Design, Synthesis, and Biological Evaluation of New Growth Inhibitors of *Trypanosoma cruzi* (Epimastigotes)

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As a continuation of our project aimed at the search for new chemotherapeutic agents against Chagas' disease, several drugs structurally related to the insect growth regulator Fenoxycarb and the naturally occurring juvenile hormone of insects were designed, synthesized, and evaluated as antiproliferative agents against the parasite responsible of this disease. Isoprenoid derivatives (compounds **33**, **34**, **36**, and **37**) were potent growth inhibitors of *Trypanosoma cruzi* epimastigotes. In addition, taking into account the high activity observed for compound **30** and the inhibitory action of related compounds, the allyl ether moiety bonded at the polar extreme of these inhibitors proved to be a promising group for the design of new drugs.

Introduction

Chagas' disease, or American trypanosomiasis, is still a major health problem that affects millions of people in Mexico and Central and South America.[1] The etiologic agent of this illness is the hemoflagellate protozoan *Trypanosoma (Schizotrypanum) cruzi* which is transmitted in rural areas to humans and other mammals by Reduviid bugs of different species such as *Rhodnius* and *Triatoma* and in large urban centers by transfusion of infected blood, even in countries where Chagas' disease is not endemic.[2] The number of infected people is estimated to be about 15−20 million, and close to 50 000 deaths attributed to Chagas' disease occur each year. As this serious health problem is closely related to poverty, there is a lack of interest from pharmaceutical companies to carry out a research and developmental program because it is not commercially attractive.

New chemotherapeutic agents are needed because the trypanocidal drugs presently in use, Nifurtimox (4-[(5-nitrofurfurylidene)amino]-3-(methylthio)morpholine 1,1-dioxide) and Benznidazole (*N*-benzyl-2-nitro-1-imidazoleacetamide), cause severe side effects in patients and lack specificity against the chronic stage of the disease.[3−5] The urgency for more selective and less toxic drugs has led to evaluation of chemical therapy based on the knowledge of *T. cruzi* biochemistry and the mode of action of these compounds.[6] In addition, due to the risk that *T. cruzi* may be transmitted by blood transfusions, it is very important to have new compounds to eliminate this parasite in blood to be transfused. At the present time, the drug in use for this action is Gentian Violet (*N*-{4-bis[[4-(dimethylamino)phenyl]methylene]-2,5-cyclohexadien-1-ylidene}-*N*-methylammonium chloride), a dye discovered to be effective for this purpose many years ago[7] which suffers from some limitations regarding its safety.[4]

The parasite occurs in three main morphological forms: the epimastigotes that are the dividing forms that replicate within the crop and midgut of Chagas' disease vectors, the nondividing highly infective metacyclic and bloodstream trypomastigotes, and, finally, the clinically more relevant form, amastigotes which are found within the cells in host tissues.[8]

Our lead structures were discovered while working on the design and preparation of juvenile hormone analogues (JHAs) of insects[9] (hormones crucial for maintaining larval stages and maturation of the reproductive system in the female) to be evaluated against the Chagas' disease vector, i.e., *Triatoma infestans.* The synthetic compounds presented a variable degree of activity against this insect, and some of them were more active than the naturally occurring juvenile hormones.[10,11] Taking into account that these insects, after treatment with JHAs, were less susceptible to natural infections with the parasite *T. cruzi* than normal nontreated vectors,[12] the designed JHAs were tested against *T. cruzi* (epimastigotes). Surprisingly, they showed a variable degree of activity, some of them being very active in inhibiting cell proliferation of this parasite.[13−15] These compounds, formerly juvenile hormone analogues of insects, became cell growth inhibitors. At the beginning, the well-known insect growth regulator Fenoxycarb (*N*-{2-[(4-phenoxyphenoxy)ethyl]-ethyl}carbamate)[16] was employed as standard control because it behaved as a highly active agent against egg eclosion and nymphal stages of *T. infestans*. However, some modified structures having the 4-phenoxyphenoxy moiety were found to be more active than Fenoxycarb in experiments involving *T. cruzi* cells. We have studied the mode of action of these drugs, and there is evidence that they inhibit sterol biosynthesis within the cells as it was observed in Leydig tumor cells.[17−19] Tumor and *T. cruzi* cells have many similarities due, mainly, to their rapid replication, and in fact, some antitumor agents have shown effects as trypanocidal drugs.[20−22]

Compounds **1** and **2**, two representative members of our designed drugs, the former structurally related to Fenoxycarb and the latter structurally related to natural juvenile hormones of insects, proved to be very active

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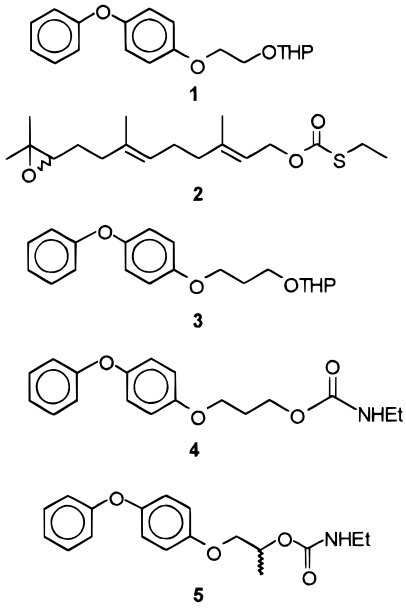
Chart 1. Chemical Structures of Five Representative Members of Antireplicative Agents for *T. cruzi*



against the intracellular form of the parasite,[23] and as occurs with other sterol biosynthesis inhibitors, they were inactive agents against trypomastigotes.[24] As part of our efforts to improve the antireplicative activity of these sterol biosynthesis inhibitors against this parasite and in order to investigate their structure−activity relationship, we prepared a series of new derivatives structurally related to our lead drugs (compounds **1**−**5**) and evaluated their biological activity (Chart 1).

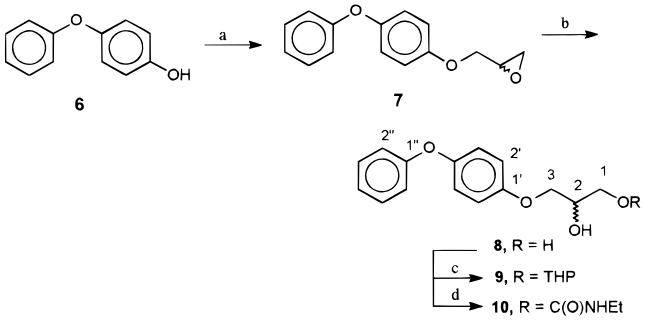
Rationale

The preparation of the new compounds in this study was motivated by the good antitrypanostatic activity[13−15] of the lead compounds **1**−**5**. These antiparasitic agents can be divided into two different families: one having an isoprenic nonpolar chain and the other possessing an aromatic hydrocarbon-like skeleton, specifically, a 4-phenoxyphenoxy moiety. Among the end polar groups, the best results were obtained when allylic ethers, tetrahydro-2*H*-pyran-2-yl ethers, and *N*-ethylcarbamates were employed.[13−15] In the last case, the positions of both nitrogen and oxygen atoms are inverted compared with Fenoxycarb. In addition, previous results had indicated that vinylic carbonates could also have potential utility as a polar extreme in our inhibitors.[15] Therefore, a new set of related compounds possessing these polar moieties was designed, prepared, and evaluated against the epimastigote forms of *T. cruzi* which is, by far, the preferred target for new drugs.

The preparation of analogues of compound **3** with an increment of hydrophilicity at the polar extreme by adding a hydroxyl group was the first modification considered. The designed compounds **9** and **10** were straightforwardly prepared from acid hydrolysis (perchloric acid) of epoxide **7**[15] followed by careful addition of 1 equiv of either dihydropyran[25,26] or ethyl isocyanate[27] to give these compounds with reasonable yields (Scheme 1). HPLC analyses showed the presence of a single isomer in both cases.

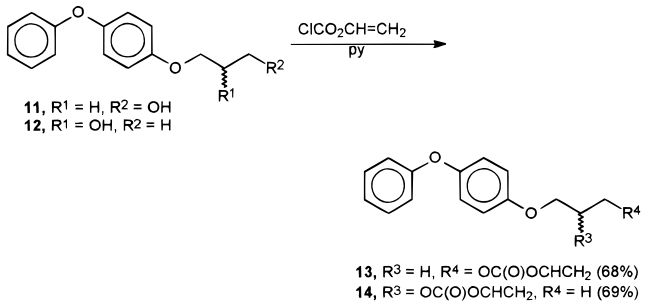
As a second variation, compounds **13** and **14**, which retain the 4-phenoxyphenoxy skeleton but with a vinyl

Scheme 1[a]



[a] Reagents: (a) allyl bromide, KOH/DMSO, rt (80%), *m*-CPBA, Cl_2CH_2, rt (61%); (b) $HClO_4$, THF−H_2O, 48 h (90%); (c) DHP, Cl_2CH_2, PPTs, rt (52%); (d) EtNCO/py, rt (39%).

