tert*-butyl isothiocyanate (96  $\mu\text{L}$ , 0.75 mmol). The reaction mixture was stirred at room temperature for 24 h. Then, the mixture was partitioned between chloroform (20 mL) and water (15 mL). The organic layer was washed with dilute hydrogen chloride solution (15 mL), water (15 mL), and saturated sodium hydrogen carbonate solution (15 mL). The solvent was dried ( $\text{MgSO}_4$ ) and evaporated. The residue was purified by column chromatography (silica gel) using hexanes/EtOAc (19:1) as eluent to afford 160 mg (62% yield) of compound **123** as a white solid:  $R_f$  = 0.42 (hexanes/EtOAc, 7:3); mp 88–90 °C; IR ( $\text{CHCl}_3$  film,  $\text{cm}^{-1}$ ) 695, 1080,



1220, 1285, 1490, 1505, 1535, 3300;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.43 (s, 9 H,  $\text{Me}_3$ ), 4.07 (t,  $J = 4.9$  Hz, 2 H, H-2), 4.15 (quintet,  $J = 4.9$  Hz, 2 H, H-1), 6.17 (br s, 2 H, NH), 6.92 (AB,  $J = 9.2$  Hz, 4 H, aromatic protons), 6.93–7.20 (m, 5 H, aromatic protons);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.5 ( $\text{Me}_3$ ), 45.2 ( $\text{CMe}_3$ ), 52.8 (C-1), 68.2 (C-2), 115.6 (C-2'), 117.8 (C-2'), 120.8 (C-3'), 122.7 (C-4'), 129.7 (C-3''), 151.0 (C-4'), 154.5 (C-1'), 158.2 (C-1''), 181.5 (CS); MS ( $m/z$ , relative intensity) 344 ( $\text{M}^+$ , 0.4), 310 (2), 271 (6), 212 (30), 186 (23), 159 (95), 103 (100), 57 (22). Anal. ( $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$ ) C, H, N, S.

**Drug Screening.** Biological assays on epimastigotes were performed as previously described.<sup>19</sup>

*Trypanosoma cruzi* epimastigotes (Y strain) were grown in 20 mL screw-cap tubes at 28 °C in a liquid medium containing brain–heart infusion (37 g/L), hemin chlorohydrate (20 mg/L) (dissolved in 50% triethanolamine), and 10% newborn calf serum. The initial inoculum contained  $(2-3) \times 10^6$  cells/mL (as determined by counting in a Neubauer chamber) in a final volume of 1 mL. The concentration of cells was determined by measuring the absorbance of the culture medium containing parasites at 600 nm against a blank with culture medium alone. Each drug was tested at four different concentrations (1, 10, 50, and 100  $\mu\text{g/mL}$ ), each one in quadruplicate. Drugs were dissolved in ethanol. A control without drug was done with each group that was tested.

To calculate the percent inhibition, the following formula was used:

$$100 - \frac{(\Delta A_d \times 100)}{\Delta A_c} = \text{percent inhibition}$$

where  $\Delta A_c$  and  $\Delta A_d$  are the differences in the absorbance of control cultures and drug-treated cultures, respectively, at the beginning and at the end of the experiment. The maximum amount of solvent used (1% ethanol) did not have any significant effect on the epimastigotes growth. The values of  $\text{IC}_{50}$  were estimated by linear and polynomial regression.

Experiments on the intracellular form of the parasite were conducted on *T. cruzi* infected  $\text{L}_6\text{E}_9$  myoblasts (Y strain) as described earlier.<sup>39</sup>

