96. Design, Synthesis, and anti-*Trypanosoma cruzi* Evaluation of a New Class of Cell-Growth Inhibitors Structurally Related to *Fenoxycarb*

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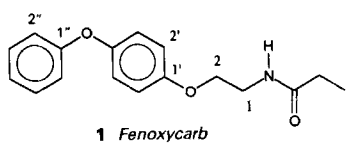
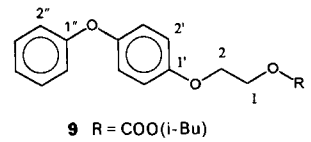
Several compounds, structurally related to the insect-growth regulator *Fenoxycarb* (**1**), were designed and synthesized. These compounds were tested as growth inhibitors of *Trypanosoma cruzi* cells (epimastigotes). Compounds **6**, **16**, **18**, and **22** were very active against *T. cruzi* making them promising good candidates either for blood-bank sterilization or *Chagas*'-disease surveillance, while compounds **11**, **12**, **13**, and **19** showed a moderate degree of activity.

Introduction. – The flagellate protozoan *Trypanosoma cruzi* is the causative agent of *Chagas*' disease which is transmitted to the human body by insects of the family *Reduviidae*, specially *Triatoma infectans*, and also by transfusion of infected blood. Despite of the progresses made in chemotherapy, new compounds are needed, because the trypanocidal drugs presently in use, *Nifurtimox* and *Benznidazole*, cause considerable side effects on patients and present lack of efficacy and specificity against all stages of the disease [1–3]. There is no effective treatment available for *Chagas*' disease in spite of the important advances made in the study of the biochemistry of the microorganism responsible for the mentioned disease. The urgency for more selective and less toxic drugs led to evaluate chemical therapy based on the knowledge of *T. cruzi* biochemistry and the mode of action of these compounds. In addition, due to the risk that *T. cruzi* may be transmitted in blood banks for transfusions, it is very important to have new compounds to kill this parasite in blood to be transfused. At present, the drug in use for this purpose, *Gentian Violet*, suffers from serious limitations concerning its safety [3].

In previous works, several juvenile-hormone analogues which presented a reasonable degree of activity against *Chagas*' disease vector, *i.e.*, the insect *Triatoma infestans* [4] [5], were tested against the microorganism *T. cruzi* (epimastigotes) taking into account that those insects, after treatment with juvenile-hormone analogues, were less susceptible to gut natural infections with *T. cruzi* than normal nontreated insects [6]. Surprisingly, they showed a variable degree of activities, some of them were very active compounds in inhibiting cell proliferation of this parasite [7] [8]. Our goal was that these compounds, formerly juvenile-hormone analogues, became cell-growth inhibitors. At the beginning, the well-known juvenile-hormone analogue *Fenoxycarb* (ethyl [2-(4-phenoxyphenoxy)-ethyl]carbamate; **1**) was employed as standard control, because it behaved as a highly active agent against eggs and nymphal stages of *T. infestans*. However, some modified



1 *Fenoxycarb*



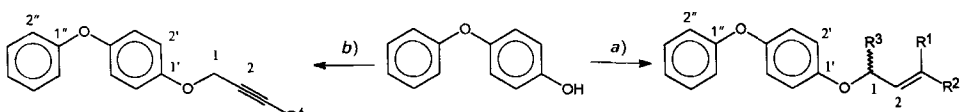
9 R = COO(i-Bu)
10 R = Thp

structures having the 4-phenoxyphenoxy moiety were found to be more active than *Fenoxycarb* in experiments involving *T. cruzi* cells. We studied the mode of action of these drugs, and there are evidences that they inhibit sterol biosynthesis within the cells as it was observed in *Leydig*-tumor cells [9]. Tumor and *T. cruzi* cells have similar metabolism due, principally, to their rapid replication and, in fact, some anti-tumor agents showed effects as trypanocidal drugs [10].

Those results encouraged us to search for more active compounds against *T. cruzi*, and we report, in this paper, the preparation of an additional related set of compounds in an attempt to correlate the chemical structure with biological activity.