Scheme 2

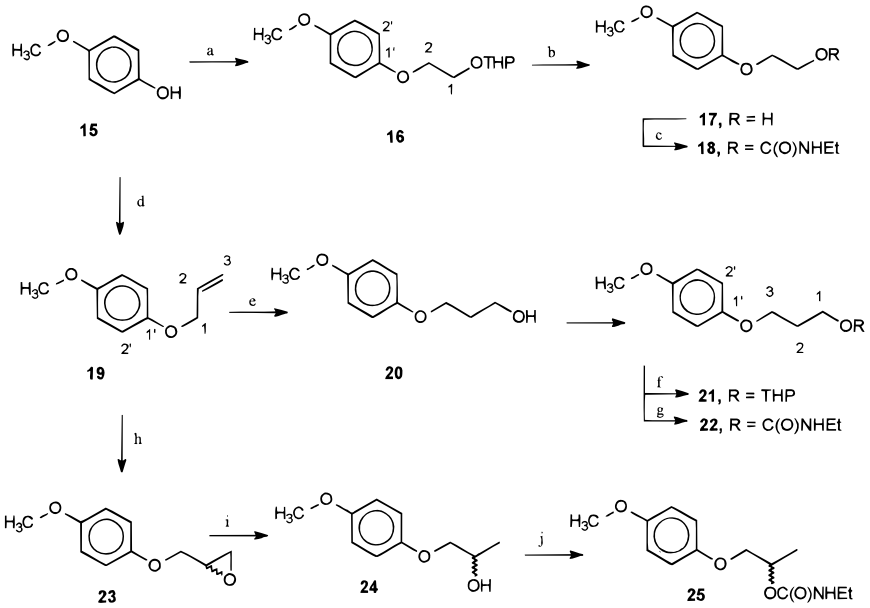


carbonate polar end, were easily prepared by treating alcohols **11** and **12**[15] with vinyl chloroformate[28] (Scheme 2).

In order to study the influence of the terminal phenyl nonpolar moiety in the aromatic series, this portion of the framework was replaced by a methyl group keeping the selected polar substructures. 4-Methoxyphenol (**15**) was used as starting material. This compound was transformed into the tetrahydropyranyl ether derivative **16** by treatment of 2-bromoethyl tetrahydro-2*H*-pyran-2-yl ether with a suspension of potassium hydroxide in dimethyl sulfoxide, employing a modified Williamson procedure.[29] Removal of the tetrahydropyranyl group of **16** with pyridinium *p*-toluenesulfonate gave alcohol **17**, which after treatment with ethyl isocyanate afforded the carbamate **18** in good yield. Phenol **15** reacted with allyl bromide to give the allylic derivative **19** in excellent yield. On reaction with diborane[30−32] followed by oxidation with hydrogen peroxide, **19** was converted into the alcohol **20** with high regioselectivity. Transformation of **20** into inhibitors **21** and **22** was achieved by treatment with dihydropyran and ethyl isocyanate, respectively. Epoxidation of allyl ether **19** with *m*-chloroperbenzoic acid gave epoxide **23** that, after regiospecific ring opening with lithium aluminum hydride,[33] afforded the secondary alcohol **24** in very good yield. Alcohol **24** reacted with ethyl isocyanate to yield the carbamate derivative **25** (Scheme 3).

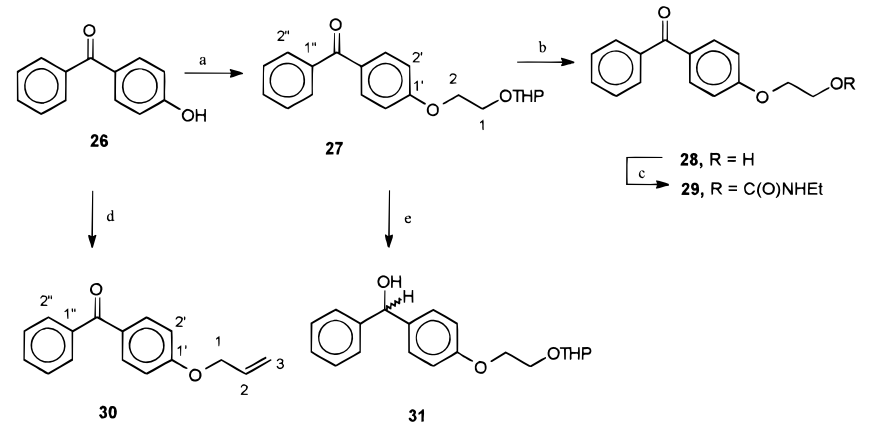
In order to study the influence of planarity on the biological activity, it was of interest to replace the oxygen atom between the phenyl groups by an sp^2 unit as a linker giving rise to a potentially planar nonpolar framework. It was decided that the carbonyl group would be suitable for this transformation. Therefore, 4-benzoylphenol (**26**) was used as starting material which, following a similar protocol to obtain **16**−**19**, afforded compounds **27**−**30** with comparable yields.

Scheme 3[a]



[a] Reagents: (a) $BrCH_2CH_2OTHP$, KOH/DMSO, rt (68%); (b) MeOH, PPTs, rt overnight (80%); (c) EtNCO/py, rt (64%); (d) allyl bromide, KOH/DMSO, rt (93%); (e) i. BH_3−THF, rt 30 min, ii. H_2O_2/NaOH, 40 °C (42%); (f) DHP, PPTs, Cl_2CH_2, rt (80%); (g) EtNCO/py, rt (37%); (h) *m*-CPBA, Cl_2CH_2, rt (77%); (i) $LiAlH_4$, THF, rt 3 h (87%); (j) EtNCO/py, rt (30%).

Scheme 4[a]

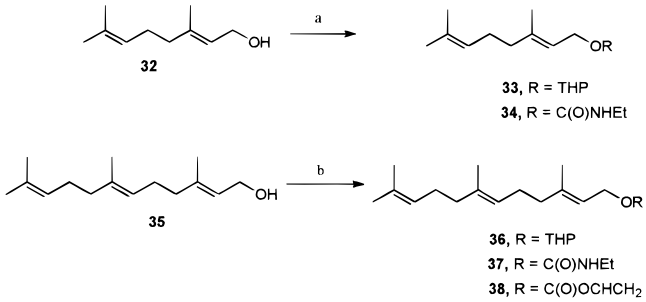


[a] Reagents: (a) $BrCH_2CH_2OTHP$, KOH/DMSO, rt (26%); (b) MeOH, PPTs, rt overnight (73%); (c) EtNCO/py, rt (98%); (d) allyl bromide, KOH/DMSO, rt (66%); (e) $LiAlH_4$, reflux (63%).

Compound **31** was easily formed from **27** by treatment with lithium aluminum hydride in tetrahydrofuran (Scheme 4).

Since one of our more potent drugs (compound **2**), which had been previously designed,[13] has an isoprenoid skeleton, it was decided to bond the selected polar groups to isoprenoid units. Therefore, geraniol (**32**) was transformed into its tetrahydropyranyl ether (**33**) and *N*-ethylcarbamate (**34**) derivatives by similar procedures as indicated above. Following the standard procedure derivatives of *trans*,*trans*-farnesol (**35**) were also prepared yielding tetrahydropyranyl, *N*-ethylcarbamate, and vinyl carbonate derivatives, compounds **36**−**38**, respectively (Scheme 5).

Scheme 5[a]



[a] Reagents: (a) DHP, Cl_2CH_2, PPTs, rt overnight (81% for **33**); EtNCO/py, rt (84% for **34**); (b) DHP, Cl_2CH_2, PPTs, rt overnight (97% for **36**); EtNCO/py, rt (99% for **37**); $ClC(O)OCH{=}CH_2$/py, rt (77% for **38**).

Drug Screening

T. 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

Table 1

compd	IC_{50} (μM)	compd	IC_{50} (μM)
1	138	**24**	>500
2	210	**25**	>350
8	270	**27**	268
9	142	**28**	>400
10	233	**29**	>300
13	260	**30**	129
14	>240	**31**	>500
16	218	**33**	68
17	>500	**34**	176
18	>300	**36**	78
19	209	**37**	147
21	>300	**38**	>500
22	>350		

(5, 10, 50, and 100 μg/mL), each one in quadruplicate. Drugs were dissolved in ethanol. A control without drug was done with each group that was tested.

To calculate percent inhibition, the following formula was used:

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

where ΔA_c and ΔA_d are the differences in the absorbance of control cultures and drug-treated cultures, respectively, at the beginning and 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 IC_{50} were estimated by linear and polynomial regression. The results are presented in Table 1.

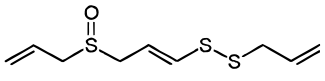
Results and Discussion

Compounds **1** and **2** were used as positive controls. Of the designed drugs, compounds **33** and **36** were shown to be potent inhibitors of *T. cruzi* replication. The geranyl derivative **33** was the most potent drug among the assayed compounds. At 210 μM complete growth arrest took place, and it even showed activity at concentrations as low as 42 μM (40% inhibition). Isoprenoid carbamate derivatives **34** and **37** were also very active inhibitors but to a lesser extent than tetrahydropyranyl ethers. In this case, contrary to what was observed for the isoprenoid tetrahydropyranyl ethers, the drug derived from farnesol (**37**) was slightly more potent than its analogue derived from geraniol (**34**). These four drugs are more active than the thiolcarbonate **2** which previously was the most potent isoprenoid derivative assayed against growth of *T. cruzi* cells.[13,14]

Careful analyses of the biological activity showed that tetrahydropyranyl ether derivatives also were more active than *N*-ethyl carbamates if compared with the same nonpolar residues. For example, the pairs of drugs **9** and **10**, **16** and **18**, **27** and **29** presented a moderate degree of activity favoring the tetrahydropyranyl ethers. The presence of a hydroxyl group at the C-2 position in compounds **9** and **10** resulted in a dramatic impairing of the biological activity compared with closely related structures in which this functionality was not present (compounds **3** and **4**). We have previously found that these latter compounds exhibited potent action as antitrypanostatic agents with an IC_{50} of 50 μM for both drugs[15] (Chart 1).