$\text{L}_6\text{E}_9$  myoblasts were exposed to 2000 rad of  $\gamma$  radiation and plated on 75  $\text{cm}^2$  flasks at a density of  $1.2 \times 10^7$  cells/flask in DMEM containing 20% fetal calf serum in a total volume of 10 mL. After 24 h of incubation at 35 °C, the cells were exposed to a suspension of  $5 \times 10^7$  trypanomastigotes/flask in DMEM containing 20% fetal calf serum for 2 h. Then cultures were washed twice with Dulbecco' PBS and the culture medium was replaced. Different concentrations of drugs were added to the cultures that were labeled with 1.0  $\mu\text{Ci}$  of  $[5,6\text{-}^3\text{H}]\text{uracil}$  and incubated for an additional 72 h. The incorporation of  $[^3\text{H}]\text{uracil}$  was measured, and the percent inhibition of  $[^3\text{H}]\text{uracil}$  incorporation (parasite proliferation) was calculated by employing the following formula:

$$\text{percent inhibition} = \frac{A - B}{A} \times 100$$

where A is the mean count per minute of infected control-treated myoblasts and B is the mean count per minute of infected drug-treated myoblasts.

**Acknowledgment.** This work was supported by grants from the CONICET (Grant PIP 635/98), the Universidad de Buenos Aires (Grant X-080) to J.B.R., and the United Nations Development Program/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases, and the National Institutes of Health (Grant AI-23259) to R.D. B.N.B. was supported by a predoctoral fellowship of the American Heart Association, Midwest Affiliate. The authors thank Ms. E. Gács-Baitz for spectroscopical assistance.