Results and Discussion. – The preparation of the allyl and propargyl ethers containing the 4-phenoxyphenoxy moiety was motivated by the biological activity shown by compound **3** (*Scheme 1*) as inhibitor of *T. cruzi* replication [8]. It was decided to modify structure **3** to reveal the influence on the biological activity of substituents at position 3 and of the oxidation degree between positions 2 and 3. These compounds were prepared

Scheme 1



7 R^4 = H
8 R^4 = Me

2

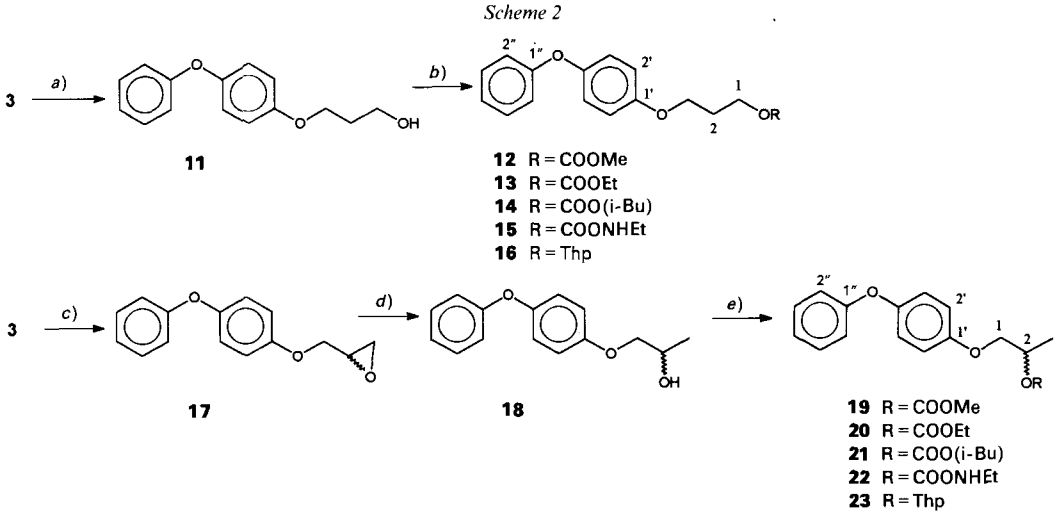
3 $R^1 = R^2 = R^3 = H$
4 $R^1 = R^3 = H$, R^2 = Me
4a $R^1 = R^2 = H$, R^3 = Me
5 $R^1 = R^2$ = Me, $R^3 = H$
6 $R^1 = R^3 = H$, R^2 = Ph

a) 3-Bromoprop-1-ene, DMSO, KOH, r.t., 93% of **3**; (*E*)-1-chlorobut-2-ene, DMSO, KOH, r.t., 22% of **4**; 1-chloro-3-methylbut-2-ene, DMSO, KOH, r.t., 99% of **5**; (*E*)-3-chloro-1-phenylprop-1-ene, DMSO, KOH, r.t., 28% of **6**. *b*) 3-Chloroprop-1-yne, DMSO, KOH, r.t., 63% of **7**; 1-chlorobut-2-yne, DMSO, KOH, r.t., 33% of **8**.

according to a modified *Williamson* procedure [11]. Thus, 4-phenoxyphenol (**2**) was condensed with 3-bromoprop-1-ene in a suspension of KOH in dimethyl sulfoxide (DMSO) to give the corresponding allyl ether **3** in good yield (*Scheme 1*). Following a similar protocol, compounds **4**–**8** were obtained starting from (*E*)-1-chlorobut-2-ene, 1-chloro-3-methylbut-2-ene, (*E*)-3-chloro-1-phenylprop-1-ene, 3-chloroprop-1-yne, and 1-chlorobut-2-yne, respectively. Compound **4** was accompanied by its isomer **4a** as deduced from the ^{1}H-NMR spectrum and HPLC analysis (**4**/**4a** 2:1). The (*E*)-configuration of the C=C bond of **4** was unambiguously established by ^{13}C-NMR spectroscopy (C(4) at 17.84 ppm, typical for an (*E*)-isomer [12]; *cf.* C(4) of a (*Z*)-isomer, < 13 ppm) and that of **6** by the coupling constant (16 Hz) between the vinylic protons in the ^{1}H-NMR spectrum (*cf.* [13]). Anal. HPLC showed **6** to be pure (no (*Z*)-isomer present).

Taking into account their biological evaluation against *T. cruzi* cells [7] [8], compounds **9** and **10** (see above) containing a carbonate and tetrahydropyranyl (Thp) ether group, respectively, were considered to belong to another class of active compounds, containing these groups at the polar end. Thus, as a first modification, the chain length of the aliphatic portion of **9** and **10** was increased by one C-atom. Hydroboration[1]) of alkene **3** followed by alkaline H_2O_2 oxidation led to alcohol **11** which was the common intermediate to prepare compounds **12–16** by treatment with methyl, ethyl, and isobutyl chloroformates [15], and ethyl isocyanate [16], respectively, using pyridine as solvent and acyl carrier (*Scheme 2*). Tetrahydropyranyl ether derivative **16** was obtained when **11** was treated with 3,4-dihydro-2*H*-pyran (Dhp) in the presence of pyridinium toluene-4-sulfonate (PPTS) as catalyst [17].