The use of vinylic carbonates as polar end group did not result in an increase in biological activity. For example, vinyl carbonate **13** was much less active than closely related carbonate derivatives: methyl, ethyl, and isobutyl carbonates bonded to the same nonpolar framework (4-phenoxyphenoxypropyl moiety).[15]

Chart 2. Ajoene, a Bioactive Compound Isolated from Garlic



39

Replacing the phenyl group by a methyl group did not result in a greater inhibitory action; in fact, the inhibition values decreased in such a way that the presence of the phenyl group seems to be important for the inhibitory effect. For example, compound **16** is only moderately active, while its analogue, compound **1**, that contains the 4-phenoxyphenoxy skeleton is a good growth inhibitor of the parasite. In addition, a similar behavior on the inhibition action was observed when the oxygen atom between the phenyl groups has been replaced by a carbonyl group which potentially contains a planar aromatic skeleton. In this case, the IC_{50} for compound **27** was almost 2 times the concentration required for compound **1**. Remarkably, when the allyl ether moiety was present in either framework, these drugs became potent antiproliferative agents (compounds **19** and **30**), although both of these drugs were not so active as the allylic ether derivative bearing the 4-phenoxyphenoxy moiety as nonpolar skeleton. This drug has potent action against *T. cruzi* proliferation and requires a concentration of around 50 μM to inhibit 50% of growth.[13,15] Moreover, substituted allyl ethers and propargyl ether derivatives structurally related to Fenoxycarb have previously been shown to possess good activity.[15]

It is worthy to point out the high inhibitory values shown when the allyl ether moiety was selected as the polar end of the drug. This group is often found among drugs that have potent biological action against proliferation of the epimastigote forms of *T. cruzi*. In addition, ajoene (**39**), a natural product isolated from garlic,[34] is a growth inhibitor of *T. cruzi* cells (epimastigotes)[35,36] and contains an allyl thioether moiety (Chart 2). The rest of the assayed compounds had small to vanishing inhibitory action.

As a result of the above observations, the allyl ether group seems to be a promising and attractive polar end group for the design of new compounds. Work aimed at exploiting the potential biological activity of allyl ethers bonded to an aromatic or isoprenoid skeleton is currently being pursued in our laboratory.

Experimental Section

Unless otherwise noted, chemicals were commercially available and used without further purification. Air and/or moisture sensitive reactions were carried out under a dry nitrogen atmosphere in flame-dried glassware. Solvents were distilled before use. Pyridine was distilled from calcium hydride and stored over KOH pellets; dimethyl sulfoxide was distilled from calcium hydride and stored over freshly activated 3 Å molecular sieves; ether and tetrahydrofuran were distilled from sodium benzophenone.

Nuclear magnetic resonance spectra were recorded using a Bruker AC-200 MHz spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. The ^{1}H-NMR spectra are referenced with respect to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at 7.26 ppm.

Coupling constants are reported in hertz. ^{13}C-NMR spectra were fully decoupled and are referenced to the middle peak of the solvent $CDCl_3$ at 77.0 ppm. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; br, broad.

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

Low-resolution mass spectra were obtained on a VG TRIO 2 instrument at 70 eV (direct inlet). Positive ion fast atom bombardment mass spectra (FABMS) were obtained on a VG ZAB BEqQ spectrometer at an accelerating voltage of 30 kV and a resolution of 2000. Thioglycerol was used as the sample matrix, and ionization was effected by a beam of cesium atoms.

Flash chromatography was run according to the Still protocol[37] 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-Plaskitkfolien, Kieselgel 60 F_{254}) and was visualized by 254 nm UV or immersion into an ethanolic solution of 5% H_2SO_4.

Preparative high-performance liquid chromatography was performed on a Micromeritics chromatograph with a solvent delivery system Model 750 and a variable wavelength detector Model 787 using a Beckmann Ultrasphere ODS-2 column (250 × 10 mm, 5 μm) at a flow rate of 3.0 mL/min. Solvents HPLC grade were employed.

Elemental analyses were performed by UMYMFOR (Facultad de Ciencias Exactas y Naturales, CONICET). The results were within ±0.4% of the theoretical values except where otherwise stated.

(±)-4-Phenoxyphenoxy 3-(1,2-Dihydroxypropyl) Ether (8). A solution of epoxide **7** (1.80 g, 6.9 mmol) in 160 mL of tetrahydrofuran−water (13:3) was treated with 70% $HClO_4$ (100 μL). The reaction mixture was stirred at room temperature for 48 h. The mixture was partitioned between a saturated aqueous solution of $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 70 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane−ethyl acetate (1:1) as eluent to afford 1.610 g (90% yield) of pure diol **8** as a white solid: R_f 0.20 (hexane−EtOAc, 1:1); mp 73−74 °C (water); IR (KBr, cm^{-1}) 3406, 2926, 2872, 1591, 1508, 1491, 1456, 1244, 1120, 1038, 874, 839, 771, 690; ^{1}H NMR ($CDCl_3$) δ 3.50−3.90 (m, 2 H, H-1), 4.01−4.20 (m, 3 H, H-2, H-3), 6.88−7.35 (m, 9 aromatic protons); ^{13}C NMR ($CDCl_3$) δ 63.7 (C-1), 69.7 (C-2), 70.5 (C-3), 115.7 (C-2″), 117.7 (C-2′), 120.7 (C-3′), 122.6 (C-4″), 129.6 (C-3″), 150.7 (C-1′), 154.7 (C-1), 158.2 (C-1″); MS (*m*/*z*, relative intensity) 260 (M$^+$, 68), 186 (100), 158 (17), 129 (23), 109 (22), 77 (68), 57 (26), 51 (51). Anal. ($C_{15}H_{16}O_4 \cdot {}^1/_3H_2O$) C, H.

(±)-2-Hydroxy-3-(4-phenoxyphenoxy)prop-1-yl Tetrahydro-2*H*-pyran-2-yl Ether (9). To a solution of diol **8** (182 mg, 0.7 mmol) in methylene chloride (20 mL) were added dihydropyran (1 mL) and PPTs (20 mg). The reaction mixture was stirred at room temperature overnight. The mixture was washed with water (3 × 20 mL) and dried, and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane−ethyl acetate (7:3) to afford 125 mg (52% yield) of a (1:1) diastereomeric mixture of compound **9** as a colorless oil. HPLC analysis revealed the presence of a single peak which corresponded to the terminal tetrahydropyranyl ether. A mixture of methanol−water (4:1) was used as eluent at a flow rate of 3.00 mL/min: R_f 0.61 (hexane−AcOEt, 1:1); IR (film, cm^{-1}) 3435, 3065, 3042, 2941, 2872, 1724, 1589, 1504, 1489, 1223, 1161, 1122, 1074, 1034, 906, 845, 750, 692, 511; ^{1}H NMR ($CDCl_3$) δ 1.50−1.85 (m, 6 H, H-3‴, H-4‴, H-5‴), 3.56−3.61 (m, 2 H, H-6‴), 3.71−4.14 (m, 5 H, H-1, H-2, H-3), 4.58−4.69 (m, 1 H, H-2‴), 6.87−7.35 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.8, 20.1 (C-4‴), 25.2, 25.7 (C-5‴), 30.7, 31.3 (C-3‴), 63.2, 63.4 (C-6‴), 68.4, 68.6 (C-1), 69.1 (C-2), 69.4 (C-3), 100.2 (C-2‴), 115.7 (C-2″), 117.7 (C-2′), 120.7 (C-3′), 122.5 (C-4″), 129.6 (C−C-3″), 150.5 (C-4′), 156.0 (C-1′), 158.4 (C-1″); MS (*m*/*z*, relative intensity) 344 (M$^+$, 6), 186 (43), 159 (9), 85 (100), 69 (25), 57 (31), 41 (48). Anal. ($C_{20}H_{24}O_5$) C, H.

(±)-2-Hydroxy-3-(4-phenoxyphenoxy)prop-1-yl Ethylcarbamate (10). Diol **8** (74 mg, 0.3 mmol) in pyridine (3 mL) was treated with ethyl isocyanate (0.1 mL) and 4-(dimethylamino)pyridine (10 mg). The reaction mixture was stirred for 3 h. The mixture was partitioned between methylene chloride (50 mL) and HCl 10% (50 mL). The organic phase was washed with 10% HCl (3 × 50 mL) and water (3 × 50 mL). Then, the organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using hexane−ethyl acetate (7:3) as eluent to give 37 mg (39% yield) of pure carbamate **10** as a white solid. HPLC analysis revealed the presence of a single isomer employing methanol−water (4:1) at a flow rate of 3.00 mL/min: R_f 0.47 (hexane−AcOEt, 2:3); mp 82−83 °C (MeOH−H_2O); IR (film, cm^{-1}) 3339, 3067, 2974, 2932, 1699, 1522, 1489, 1221, 1163, 1103, 1034, 872, 843, 798, 692, 511; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 7.2 Hz, 3 H, -NCH$_2$C*H*$_3$), 3.07 (s, 1 H, -O*H*), 3.25 (m, 2 H, -NC*H*$_2$CH$_3$), 4.02 (m, 2 H, H-3), 4.23 (m, 1 H, H-2), 4.31 (m, 2 H, H-1), 4.80 (s, 1 H, -N*H*), 6.88−7.35 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 15.3 (*Me*CH$_2$), 35.6 (MeCH$_2$NH), 63.2 (C-3), 69.7 (C-2), 70.3 (C-1), 115.2 (C-2″), 117.3 (C-2′), 120.5 (C-3′), 122.5 (C-4″), 129.7 (C-3″), 154.6 (C-4′), 158.4 (C-1″); MS (*m*/*z*, relative intensity) 331 (M$^+$, 26), 186 (36), 146 (100). Anal. ($C_{18}H_{21}O_5N$) C, H, N.