**Supporting Information Available:** NMR spectral data for compounds 7–10, 12, 14, 15, 18–21, 25–27, 31, 32, 35–37, 40–42, 45–47, 50–52, 55, 58–60, 63–65, 68–70, 73–75, 78, 80–85, 87–89, 92–98, 102, and 113–116 and tables of data needed to calculate percent inhibition. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) (a) Rodriguez, J. B. Specific Molecular Targets To Control Tropical Diseases. *Curr. Pharm. Des.* **2001**, *7*, 1105–1116. (b) Augustyns, K.; Amssoms, K.; Yamani, A.; Rajan, P. K.; Haemers, A. Trypanothione as a Target in the Design of Antitrypanosomal and Antileishmanial Agents. *Curr. Pharm. Des.* **2001**, *7*, 1117–1141. (c) Cazzulo, J. J.; Stoka, V.; Turk, V. The Major Cysteine Proteinase of *Trypanosoma cruzi*: A Valid Target for Chemotherapy of Chagas Disease. *Curr. Pharm. Des.* **2001**, *7*, 1143–1156. (d) Docampo, R. Recent Developments in the Chemotherapy of Chagas' Disease. *Curr. Pharm. Des.* **2001**, *7*, 1157–1164. (e) de Lederkremer, R. M.; Bertello, L. E. Glycoinositolphospholipids, Free and as Anchors of Proteins, in *Trypanosoma cruzi*. *Curr. Pharm. Des.* **2001**, *7*, 1165–1179.
- (2) *Control of Chagas' Disease*. WHO Technical Report Series, No. 811; World Health Organization: Geneva, 1991.
- (3) De Castro, S. L. The challenge of Chagas' disease chemotherapy: an update of drugs assayed against *Trypanosoma cruzi*. *Acta Trop.* **1993**, *53*, 83–98.
- (4) Docampo, R.; Moreno, S. N. J. Biochemical Toxicology of Antiparasitic Compounds Used in the Chemotherapy and Chemoprophylaxis of American Trypanosomiasis (Chagas' Disease). *Rev. Biochem. Toxicol.* **1985**, *7*, 159–204.
- (5) Brener, Z. Present Status of the Chemotherapy and Chemoprophylaxis of Human Trypanosomiasis in the Western Hemisphere. *Pharmacol. Ther.* **1979**, *7*, 71–90.
- (6) Rodriguez, J. B.; Gros, E. G. Recent developments in the control of *Trypanosoma cruzi*, the causative agent for Chagas' disease. *Curr. Med. Chem.* **1995**, *2*, 723–742.
- (7) Brener, Z. Biology of *Trypanosoma cruzi*. *Annu. Rev. Microbiol.* **1973**, *27*, 347–382.
- (8) Docampo, R.; Schmuñis, G. Sterol Biosynthesis Inhibitors: Potential Chemotherapeutics against Chagas Disease. *Parasitol. Today* **1997**, *13*, 129–130.
- (9) Urbina, J. A.; Payares, G.; Molina, J.; Sanoja, C.; Liendo, A.; Lizardi, K.; Piras, M. M.; Piras, R.; Perez, N.; Wincker, P.; Ryley, J. F. Cure of Short- and Long-Term Experimental Chagas' Disease Using D0870. *Science* **1996**, *273*, 969–971.
- (10) Liendo, A.; Lizardi, K.; Urbina, J. A. In-vitro antiproliferative effects and mechanism of action of the bis-triazole D0870 and its *S*(–) enantiomer against *Trypanosoma cruzi*. *J. Antimicrob. Chemother.* **1998**, *41*, 197–205.
- (11) Urbina, J. A.; Payares, G.; Contreras, L. M.; Liendo, A.; Sanoja, C.; Molina, J.; Piras, M.; Perez, N.; Wincker, P.; Loebenberg, D. Antiproliferative Effects and Mechanism of Action of SCH 56592 against *Trypanosoma (Schizotrypanum) cruzi*: In Vitro and In Vivo Studies. *Antimicrob. Agents Chemother.* **1998**, *42*, 1771–1777.
- (12) Docampo, R.; Moreno, S. N. J.; Turrens, J. F.; Katzin, A. M.; Gonzalez-Cappa, S. M.; Stoppani, A. O. M. Biochemical and Ultrastructural Alterations Produced by Miconazole and Econazole in *Trypanosoma cruzi*. *Mol. Biochem. Parasitol.* **1981**, *3*, 169–180.
- (13) Urbina, J. A. Chemotherapy of Chagas' disease: the how and the why. *J. Mol. Med.* **1999**, *77*, 332–338.
- (14) Cinque, G. M.; Szajnman, S. H.; Zhong, L.; Docampo, R.; Rodriguez, J. B.; Gros, E. G. Structure–Activity Relationship of New Growth Inhibitors of *Trypanosoma cruzi*. *J. Med. Chem.* **1998**, *41*, 1540–1554.
- (15) Szajnman, S. H.; Yan, W.; Bailey, B. N.; Docampo, R.; Elhalem, E.; Rodriguez, J. B. Design and Synthesis of Aryloxyethyl Thiocyanate Derivatives as Potent Inhibitors of *Trypanosoma cruzi* Proliferation. *J. Med. Chem.* **2000**, *43*, 1826–1840.
- (16) Urbina, J. A.; et al. Unpublished results.
- (17) Docampo, R. Personal communication.
- (18) Montalvetti, A.; Bailey, B. N.; Martin, M. B.; Severin, G. W.; Oldfield, E.; Docampo, R. Bisphosphonates are potent inhibitors of *Trypanosoma cruzi* farnesyl pyrophosphate synthase. *J. Biol. Chem.* **2001**, *276*, 33930–33937.
- (19) Schwartzapel, A. J.; Zhong, L.; Docampo, R.; Rodriguez, J. B.; Gros, E. G. Design, Synthesis, and Biological Evaluation of New Growth Inhibitors of *Trypanosoma cruzi* (Epimastigotes). *J. Med. Chem.* **1997**, *40*, 2314–2322.
- (20) Schwartzapel, A. J.; Fichera, L.; Esteve, M.; Rodriguez, J. B.; Gros, E. G. Design, Synthesis, and anti-*Trypanosoma cruzi* Evaluation of a New Class of Cell Growth Inhibitors Structurally Related to Fenoxycarb. *Helv. Chim. Acta* **1995**, *78*, 1207–1214.