Scheme 2



a) 1. $BH_3 \cdot THF$/THF, r.t.; 2. H_2O_2, 46%. *b*) ClCOOR/py, 20% of **12**, 61% of **13**, 76% of **14**; for **15**, OCNEt/py, r.t., 99%; for **16**, Dhp, PPTS, CH_2Cl_2, r.t., 77%. *c*) 3-$ClC_6H_4CO_3H$, CH_2Cl_2, r.t., 61%. *d*) $LiAlH_4$, THF, r.t., 88%. *e*) ClCOOR/py, 46% of **19**, 56% of **20**, 86% of **21**; for **22**, OCNEt/py, r.t., 73%; for **23**, Dhp, PPTS, CH_2Cl_2, r.t., 60%.

The skeleton of **9** and **10** was further modified by adding an extra Me group at C(1). This family of compounds was obtained *via* alcohol **18** which was easily prepared by epoxidation of alkene **3** employing 3-chloroperbenzoic acid to form the epoxy derivative **17** followed by regiospecific ring opening with $LiAlH_4$ [18]. No traces of primary alcohol **11** was observed. Thus, compounds **19–23** were prepared from **18** in a similar way as previously described.

For the biological assays, *Trypanosoma cruzi* (epimastigotes, tulahuen strain, Tul-2 stock) were grown in a culture medium containing brain heart infusion (*Difco*; 33 g/l), tryptose (*Difco*; 3 g/l), Na_2HPO_4 (4 g/l), KCl (33 g/l), and glucose (0.3 g/l). The pH was 7.4, and after sterilization, penicillin (200 UI/ml), streptomycin (200 µg/ml), and haemin (20 µg/ml) were added as a solution in 0.1N NaOH, followed by 10% (*v*/*v*) heat-inacti-

[1]) Better yields were obtained, when $BH_3 \cdot THF$ was freshly prepared and used immediately according to *Brown*'s methodology, see [14].

vated (30 min at 56°) fetal calf serum (GEN, SA). Stock cultures were kept at 25° in 50-ml cylindrical tubes with screw caps containing 30 ml of medium. Experimental cultures, containing 5 ml of medium, were conducted in polystyrene disposable tubes (100 × 17 mm). The cultures were started with inocula from exponentially dividing cultures in the same medium. Samples were taken at different times (2, 4, 6, 11, and 14 days) after inoculation of *T. cruzi* in the culture medium used. Cells were counted in a *Neubauer* chamber.

Table. *Biological Results: Inhibition of* Trypanosoma cruzi *Replication*

	μmol/l	% Inhibition		μmol/l	% Inhibition
3	50	47.0	**15**	50	51.0
	100	67.0		100	20.3
4	50	14.0	**16**	50	50.0
	100	24.0		100	96.1
5	50	39.1	**18**	50	33
	100	4.0		100	100
6	50	27.7	**19**	50	5.0
	100	99.5		100	91.0
7	50	51.5	**20**	50	18.3
	100	71.1		100	35.6
8	50	22.0	**21**	50	33.0
	100	45.6		100	0
11	50	65.5	**22**	50	17.7
	100	81.0		100	99.5
12	50	52.0	**23**	50	0
	100	80.0		100	49.5
13	50	45.1	**10**	50	14.0
	100	66.2		100	77.4
14	50	26.0			
	100	15.1			

Biological results are presented in the *Table*. Compounds **3** and **10** were used as standard controls bearing in mind that the biological activities observed for these compounds were higher than that shown by *Fenoxycarb* [7] [8]. Unexpectedly, as they were thought to be intermediates and not inhibitors, free alcohol **18** showed high inhibition values, and alcohol **11** presented a moderate degree of activity. From the designed compounds, tetrahydropyranyl-ether derivative **16** was a very active inhibitor in these cell-culture experiments, as well as compound **6** and carbamate **22**, while compounds **12**, **13**, and **19** exhibited a moderate degree of activity. Compounds **5**, **14**, **15**, and **21** behaved peculiarly by impairing their action against *T. cruzi* replication, when inhibitor concentrations were increased.

The present results constitute a good approach for *Chagas*'-disease control. Further modifications on this skeleton seem to have potential utility in the development of new trypanocidal agents, and the research for more active drugs are currently being pursued in our laboratory.