4-Phenoxyphenoxypropyl Ethenyl Carbonate (13). A solution of alcohol **11** (54 mg, 0.22 mmol) in pyridine (2 mL) in the presence of 4-(dimethylamino)pyridine (5 mg) was treated with vinyl chloroformate (0.1 mL). The mixture was stirred overnight. The reaction mixture was partitioned between methylene chloride (50 mL) and 10% HCl (50 mL). The organic phase was washed with 10% HCl (3 × 50 mL) and water (3 × 50 mL). The organic layers were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography eluting with hexane−ethyl acetate (9:1) to yield 47 mg (68% yield) of pure carbonate **13** as a colorless oil: R_f 0.50 (hexane−AcOEt, 4:1); IR (film, cm^{-1}) 3042, 2986, 2943, 2879, 1765, 1652, 1595, 1488, 1410, 1269, 1226, 1169, 1084, 1049, 942, 878, 701, 509; ^{1}H NMR ($CDCl_3$) δ 2.20 (q, J = 6.1 Hz, 2 H, H-2), 4.08 (t, J = 6.0 Hz, 2 H, H-1), 4.44 (t, J = 6.3 Hz, 2 H, H-3), 4.60 (dd, J = 6.2, 2.0 Hz, 1 H, H-2‴$_{cis}$), 4.94 (dd, J = 13.8, 2.0 Hz, 1 H, H-2‴$_{trans}$), 6.85−7.10 (m, 6 H, aromatic protons), 7.10 (dd, J = 13.8, 6.2 Hz, 1 H, H-1‴), 7.25−7.35 (m, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 31.6 (C-2), 64.4 (C-3), 65.4 (C-1), 97.7 (C-2‴), 115.6 (C-2″), 117.7 (C-2′), 120.8 (C-3′), 122.5 (C-4″), 129.6 (C-3″), 142.7 (C-1‴), 152.7 (C-4′), 155.0 (C-1′), 158.5 (C-1″); MS (*m*/*z*, relative intensity) 314 (M$^+$, 7), 227 (3), 199 (6), 185 (10), 129 (71), 85 (72), 41 (100). Anal. ($C_{18}H_{18}O_5$) C, H.

(±)-4-Phenoxyphenoxypropan-2-yl Ethenyl Carbonate (14). To alcohol **12** (78 mg, 0.3 mmol) in pyridine (3 mL) was added vinyl chloroformate (0.1 mL), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up as described for compound **13** and purified by column chromatography eluting with hexane−ethyl acetate (4:1) to afford 70 mg (69% yield) of pure compound **14** as a colorless oil: R_f 0.50 (hexane−AcOEt, 4:1); IR (film, cm^{-1}) 3094, 3043, 2986, 2937, 2876, 1767, 1647, 1589, 1504, 1492, 1396, 1356, 1263, 1220, 1088, 1045, 945, 845, 783, 697, 521; ^{1}H NMR ($CDCl_3$) δ 1.47 (d, J = 6.4 Hz, 3 H, H-3), 4.06 (m *AB*, 2 H, H-1), 4.61 (dd, J = 6.2, 1.9 Hz, 1 H, H-2‴$_{cis}$), 4.95 (dd, J = 13.9, 1.9 Hz, 1 H, H-2‴$_{trans}$), 5.20 (m, 1 H, H-2), 6.85−7.10 (m, 6 H, aromatic protons), 7.12 (dd, J = 13.9, 6.2 Hz, 1 H, H-1‴), 7.25−7.35 (m, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 16.5 (C-3), 70.4 (C-1), 73.7 (C-2), 97.9 (C-2‴), 115.8 (C-2″), 117.8 (C-2′), 120.7 (C-3′), 122.6 (C-4″), 129.6 (C-3″), 142.6 (C-1‴), 152.2 (C-4′), 154.7 (C-1′), 158.3 (C-1″); MS (*m*/*z*, relative intensity) 314 (M$^+$, 12), 227 (13), 185 (22), 129 (100), 59 (93). Anal. ($C_{18}H_{18}O_5$) C, H.

4-Methoxyphenoxyethyl Tetrahydro-2*H*-pyran-2-yl Ether (16). 4-Methoxyphenol (**15**) (1.110 g, 8.9 mmol) in dimethyl sulfoxide (10 mL) was treated with potassium hydroxide (36 mmol). The suspension was stirred for 5 min. Then, bromoethyl tetrahydropyranyl ether (3.730 g, 17.0 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 layer was extracted with methylene chloride (2 × 50 mL). The combined organic layers were washed with brine (5 × 100 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography eluting with hexane−ethyl acetate (7:3) to afford 1.532 g of compound **16** (68% yield) as a colorless oil: R_f 0.28 (hexane−AcOEt, 7:3); IR (film, cm^{-1}) 3057, 2943, 2872, 1587, 1510, 1460, 1354, 1290, 1247, 1134, 1084, 992, 935, 836, 744, 531; ^1H NMR ($CDCl_3$) δ 1.50−1.90 (m, 6 H, H-3″, H-4″, H-5″), 3.52 (m, 1 H, H-6″a), 3.75 (s, 3 H, OC*Me*), 3.76−4.20 (m, 5 H, H-1, H-2, H-6″b), 4.70 (distorted t, J = 3.2 Hz, 1 H, H-2″), 6.84 (m *AB*, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.1 (C-4″), 25.2 (C-3″), 30.3 (C-5″), 55.3 (OCH_3), 61.8 (C-1), 65.7 (C-2″), 67.9 (C-2), 98.6 (C-6″), 114.3 (C-3′), 115.5 (C-2′), 152.8 (C-1′), 153.7 (C-4′); MS (*m*/*z*, relative intensity) 252 (M^+, 24), 129 (88), 109 (20), 85 (100), 73 (75). Anal. ($C_{14}H_{20}O_4$) C, H.

4-Methoxyphenoxyethanol (17). To a solution of compound **16** (145 mg, 0.57 mmol) in methanol (5 mL) was added PPTs (10 mg), and the reaction mixture was stirred for 48 h at room temperature. The mixture was partitioned between methylene chloride (50 mL) and water (50 mL). The aqueous layer was extracted with water (2 × 50 mL), and the combined organic layers were washed with brine (3 × 70 mL), dried, and evaporated. The residue was purified by column chromatography (silica gel) employing hexane−ethyl acetate (7:3) as eluent to yield 77 mg of pure alcohol **17** (80% yield) as a white solid: R_f 0.35 (hexane−AcOEt, 1:1); mp 68−69 °C (H_2O); IR (KBr, cm^{-1}) 3302, 2955, 2390, 2870, 2837, 1890, 1869, 1637, 1512, 1443, 1398, 1294, 1244, 1178, 1053, 932, 827, 729, 689, 532; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3 H, OC*Me*), 3.93 (m, 2 H, H-1), 4.01 (m, 2 H, H-2), 6.84 (m *AB*, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 55.7 (OCH_3), 61.5 (C-1), 70.0 (C-2), 114.7 (C-3′), 115.6 (C-2′), 152.8 (C-1′), 154.1 (C-4′); MS (*m*/*z*, relative intensity) 168 (M^+, 66), 124 (94), 109 (100), 81 (39). Anal. ($C_9H_{12}O_3$) C, H.

2-(4-Methoxyphenoxy)ethyl Ethylcarbamate (18). Alcohol **17** (74 mg, 0.44 mmol) in pyridine (3 mL) was treated with ethyl isocyanate (0.1 mL) in the presence of 4-(dimethylamino)pyridine. The reaction mixture was worked up as described for compound **10** and the residue purified by column chromatography eluting with hexane−ethyl acetate (3:2) to afford 66 mg of carbamate **18** as a white solid: R_f 0.47 (hexane−AcOEt, 1:1); mp 86−87 °C (H_2O); IR (KBr, cm^{-1}) 3337, 3053, 2978, 2935, 1690, 1537, 1508, 1460, 1356, 1294, 1261, 1178, 1076, 1034, 825, 733, 646, 521; ^1H NMR ($CDCl_3$) δ 1.14 (t, J = 7.3 Hz, 3 H, -NCH_2CH_3), 3.23 (m, 2 H, -NCH_2-CH_3), 3.77 (s, 3 H, OC*Me*), 4.11 (m, 2 H, H-2), 4.39 (m, 2 H, H-1), 4.74 (s, 1 H, N*H*), 6.84 (m *AB*, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 15.1 (*Me*CH_2NH), 35.9 (MeCH_2NH), 55.7 (OCH_3), 63.2 (C-1), 67.2 (C-2), 114.7 (C-3′), 115.7 (C-2′), 152.7 (C-1′), 154.1 (C-4′), 156.2 (C═O); MS (*m*/*z*, relative intensity) 239 (M^+, 5), 151 (4), 124 (12), 116 (100), 72 (66), 44 (70). Anal. ($C_{12}H_{17}O_4N$) C, H, N.

4-Methoxyphenyl Prop-2-en-1-yl Ether (19). 4-Methoxyphenol (3.332 g, 2.7 mmol) in dimethyl sulfoxide (10 mL) was treated with potassium hydroxide (10 mmol), and the mixture was stirred for 5 min. Then, allyl bromide (3.8 mL, 4.3 mmol) was added, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was worked up as depicted for compound **16**. The residue was purified by column chromatography employing hexane−ethyl acetate (19:1) as eluent to obtain 4.071 g of pure ether **19** (93% yield) as a colorless oil: R_f 0.83 (hexane−AcOEt, 7:3); IR (film, cm^{-1}) 3080, 2997, 2951, 2908, 2833, 1508, 1464, 1231, 1107, 1039, 928, 754, 523; ^1H NMR ($CDCl_3$) δ 3.77 (s, 3 H, OC*Me*), 4.49 (dt, J = 5.3, 1.5 Hz, 2 H, H-1), 5.28 (dq, J = 10.5, 1.5 Hz, 1 H, H-$3_{cis\ to\ 2}$), 5.40 (dq, J = 17.3, 1.6 Hz, 1 H, H-$3_{trans\ to\ 2}$), 6.06 (ddt, J = 17.2, 10.5, 5.3 Hz, 1 H, H-2), 6.85 (m A_2B_2, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 55.7 (OCH_3), 69.5 (C-1), 114.6 (C-3′), 115.7 (C-2′), 117.3 (C-3), 133.6 (C-2), 152.7 (C-1′), 153.9 (C-4′); MS (*m*/*z*, relative intensity) 164 (M^+, 29), 123 (100), 95 (44), 69 (34), 41 (81). Anal. ($C_{10}H_{12}O_2$) C, H.