- (21) Tarbell, D. S.; Petropoulos, J. C. The Action of Aluminum Bromide on Benzyl Phenyl Ether. *J. Am. Chem. Soc.* **1952**, *74*, 244–248.
- (22) Johnstone, R. A. W.; Rose, M. E. A Rapid, Simple, and Mild Procedure for Alkylation of Phenols, Alcohols, Amides and Acids. *Tetrahedron* **1979**, *75*, 2169–2172.
- (23) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. Pyridinium *p*-Toluenesulfonate. A Mild and Efficient Catalyst for the Tetrahydropyranylation of Alcohols. *J. Org. Chem.* **1977**, *42*, 3772–3774.
- (24) Witzack, Z. J. Monosaccharide Isothiocyanates and Thiocyanates: Synthesis, Chemistry, and Preparative Applications. *Adv. Carbohydr. Chem. Biochem.* **1986**, *44*, 91–145.
- (25) (a) Bellus, D. Photo-Fries rearrangement and related photochemical [1, *j*]-shifts (*j* = 3, 5, 7) of carbonyl and sulfonyl groups. In *Advances in Photochemistry*; Pitts, J. N., Jr., Hammond, G., Noyes, W. A., Jr., Eds.; Wiley-Interscience: New York, 1971; Vol. 8, pp 109–159. (b) Meyer, J. W.; Hammond, G. S. Mechanism of Photochemical Reaction in Solution. LXX. Photolysis of Aryl Ethers. *J. Am. Chem. Soc.* **1972**, *94*, 2219–2228. (c) Kalmus, C. E.; Hercules, D. M. A Mechanistic Study of the Photo-Fries Rearrangement of Phenyl Acetate. *J. Am. Chem. Soc.* **1974**, *96*, 449–456. (d) Adam, W.; de Sanabia, J. A.; Fischer, H. Transient Intermediates in the Photo-Fries Isomerization of Phenyl Acetate via Spontaneous Raman Spectroscopy. *J. Org. Chem.* **1973**, *38*, 2571–2572. (e) Beck, S. M.; Brus, L. E. CIDNP Evidence for Radical Pair Mechanism in Photo-Fries Rearrangement. *J. Am. Chem. Soc.* **1982**, *104*, 1805–1808. (f) Nakagaki, R.; Hiramatsu, M.; Watanabe, T.; Tanimoto, Y.; Hagakura, S. Magnetic Isotope and External Magnetic Field upon the Photo-Fries Rearrangement of 1-Naphthyl Acetate. *J. Phys. Chem.* **1985**, *89*, 3222–3226.
- (26) López Quiroga, I.; Cimino, R.; Nasser, J. R.; Rodriguez, J. B. Unpublished results.
- (27) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. New N- and O-Arylations with Phenylboronic Acids and Cupric Acetate. *Tetrahedron Lett.* **1998**, *39*, 2933–2936. (b) Evans, D. A.; Katz, J. L.; West, T. R. Synthesis of Diaryl Ethers through the Copper-Promoted Arylation of Phenols with Arylboronic Acids. An Expedient Synthesis of Thyroxine. *Tetrahedron Lett.* **1998**, *39*, 2937–2940. (c) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, M. P. T.; Combs, A. New Aryl/Heteroaryl C–N Bond Cross-Coupling Reactions via Arylboronic Acid/Cupric Acetate Arylation. *Tetrahedron Lett.* **1998**, *39*, 2941–2944.
- (28) Node, N.; Nishide, K.; Fuji, K.; Fujita, E. Hard Acid and Soft Nucleophile System. 2. Demethylation of Methyl Ethers of Alcohol and Phenol with an Aluminum Halide–Thiol System. *J. Org. Chem.* **1980**, *45*, 4275–4277.
- (29) Jung, M. E.; Lyster, M. A. Quantitative Dealkylation of Alkyl Ethers via Treatment with Trimethylsilyl Iodide. A New Method for Ether Hydrolysis. *J. Org. Chem.* **1977**, *42*, 3761–3764.