3-(4-Methoxyphenyl)propanol (20). To a solution of **19** (423 mg, 2.6 mmol) in anhydrous tetrahydrofuran (5 mL) cooled to 0 °C under a nitrogen atmosphere was added dropwise 0.85 M diborane in tetrahydrofuran (1.5 mL), and the mixture was stirred at room temperature for 1 h. The excess of the reagent was decomposed by careful addition of water. The reaction mixture was warmed to 50 °C, and NaOH 1.0 M (2.0 mL) was added followed by slow addition of a 30% solution of hydrogen peroxide (0.32 mL). The mixture was stirred for 1 h at room temperature. Solid K_2CO_3 (2 g) was added and the organic layer separated. The aqueous phase was extracted with methylene chloride (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography employing hexane−EtOAc (4:1) as eluent to give 199 mg (42% yield) of alcohol **20** as a white solid: R_f 0.34 (hexane−AcOEt, 1:1); mp 65−66 °C (H_2O); IR (KBr, cm^{-1}) 3277, 2953, 2934, 2837, 2870, 1682, 1512, 1471, 1392, 1292, 1244, 1115, 1061, 1034, 947; ^1H NMR ($CDCl_3$) δ 1.86 (s, 1 H, O*H*), 2.03 (p, J = 5.9 Hz, 2 H, H-2), 3.77 (s, 3 H, OC*Me*), 3.86 (t, J = 5.8 Hz, 2 H, H-1), 4.08 (t, J = 5.9 Hz, 2 H, H-3), 6.84 (m A_2B_2, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 32.1 (C-2), 55.7 (OCH_3), 60.5 (C-1), 66.5 (C-3), 114.7 (C-3′), 115.5 (C-2′), 152.9 (C-1′), 153.9 (C-4′); MS (*m*/*z*, relative intensity) 182 (M^+, 48), 124 (100), 109 (79). Anal. ($C_{10}H_{14}O_3$) C, H.

4-Methoxyphenylpropyl Tetrahydro-2*H*-pyran-2-yl Ether (21). Alcohol **20** (60 mg, 0.33 mmol) was treated with DHP according to the protocol depicted for **8**. The product was purified by column chromatography (silica gel) eluting with hexane−EtOAc (4:1) to afford 70 mg (80% yield) of pure tetrahydropyranyl ether derivative **21** as a colorless oil: R_f 0.64 (hexane−AcOEt, 7:3); IR (film, cm^{-1}) 3054, 2947, 1591, 1509, 1468, 1387, 1352, 1288, 1234, 1182, 1138, 1122, 1066, 1036, 985, 868, 825, 741, 523; ^1H NMR ($CDCl_3$) δ 1.45−1.95 (m, 6 H, H-3″, H-4″, H-5″), 2.05 (p, J = 6.3 Hz, 2 H, H-2), 3.43−3.98 (m, 4 H, H-1, H-6″), 3.76 (s, 3 H, OC*Me*), 4.02 (t, J = 6.3 Hz, 2 H, H-3), 4.59 (dd, J = 4.0, 2.7 Hz, 1 H, H-2″), 6.83 (m *AB*, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.5 (C-4″), 25.4 (C-5″), 29.8 (C-2), 30.7 (C-3″), 55.7 (OCH_3), 62.2 (C-6″), 64.0 (C-1), 65.6 (C-3), 98.9 (C-2″), 114.6 (C-3′), 115.5 (C-2′), 151.2 (C-1′), 153.7 (C-4′); MS (*m*/*z*, relative intensity) 266 (M^+, 23), 165 (8), 143 (76), 124 (80), 109 (33), 95 (11), 85 (100). Anal. ($C_{15}H_{22}O_4$) C, H.

3-(4-Methoxyphenoxy)propyl Ethylcarbamate (22). A solution of compound **20** (68 mg, 0.38 mmol) in pyridine (3 mL) was treated with ethyl isocyanate (0.1 mL) and 4-(dimethylamino)pyridine (10 mg), and the mixture was stirred at room temperature overnight. The reaction mixture was worked up as depicted for compound **10**. The residue was purified by column chromatography eluting with hexane−EtOAc (4:1) to give 35 mg (37% yield) of pure **22** as a white solid: R_f 0.41 (hexane−AcOEt, 1:1); mp 63−64 °C (H_2O); IR (KBr, cm^{-1}) 3344, 2976, 2961, 2930, 2870, 2833, 1681, 1537, 1510, 1468, 1437, 1387, 1358, 1293, 1259, 1225, 1117, 1065, 1034, 947, 831, 723, 638, 530; ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.2 Hz, 3 H, -NCH_2CH_3), 2.07 (p, J = 6.3 Hz, 2 H, H-2), 3.20 (m, 2 H, -NCH_2CH_3), 3.76 (s, 3 H, OC*Me*), 3.98 (t, J = 6.2 Hz, 2 H, H-3), 4.24 (t, J = 6.3 Hz, 2 H, H-1), 4.64 (s, 1 H, N*H*), 6.83 (m *AB*, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 15.3 (*Me*CH_2NH), 29.2 (C-2), 35.8 (MeCH_2NH), 55.7 (OCH_3), 61.6 (C-1), 65.2 (C-3), 114.7 (C-3′), 115.5 (C-2′), 153.0 (C-1′), 153.9 (C-4′); MS (*m*/*z*, relative intensity) 253 (M^+, 12), 182 (11), 165 (5), 149 (10), 130 (100), 124 (66), 109 (75). Anal. ($C_{13}H_{19}O_4N$) C, H, N.

(±)-Oxiranylmethyl 4-Methoxyphenyl Ether (23). To a solution of allyl ether **19** (564 mg, 3.4 mmol) in methylene chloride (20 mL) was added 80% 3-(chloroperoxy)benzoic acid (710 mg) in methylene chloride (10 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The organic layer was washed with a saturated solution of $NaHCO_3$ (2 × 30 mL) and water (2 × 30 mL), dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography employing hexane−EtOAc (9:1) as eluent to afford 471 mg (77% yield) of pure epoxide **23** as a colorless oil: R_f 0.52 (hexane−AcOEt, 7:3); ^1H NMR ($CDCl_3$) δ 2.74 (dd, J = 4.9, 2.7 Hz, 1 H, H-3a), 2.89 (distorted t, J = 4.5 Hz, 1 H, H-3b), 3.33 (m, 1 H, H-2), 3.77 (s, 3 H, OC*Me*), 3.92 (dd, J = 11.1, 5.6 Hz, 1 H, H-1a), 4.17 (dd, J = 11.1, 3.3 Hz, 1 H, H-1b), 6.85 (m

AB, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 44.7 (C-3), 50.2 (C-2), 55.7 (O*C*H$_3$), 69.6 (C-1), 114.7 (C-3′), 115.8 (C-2′), 152.7 (C-1′), 154.3 (C-4′); MS (*m*/*z*, relative intensity) 180 (M$^+$, 51), 124 (100), 109 (92), 95 (42).

(±)-1-(4-Methoxyphenoxy)propan-2-ol (24). To a 1.0 M solution of $LiAlH_4$ in tetrahydrofuran (20 mL) was added dropwise epoxide **23** (378 mg, 2.1 mmol) in anhydrous tetrahydrofuran (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 5 h at room temperature. The reaction was quenched by addition of ethyl acetate (1.0 mL), and the mixture was partitioned between a saturated solution of sodium potassium tartrate (100 mL) and methylene chloride (100 mL). The aqueous phase was extracted with methylene choride (2 × 50 mL). The combined organic layers were washed with the tartrate solution (2 × 100 mL) and water (2 × 70 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography eluting with hexane−AcOEt (9:1) to afford 332 mg (87% yield) of pure alcohol **24** as a white solid: R_f 0.43 (hexane−AcOEt, 7:3); mp 62−63 °C (H_2O); IR (KBr, cm^{-1}) 3412, 2924, 2835, 1869, 1637, 1514, 1456, 1369, 1337, 1292, 1242, 1178, 1161, 1111, 1084, 1043, 866, 744, 532; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 6.5 Hz, 3 H, H-3), 2.38 (s, 1 H, -O*H*), 3.74 (dd, J = 9.3, 7.7 Hz, 1 H, H-1a), 3.77 (s, 3 H, OC*Me*), 3.90 (dd, J = 9.3, 3.2 Hz, 1 H, H-1b), 4.17 (m, 1 H, H-2), 6.83 (m *AB*, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 18.7 (C-3), 55.7 (O*C*H$_3$), 66.3 (C-1), 74.2 (C-2), 114.7 (C-3′), 115.6 (C-2′), 152.8 (C-1′), 154.1 (C-4′); MS (*m*/*z*, relative intensity) 182 (M$^+$, 42), 137 (3), 124 (100), 109 (75). Anal. ($C_{10}H_{14}O_3$) C, H.

(±)-1-(4-Methoxyphenoxy)propan-2-yl Ethylcarbamate (25). A solution of alcohol **24** (80 mg, 0.44 mmol) in pyridine (3 mL) was treated with ethyl isocyanate (0.1 mL) and 4-(dimethylamino)pyridine (10 mg), and the mixture was stirred at room temperature overnight. The reaction mixture was worked up as described for compound **10**. The residue was purified by column chromatography eluting with hexane−EtOAc (4:1) to give 33 mg (30% yield) of pure **25** as a white solid: R_f 0.54 (hexane−AcOEt, 7:3); mp 44−45 °C (H_2O); IR (KBr, cm^{-1}) 3342, 2978, 2935, 2876, 2876, 1703, 1508, 1460, 1230, 1086, 1045, 997, 825, 746; ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.2 Hz, 3 H, -NCH$_2$C*H*$_3$), 1.34 (d, J = 6.5 Hz, 3 H, H-3), 3.20 (m, 2 H, -NC*H*$_2$CH$_3$), 3.76 (s, 3 H, OC*Me*), 3.94 (dd, J = 5.3, 1.5 Hz, 2 H, H-1), 4.24 (t, J = 6.3 Hz, 2 H, H-1), 4.65 (s, 1 H, N*H*), 5.12 (m, 1 H, H-2), 6.83 (m *AB*, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 15.2 (*Me*CH$_2$NH), 17.0 (C-3), 35.4 (MeCH$_2$-NH), 55.7 (O*C*H$_3$), 69.2 (C-1), 71.2 (C-2), 114.7 (C-3′), 115.8 (C-2′), 153.0 (C-1′), 154.1 (C-4′); MS (*m*/*z*, relative intensity) 253 (M$^+$, 16), 182 (8), 165 (12), 137 (5), 130 (100), 109 (34). Anal. ($C_{13}H_{19}O_4N$) C, H, N.

2-(4-Benzoylphenoxy)ethyl Tetrahydro-2*H*-pyran-2-yl Ether (27). 4-Benzoylphenol (**26**) (1.420 g, 7.2 mmol) in dimethyl sulfoxide (10 mL) was treated with potassium hydroxide (28 mmol). The suspension was stirred for 5 min. Then, bromoethyl tetrahydropyranyl ether (3.160 g, 14.4 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The mixture was treated as described for compound **16**. The residue was purified by column chromatography eluting with hexane−ethyl acetate (7:3) to obtain 587 mg (26% yield) of compound **27** as a colorless oil: R_f 0.51 (hexane−AcOEt, 3:2); IR (film, cm^{-1}) 3061, 2943, 2872, 1733, 1655, 1601, 1508, 1446, 1419, 1256, 1078, 1034, 743, 700, 638, 627; ^{1}H NMR ($CDCl_3$) δ 1.51−1.82 (m, 6 H, H-3‴, H-4‴, H-5‴), 3.56 (m, 1 H, H-6‴a), 3.75−4.05 (m, 3 H, H-1, H-6‴b), 4.25 (m, 2 H, H-2), 4.71 (t, J = 3.3 Hz, 1 H, H-2‴), 6.98−7.84 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.3 (C-4‴), 25.3 (C-5‴), 30.4 (C-3‴), 62.1 (C-6‴), 65.6 (C-1), 67.6 (C-2), 99.0 (C-2‴), 114.1 (C-2′), 128.1 (C-3″), 129.6 (C-2″), 130.2 (C-3′), 131.8 (C-4′), 132.4 (C-4″), 138.2 (C-1″), 162.5 (C-1′), 195.4 (C═O); MS (*m*/*z*, relative intensity) 326 (M$^+$, 67), 242 (11), 198 (12), 121 (25), 105 (33), 85 (100). Anal. ($C_{20}H_{22}O_4$) C, H.

4-Benzoylphenoxyethanol (28). Compound **27** (316 mg, 1.0 mmol) dissolved in methanol (20 mL) was treated with pyridinium *p*-toluenesulfonate (20 mg) following the procedure for compound **17**. Purification by flash chromatography eluting with hexane−EtOAc (3:3) afforded 172 mg (73% yield) of pure alcohol **28** as a white solid: R_f 0.22 (hexane−AcOEt, 3:2); mp 84−85 °C; IR (film, cm^{-1}) 3275, 2951, 2930, 2878, 1639, 1603, 1576, 1504, 1445, 1418, 1379, 1308, 1290, 1256, 1176, 1149, 1094, 1053, 922, 797, 739, 692, 636, 511; ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 1 H, -O*H*), 4.00 (m, 2 H, H-1), 4.17 (distorted t, J = 4.5 Hz, 2 H, H-2), 6.95−7.86 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 61.1 (C-1), 69.4 (C-2), 114.1 (C-2′), 128.1 (C-3″), 129.6 (C-2″), 130.3 (C-3′), 131.9 (C-4′), 132.5 (C-4″), 138.1 (C-1″), 162.3 (C-1′), 195.5 (C═O); MS (*m*/*z*, relative intensity) 242 (M$^+$, 43), 198 (11), 121 (100), 105 (48). Anal. ($C_{14}H_{14}O_3$) C, H.

2-(4-Benzoylphenoxy)ethyl Ethylcarbamate (29). A solution of alcohol **28** (77 mg, 0.32 mmol) in pyridine (3 mL) was treated with ethyl isocyanate (0.1 mL) and 4-(dimethylamino)pyridine (10 mg), and the mixture was stirred at room temperature overnight. The reaction mixture was worked up as described for **10**. The residue was purified by column chromatography eluting with hexane−EtOAc (3:2) to yield 98 mg (98% yield) of pure **29** as a white solid: R_f 0.34 (hexane−AcOEt, 3:2); mp 89−90 °C (H_2O); IR (KBr, cm^{-1}) 3342, 3065, 2976, 2937, 2878, 1705, 1647, 1603, 1541, 1446, 1250, 1148, 999, 918, 847, 791, 708, 638, 625; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.3 Hz, 3 H, -NCH$_2$C*H*$_3$), 3.24 (m, 2 H, -NC*H*$_2$CH$_3$), 4.24 (distorted t, J = 5.0 Hz, 2 H, H-2), 4.46 (distorted t, J = 4.3 Hz, 2 H, H-1), 4.72 (s, 1 H, N*H*), 6.96−7.85 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 15.1 (*Me*CH$_2$NH), 35.8 (MeCH$_2$-NH), 62.7 (C-1), 66.6 (C-2), 114.0 (C-2′), 128.1 (C-3″), 129.6 (C-2″), 130.4 (C-3′), 131.8 (C-4′), 132.4 (C-4″), 138.1 (C-1″), 162.1 (C-1′), 195.4 (C═O); MS (*m*/*z*, relative intensity) 313 (M$^+$, 1), 147 (9), 116 (100). Anal. ($C_{18}H_{19}O_4N$) C, H.

4-Benzoylphenyl Prop-2-en-1-yl Ether (30). Compound **30** was obtained as described for **19** from 4-benzoylphenol (**26**) (2.116 g, 10 mmol). After the usual workup the residue was purified by column chromatography (silica gel) eluting with hexane−ethyl acetate (9:1) to obtain 1.587 g of pure ether **30** (66% yield) as a white solid: R_f 0.47 (hexane−AcOEt, 4:1); mp 77−78 °C; IR (KBr, cm^{-1}) 3080, 3059, 3022, 2939, 2868, 1639, 1603, 1574, 1506, 1445, 1418, 1364, 1306, 1284, 1252, 1175, 1148, 1364, 1306, 1284, 1252, 1175, 1148, 1113, 1076, 1011, 935, 920, 849, 795, 744, 700, 640, 600; ^{1}H NMR ($CDCl_3$) δ 4.63 (ddd, J = 5.2, 1.5, 1.3 Hz, 2 H, H-1), 5.33 (ddt, J = 17.2, 1.5, 1.2, 1.5 Hz, 1 H, H-3$_{trans\ to\ 2}$), 5.44 (ddt, J = 10.4, 1.4, 1.2 Hz, 1 H, H-3$_{cis\ to\ 2}$), 6.07 (ddt, J = 17.2, 10.4, 5.2 Hz, 1 H, H-2), 6.94−7.86 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 68.9 (C-1), 114.2 (C-3), 118.1 (C-2′), 128.1 (C-3″), 129.6 (C-2″), 130.2 (C-3′), 131.8 (C-4′), 132.4 (C-2, C-4″), 138.2 (C-1″), 162.2 (C-1′), 195.4 (C═O); MS (*m*/*z*, relative intensity) 238 (M$^+$, 44), 197 (18), 161 (44), 141 (21), 105 (59), 77 (68), 41 (100). Anal. ($C_{16}H_{14}O_2$) C, H.

2-[4-(α-Hydroxy-α-phenylmethyl)phenoxy]ethyl Tetrahydro-2*H*-pyran-2-yl Ether (31). To a 1.0 M solution of $LiAlH_4$ in tetrahydrofuran (30 mL) was added dropwise compound **27** (772 g, 2.4 mmol) in anhydrous tetrahydrofuran (10 mL) under a nitrogen atmosphere. The reaction mixture was refluxed for 7 h. The mixture was allowed to cooled to room temperature, and the reaction was quenched as described for **24**. The residue was purified by flash chromatography eluting with hexane−EtOAc (7:3) to give 510 mg (63% yield) of pure **31** as a colorless oil: R_f 0.48 (hexane−AcOEt, 3:2); IR (film, cm^{-1}) 3427, 3061, 3030, 2941, 2872, 1653, 1610, 1601, 1510, 1454, 1418, 1387, 1352, 1250, 1202, 1173, 1139, 1124, 1080, 1034, 987, 924, 872, 812, 742, 700, 627; ^{1}H NMR ($CDCl_3$) δ 1.51−1.78 (m, 6 H, H-3‴, H-4‴, H-5‴), 2.38 (s, 1H, O*H*), 3.54 (m, 1 H, H-6‴a), 3.76−4.16 (m, 5 H, H-1, H-2, H-6‴b), 4.25 (m, 2 H, H-2), 4.69 (t, J = 3.3 Hz, 1 H, H-2‴), 5.79 (s, 1 H, PhC*H*(OH)), 6.86−7.39 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.1 (C-4‴), 25.3 (C-5‴), 30.3 (C-3‴), 62.0 (C-6‴), 65.7 (C-1), 67.3 (C-2), 75.5 (Ph*C*OH), 98.8 (C-2‴), 114.5 (C-2′), 126.3 (C-4″), 127.2 (C-2″), 127.7 (C-3′), 128.2 (C-3″), 136.4 (C-4′), 144.1 (C-1″), 158.2 (C-1′); MS (*m*/*z*, relative intensity) 328 (M$^+$, 5), 182 (3), 129 (25), 105 (8), 85 (100). Anal. ($C_{20}H_{24}O_4$) C, H.