- (30) Gallo-Rodriguez, C.; Ji, X.-D.; Melman, N.; Siegman, B. D.; Sanders, L. H.; Orlina, J.; Fischer, B.; Pu, Q.; Olah, M. E.; van Galen, P. J. M.; Stiles, G. L.; Jacobson, K. A. Structure–Activity Relationships of *N*<sup>6</sup>-Benzyladenosine-5'-uronamides as A<sub>3</sub>-Selective Adenosine Agonists. *J. Med. Chem.* **1994**, *37*, 636–646.
- (31) Rodriguez, J. B.; Docampo, R.; Gros, E. G. Sulfur-Containing Derivatives Structurally Related to Fenoxycarb Are Potent Growth Inhibitors against the Intracellular Form of *Trypanosoma cruzi*. *Int. J. Antimicrob. Agents* **2000**, *13*, 215–218.
- (32) (a) Brown, S.; Bernardo, M. M.; Li, Z.-H.; Kotra, L. P.; Tanaka, Y.; Fridman, R.; Mobashery, S. Potent and Selective Mechanism-Based Inhibition of Gelatinases. *J. Am. Chem. Soc.* **2000**, *122*, 6799–6800. (b) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. Privileged Molecules for Protein Binding Identified from NMR-Based Screening. *J. Med. Chem.* **2000**, *43*, 3443–3447.
- (33) Ittah, Y.; Shahak, I.; Tsaroom, S.; Blum, J. A New Aziridine Synthesis from 2-Azido Alcohols and Tertiary Phosphines. Preparation of Phenanthrene-9,10-Imine. *J. Org. Chem.* **1978**, *43*, 4271–4273.
- (34) (a) Hiskey, R. G.; Harpold, M. A. Chemistry of Aliphatic Disulfides. XIV. The Preparation of Disulfides Sulfoxides by Selective Oxidation. *J. Org. Chem.* **1967**, *32*, 3191–3199. (b) Leonard, N. J.; Johnson, C. R. Periodate Oxidation of Sulfides to Sulfoxides. Scope of the Reaction. *J. Org. Chem.* **1962**, *27*, 282–284.
- (35) Rodriguez, J. B.; Zhong, L.; Docampo, R.; Wimmer, Z.; Gros, E. G. Growth Inhibitory Effect of Juvenile Hormone Analogues on Epimastigotes of *Trypanosoma cruzi*. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3257–3260.
- (36) Ujváry, I.; Matolcsy, G.; Riddiford, L. M.; Hiruma, K.; Horwarth, K. L. Inhibition of Spiracle and Crochet Formation and Juvenile Hormone Activity of Isothiocyanate Derivatives in the Tobacco Hornworm, *Manduca sexta*. *Pestic. Biochem. Physiol.* **1989**, *35*, 259–274.
- (37) (a) Buerstinghaus, R.; Hofmeister, P.; Kuenast, C. Pesticidal Composition and Process for Combating Pests Employing Carboxamides. U.S. Patent 4,859,706, August 22, 1989. (b) Fischer, U.; Schneider, F.; Zurflueh, R. Carbamic Acid Derivatives. U.S. Patent 4,215,139, July 29, 1980.
- (38) (a) Zhang, Y.; Talalay, P.; Cho, C.-G.; Posner, G. H. A Major Inducer of Anticarcinogenic Protective Enzymes from Broccoli: Isolation and Elucidation of Structure. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 2399–2403. (b) Posner, G. H.; Cho, C.-G.; Green, J. V.; Zhang, Y.; Talalay, P. Design and Synthesis of Bifunctional Isothiocyanate Analogs of Sulforaphane: Correlation between Structure and Potency as Inducers of Anticarcinogenic Detoxification Enzymes. *J. Med. Chem.* **1994**, *37*, 170–176. (c) Zhang, Y.; Kensler, T. W.; Cho, C.-G.; Posner, G. H.; Talalay, P. Anticarcinogenic Activities of Sulforaphane and Structurally Related Synthetic Norbornyl Isothiocyanates. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3147–3150.
- (39) Yan, W.; Moreno, S. N. A method to assess invasion and intracellular replication of *Trypanosoma cruzi* based on differential uracil incorporation. *J. Immunol. Methods* **1998**, *220*, 123–128.
- (40) Signal attributions may be interchanged.

JM0201518