(±)-3,7-Dimethylocta-2,6-dien-1-yl Tetrahydro-2*H*-pyran-2-yl Ether (33). A solution of geraniol (**32**) (131 mg, 0.85 mmol) in methylene chloride (30 mL) was treated with dihydropyran (0.1 mL) as described for **9**. Purification by flash

chromatography employing hexane−EtOAc (19:1) as eluent afforded 163 mg (81% yield) of pure **33** as a colorless oil: R_f 0.55 (hexane−AcOEt, 9:1); IR (film, cm^{-1}) 2926, 2872, 1464, 1377, 1261, 1117, 1076, 1024, 906, 869, 816; ^1H NMR ($CDCl_3$) δ 1.60 (s, 3 H, Me at C-7), 1.68 (s, 6 H, Me at C-3, H-8), 1.42−1.80 (m, 6 H, H-3′, H-4′, H-5′), 2.00−2.20 (m, 4 H, H-4, H-5), 3.51 (m, 1 H, H-6′a), 3.89 (m, 1 H, H-6′b), 4.03 (dd, J = 11.9, 7.5 Hz, 1 H, H-1a), 4.23 (dd, J = 11.9, 6.3 Hz, 1 H, H-1b), 4.63 (t, J = 3.3 Hz, 1 H, H-2′), 5.09 (m, 1 H, H-6), 5.36 (m, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 16.3 (Me at C-3), 17.6 (Me at C-7), 19.6 (C-4′), 25.5 (C-5, C-5′), 26.3 (C-8), 30.7 (C-3′), 39.6 (C-4), 62.2 (C-6′), 63.6 (C-1), 97.7 (C-2′), 120.6 (C-2), 124.0 (C-6), 131.5 (C-7), 140.1 (C-3); MS (m/z, relative intensity) 238 (M^+, 1), 137 (19), 85 (100), 69 (75). Anal. ($C_{15}H_{26}O_2$) C, H.

3,7-Dimethylocta-2,6-dien-1-yl Ethylcarbamate (34). A solution geraniol (128 mg, 0.32 mmol) in pyridine (3.0 mL) was treated as described for **10**. The residue was purified by column chromatography eluting with hexane−EtOAc (19:1) to give 158 mg (84% yield) of pure **34** as a colorless oil: R_f 0.43 (hexane−AcOEt, 4:1); IR (film, cm^{-1}) 3333, 2971, 2922, 1694, 1531, 1460, 1382, 1262, 1141, 1020,907, 779; ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 3 H, -NCH_2CH_3), 1.58 (s, 3 H, Me at C-7), 1.66 (s, 3 H, H-8), 1.68 (s, 3 H, Me at C-3), 1.95−2.15 (m, 4 H, H-4, H-5), 3.19 (dt, J = 7.1, 6.0 Hz, 2 H, -NCH_2CH_3), 4.56 (d, J = 7.0 Hz, 2 H, H-1), 5.06 (m, 1 H, H-6), 5.32 (t, J = 7.0 Hz, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 15.2 ($MeCH_2NH$), 16.4 (Me at C-3), 17.6 (Me at C-7), 25.6 (C-5), 26.3 (C-8), 35.9 ($MeCH_2$-NH), 39.5 (C-4), 61.5 (C-1), 119.0 (C-2), 123.8 (C-6) 131.7 (C-7), 141.5 (C-3), 156.6 (C═O); MS (m/z, relative intensity) 225 (M^+, 1), 161 (7), 137 (100) 121 (29). Anal. ($C_{13}H_{23}O_2N$) C, H, N.

(±)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl Tetrahydro-2*H*-pyran-2-yl Ether (36). The procedure for the preparation of **9** was followed, using *trans*,*trans*-farnesol (**35**) (134 mg, 6.0 mmol) and dihydropyran (0.1 mL) in methylene chloride (20 mL). Purification by flash chromatography eluting with hexane−EtOAc (19:1) yielded 176 mg (97% yield) of pure compound **36** as a colorless oil: R_f 0.50 (hexane−AcOEt, 4:1); IR (film, cm^{-1}) 2939, 2872, 1681, 1452, 1383, 1200, 1024, 870, 826; ^1H NMR ($CDCl_3$) δ 1.42−1.80 (m, 6 H, H-3′, H-4′, H-5′), 1.56 (s, 6 H, Me at C-7, Me at C-11), 1.66 (s, 6 H, H-12, Me at C-3), 1.90−2.20 (m, 8 H, H-4, H-5, H-8, H-9), 3.51 (m, 1 H, H-6′a), 3.87 (m, 1 H, H-6′b), 4.00 (dd, J = 11.8, 7.4 Hz, 1 H, H-1a), 4.21 (dd, J = 11.8, 6.3 Hz, 1 H, H-1b), 4.61 (distorted t, 1 H, H-2′), 5.09 (m, 2 H, H-6, H-10), 5.34 (t, J = 7.0 Hz, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 15.9 (Me at C-3), 16.3 (Me at C-7), 17.6 (Me at C-11), 19.6 (C-4′), 25.5 (C-9, C-5′), 26.3 (C-5)*, 26.7 (C-8)*, 30.7 (C-3′), 39.6 (C-4), 39.6 (C-8), 62.1 (C-6′)*, 63.6 (C-1)*, 99.7 (C-2′), 120.7 (C-2), 123.9 (C-10), 124.3 (C-6), 131.1 (C-11), 135.1 (C-7), 140.0 (C-3); FABMS (m/z, relative intensity) 306 (M^+, 45), 305 (100). Anal. ($C_{20}H_{34}O_2$) C, H.

3,7,11-Trimethyldodeca-2,6,10-trien-1-yl Ethylcarbamate (37). The procedure for the synthesis of **10** was followed, employing farnesol (172 mg, 0.77 mmol), ethyl isocyanate (0.1 mL), and 4-(dimethylamino)pyridine (10 mg) in pyridine (3 mL). Purification by column chromatography eluting with hexane−EtOAc (9:1) afforded 227 mg (99% yield) of pure **37** as a colorless oil: R_f 0.38 (hexane−AcOEt, 4:1); IR (film, cm^{-1}) 3355, 2978, 2936, 2865, 1694, 1531, 1389, 1262, 1148, 1084, 786; ^1H NMR ($CDCl_3$) δ 1.12 (t, J = 7.2 Hz, 3 H, -NCH_2CH_3), 1.59 (s, 6 H, Me at C-7, Me at C-11), 1.67 (s, 3 H, H-12), 1.70 (s, 3 H, Me at C-3), 1.90−2.15 (m, 8 H, H-4, H-5, H-8, H-9), 3.20 (q, J = 7.1 Hz, 2 H, -NCH_2CH_3), 4.57 (d, J = 7.0 Hz, 2 H, H-1), 5.09 (m, 2 H, H-6), 5.33 (t, J = 7.0 Hz, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 15.2 ($MeCH_2NH$), 15.9 (Me at C-3), 16.3 (Me at C-7), 17.5 (Me at C-11), 25.5 (C-9), 26.1 (C-5), 26.7 (C-8), 35.8 ($MeCH_2NH$), 39.5 (C-4), 39.6 (C-8), 61.5 (C-1), 119.0 (C-2), 123.6 (C-10), 124.3 (C-6), 131.1 (C-11), 135.3 (C-7), 141.4 (C-3), 156.5 (C═O); MS (m/z, relative intensity) 293 (M^+, 5), 221 (46), 204 (20), 177 (54), 162 (100), 147 (81), 138 (78). Anal. ($C_{18}H_{31}O_2N$) C, H.

3,7,11-Trimethyldodeca-2,6,10-trien-1-yl Ethenyl Carbonate (38). The procedure for the preparation of **13** was followed, employing farnesol (172 mg, 0.77 mmol) and vinyl chloroformate (0.1 mL) in pyridine (3.0 mL). Purification by flash chromatography eluting with hexane−EtOAc (49:1) afforded 175 mg (77% yield) of pure carbonate **38** as a colorless oil: R_f 0.40 (hexane−AcOEt, 19:1); IR (film, cm^{-1}) 2966, 2924, 2856, 1761, 1664, 1456, 1387, 1244, 1157, 945, 920, 899, 783; ^1H NMR ($CDCl_3$) δ 1.60 (s, 6 H, Me at C-7, Me at C-11), 1.68 (s, 3 H, H-12), 1.74 (s, 3 H, Me at C-3), 1.90−2.15 (m, 8 H, H-4, H-5, H-8, H-9), 4.55 (dd, J = 6.2, 1.3 Hz, 1 H, $H\text{-}2'_{\text{cis to H-1'}}$), 4.71 (d, J = 7.2 Hz, 2 H, H-1), 4.90 (d, J = 13.8 Hz, 1 H, $H\text{-}2'_{\text{trans to H-1'}}$), 5.09 (m, 2 H, H-6, H-10), 5.40 (t, J = 7.1 Hz, 1 H, H-1′), 7.08 (dd, J = 13.8, 6.1 Hz, 1 H, H-1′); ^{13}C NMR ($CDCl_3$) δ 16.0 (Me at C-3), 16.5 (Me at C-7), 17.6 (Me at C-11), 25.6 (C-9), 26.1 (C-5), 26.7 (C-8), 39.5 (C-4), 39.7 (C-8), 65.2 (C-1), 97.5 (C-2′), 117.2 (C-2), 123.5 (C-10), 124.3 (C-6), 131.3 (C-11), 135.6 (C-7), 142.7 (C-3), 144.0 (C-1′), 156.5 (C═O); MS (m/z, relative intensity) 292 (M^+, 5), 204 (8), 189 (11), 161 (13), 147 (12), 136 (69), 121 (46), 93 (54), 81 (100). Anal. ($C_{18}H_{28}O_3$) C, H.

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Supporting Information Available: Table of data needed to calculate percent inhibition (5 pages). Ordering information is given on any current masthead page.

References

(1) Kirchhoff, L. V. American Trypanosomiasis (Chagas' Disease)-A Tropical Disease now in the United States. *N. Engl. J. Med.* **1993**, *329*, 639−644.
(2) Galel, S. A.; Kirchhoff, L. V. Risk factors for *Trypanosoma cruzi* infection in California blood donors. *Transfusion* **1996**, *36*, 227−231.
(3) Marr, J. J.; Docampo, R. Chemotherapy for Chagas' Disease: a Perspective of Current Therapy and Considerations for Future Research. *Rev. Infect. Dis.* **1986**, *8*, 884−903.
(4) Docampo, R.; Moreno, S. N. J. Biochemical Toxicology of Antiparasitic Compounds Used in the Chemotherapy and Chemoprophilaxis of American Trypanosomiaisis (Chagas' Disease). *Rev. Biochem. Toxicol.* **1985**, *7*, 159−204.
(5) Gutteridge, W. E. Existing Chemotherapy and its Limitations. *Br. Med. Bull.* **1985**, *41*, 162−168.
(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) Nussenzweig, V.; Sonntag, R.; Biancalana, A.; Pedreira de Fleitas, J. L.; Amato Neto, V.; Kloetzel, J. Acão de Corantes Trifenil-metanicos sobre o *Trypanosoma cruzi* "in vitro." Emprêgo de Violeta de Genciana na Profilaxia da Transmissão da Moléstia de Chagas por Transfusão de Sangue. *Hospital* (*Rio de Janeiro*) **1953**, *44*, 731−744.
(8) De Souza, W. Cell Biology of *Trypanosoma cruzi*. *Int. Rev. Cytol.* **1984**, *86*, 197−283.
(9) For a review of the action of juvenile hormones of insects, see: Kramer, S. J.; Law, J. H. Synthesis and Transport of Juvenile Hormones in Insects. *Acc. Chem. Res.* **1980**, *13*, 297−303.
(10) Rodriguez, J. B.; Gros, E. G.; Stoka, A. M. Synthesis and Activity of Juvenile Hormone Analogues (JHA). *Z. Naturforsch.* **1988**, *43b*, 1038−1042.
(11) Rodriguez, J. B.; Gros, E. G.; Stoka, A. M. Synthesis and Activity of Juvenile Hormone Analogues (JHA). Part II. *Z. Naturforsch.* **1989**, *44b*, 983−987.
(12) Perlawagora-Szumlewicz, A.; Petana, W. P.; Figueiredo, M. J. The Evaluation of Host Efficiency and Vector Potential of Laboratory Juvenilized Vector of Chagas' Disease. I - Effects of Developmental Changes Induced by Juvenile Hormone Analogues in *Pantrongylus megistus* (Hemiptera -Reduviidae) on the Susceptibility of Insects to gut Infection with *Trypanosoma cruzi*. *Rev. Inst. Med. Trop.* **1975**, *17*, 97.
(13) Rodriguez, J. B.; Gros, E. G.; Stoka, A. M. Synthesis and Activity of Juvenile Hormone Analogues (JHA) for *Trypanosoma cruzi*. *BioMed. Chem. Lett.* **1991**, *1*, 679−682.
(14) Stoka, A. M.; Rivas, C.; Segura, E.; Rodriguez, J. B.; Gros, E. G. Biological Activity of Synthetic Juvenile Hormone Analogues for *Trypanosoma cruzi*. *Z. Naturforsch.* **1990**, *45b*, 96−98.
(15) Schvartzapel, A. J.; Fichera, L.; Esteva, 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.
(16) Masner, P.; Dorn, S.; Vogel, W.; Kaelin, M.; Graf, O.; Guenthart, E. Types of Response of Insects to a New Insect Growth Regulators and to a Proven Standards. *Pr. Nauk. Inst. Chem. Org. Fiz. Politech. Wroclaw* **1981,** *22*, 809−818.

(17) Vladusic, E. A.; Bussmann, L. E.; Visconti, P. E.; Stoka, A. M.; Rodriguez, J. B.; Gros, E. G.; Charreau, E. H. Effect of Juvenile Hormone on Mammalian Steroidogenesis. *J. Steroid. Biochem. Mol. Biol.* **1994**, *50*, 181−187.
(18) Vladusic, E. A.; Pignataro, O. P.; Bussmann, L. E.; Charreau, E. H. Regulation of the Cholesterol Ester Cycle and Progesterone Synthesis by Juvenile Hormone in MA-10 Leydig Tumor Cells. *J. Steroid. Biochem. Mol. Biol.* **1995**, *52*, 83−90.
(19) Very recently, an interesting paper has been published in which the authors report a cure on experimental Chagas' disease employing a bis-triazole derivative as the chemotherapeutic agent. The sterol biosynthetic pathway is also the target for this drug; see: Urbina, J. A.; Payares, G.; Molina, J.; Sanoja, C.; Liendo, A.; Lazardi, 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.
(20) Sánchez Delgado, R. A.; Lazardi, K.; Rincón, L.; Urbina, J. A.; Hubert, A. J.; Noels, A. N. Toward a Novel Metal-Based Chemotherapy against Tropical Diseases. 1. Enhancement of the Efficacy of Clotrimazole against *Trypanosoma cruzi* by Complexation to Ruthenium in $RuCl_2$(clotrimazole)$_2$. *J. Med. Chem.* **1993**, *36*, 2041−2043.
(21) Farrell, N. P.; Williamson, J.; McLaren, D. J. M. Trypanocidal and Antitumor Activity of Platinum-Metal and Platinum-Metal-Drug Dual-Function Complexes. *Biochem. Pharmacol.* **1984**, *33*, 961−971.
(22) Mesa Valle, C. M.; Moraleda-Lindez, V.; Craciunescu, D. G.; Alonso, M. P.; Osuna, A. In vitro Action of New Organometallic Compounds against Trypanosomatidae Protozoa. *Arzneim.-Forsch./Drug Res.* **1993**, *43* (II), 1010−1013.
(23) Rodriguez, J. B.; Zhong, L.; Docampo, R.; Gros, E. G. Biological Evaluation of Two Potent Inhibitors of *Trypanosoma cruzi* epimastigotes against the Intracellular Form of the Parasite. *BioMed. Chem. Lett.* **1996**, *6*, 2783−2786.
(24) Fichera, L.; Esteva, M.; Wimmer, Z.; Rodriguez, J. B.; Gros, E. G. Effects of Juvenile Hormone Analogues (JHA) on the Development of *Trypanosoma cruzi*. *Z. Naturforsch.* **1995**, *50c*, 578−580.
(25) Scrimin, P.; Tecilla, P.; Tonellato, U. Cationic Metallovesicles: Catalysis of the Cleavage of *p*-Nitrophenyl Picolinate and Control of Copper(II) Permeation. *J. Am. Chem. Soc.* **1992**, *114*, 5086−5092.
(26) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. Pyridinium *p*-Toluensulfonate. A Mild and Efficient Catalyst for the Tetrahydropyranylation of Alcohols. *J. Org. Chem.* **1977**, *42*, 3772−3774.
(27) Agarwal, K. L.; Khorana, H. G. Studies on Polynucleotides. CII. The Use of Aromatic Isocyanates for Selective Blocking of the Terminal 3′-Hydroxyl Group in Protected Deoxyribooligonucleotides. *J. Am. Chem. Soc.* **1972**, *94*, 3578−3585.
(28) Fieser, L. F.; Herz, J. E.; Klohs, M. W.; Romero, M. A.; Utne, T. Cathylation (Carbethoxylation) of Steroid Alcohols. *J. Am. Chem. Soc.* **1952**, *74*, 3309−3313.
(29) 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.
(30) Better yields were obtained when BH_3·THF was freshly prepared and used immediately according to Brown methodology; see: Brown, H. C. *Organic Syntheses via Boranes*; John Wiley: New York, 1975; pp 18−21.
(31) Zweifel, G.; Brown, H. C. Hydration of Olefins, Dienes, and Acetylenes *via* Hydroboration. *Org. React.* **1963**, *13*, 1−53.
(32) Brown, H. C. Hydroboration - A Powerful Synthetic Tool. *Tetrahedron* **1961**, *12*, 117−138.
(33) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley: New York, 1992; pp 443−444.
(34) Block, E.; Ahmat, S.; Catafalmo, J. L.; Jain, M. K.; Apitz-Castro, R. Antithrombotic Organosulfur Compounds from Garlic: Structural, Mechanistic and Synthetic Studies. *J. Am. Chem. Soc.* **1986**, *108*, 7045−7055.
(35) Apitz-Castro, R.; Jain, M. K.; Bartoli, F.; Ledezma, E.; Ruiz, M. C.; Salas, R. Evidence for Direct Coupling of Primary Agonist-Receptor Interacion to the Exposure of Functional IIb-IIIa Complexes in Human Blood Platelets. Results from Studies with the Antiplatelet Ajoene. *Biochem. Biophys. Acta* **1991**, *1095*, 269−280.
(36) Urbina, J. A.; Marchan, E.; Lazardi, K.; Visbal, G.; Apitz-Castro, R.; Gil, F.; Aguirre, T.; Piras, M. M.; Piras, R. Inhibition of Phosphatidylcholine Biosynthesis and Cell Proliferation in *Trypanosoma cruzi* by Ajoene, an Antiplatelet Compound Isolated from Garlic. *Biochem. Pharmacol.* **1993**, *45*, 2381−2387.
(37) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923−2925.

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