Experimental Part

General. Unless otherwise noted, chemicals were commercially available and used without further purification. Air- and/or moisture-sensitive reaction were carried out under dry N_2 in flame-dried glassware. Solvents were distilled before use; pyridine from CaH_2 (stored over KOH pellets), DMSO from CaH_2 (stored over freshly activated 3-Å molecular sieves), and Et_2O and THF from Na. Flash chromatography (FC) [19]: silica gel *60*, 230–400 mesh. Anal. TLC: 0.2-mm coated commercial silica-gel plates (*Merck*, silica gel *60* F_{254}). Prep. HPLC: *Micromeritics* chromatograph with a solvent-delivery system model *750*, and a variable-wavelength detector model *787*; *Beckman-Ultrasphere-ODS-2* column 250 × 10 mm (5 μm), flow rate 3.0 ml/min. M.p.: *Fisher-Johns* apparatus: uncorrected. IR: *Nicolet Magna 550* FT-IR spectrophotometer; solids in KBr pellets, liquids as thin films; characteristic bands in cm^{-1}. NMR Spectra: *Bruker-AC-200* spectrometer; chemical shifts in δ (ppm), $SiMe_4$ as internal standard, coupling constants J in Hz; ^{13}C-NMR spectra were fully decoupled. MS: *VG-TRIO-2* instrument, 70 eV (direct inlet); m/z (rel.-%). Elemental analyses were performed by *UMYMFOR* (Facultad de Ciencias Exactas y Naturales-CONICET).

Alkyl 4-Phenoxyphenyl Ethers **3**–**8***: General Procedure.* To a suspension of KOH (4 mmol) in DMSO (5 ml), 4-phenoxyphenol (**2**; 1 mmol) was added. After 5 min, the mixture became dark and was treated with the corresponding alkyl halide (2 mmol). The mixture was vigorously stirred overnight at r.t., then poured into H_2O (50 ml), and extracted with CH_2Cl_2 (3 × 30 ml). The combined org. layers were washed with brine (5 × 70 ml) and H_2O (2 × 70 ml), dried ($MgSO_4$), and evaporated. The residue was purified by FC.

Carbonate and Carbamate Derivatives **12**–**15** *and* **19**–**22***: General Procedure.* A soln. of alcohol **11** or **18** (0.5 mmol) in pyridine (3 ml) was treated, in separated experiments, with methyl, ethyl, and isobutyl chloroformate and ethyl isocyanate (1.0 mmol). The mixture was stirred at r.t. for 14 h. CH_2Cl_2 (20 ml) was added and the soln. washed with 1N HCl (3 × 20 ml), sat. $NaCO_3H$ soln. (2 × 20 ml), and H_2O (2 × 20 ml). The org. phase was dried ($MgSO_4$) and evaporated. The residue was purified by FC. For the preparation of carbamates, 4-(dimethylamino)pyridine (0.05 mmol) was employed as catalyst.

4-Phenoxyphenyl Prop-2-en-1-yl Ether (**3**). FC (silica gel, hexane/AcOEt 9:1) afforded **3** (93%). Yellow pale oil. IR: 3050, 2950, 1580, 1470, 1200, 1100, 900, 800. ^{1}H-NMR: 4.55 (*dd*, J = 5.1, 0.7, 2 H–C(1)); 5.33 (*d*, J = 10.1, H–C(3) *cis* to H–C(2)); 5.46 (*dd*, J = 17.3, 1.2, H–C(3) *trans* to H–C(2)); 6.10 (*ddt*, J = 17.3, 10.1, 5.2, H–C(2)); 6.90–7.37 (*m*, 9 arom. H). ^{13}C-NMR: 69.31 (C(1)); 115.81 (C(2″)); 117.59 (C(3)); 117.67 (C(2′)); 120.67 (C(3′)); 122.45 (C(4″)); 129.58 (C(3″)); 133.35 (C(2)); 150.35 (C(4′)); 154.87 (C(1′)); 158.42 (C(1″)). MS: 226 (26, M^+), 185 (51), 129 (28), 77 (100).

*(*E*)-But-2-en-1-yl 4-Phenoxyphenyl Ether* (**4**) *and But-3-en-2-yl 4-Phenoxyphenyl Ether* (**4a**). FC (silica gel, hexane/AcOEt 95:5) afforded **4**/**4a** as a colorless oil (34%). Semi-prep. HPLC (MeOH/H_2O 85:15; detection by UV at 275 nm; *ca.* 3 mg in MeOH per injection, 20 injections) gave 40 mg of **4** (t_R 11.91 min) and 20 mg of **4a** (t_R 10.73 min).

Data of **4***:* M.p. 45–46°. IR: 3041, 3026, 2974, 2937, 1589, 1489, 1219, 1008, 966, 871, 842, 754. ^{1}H-NMR: 1.76 (*dd*, J = 5.4, 0.9, Me(4)); 4.44 (*dd*, J = 5.7, 0.9, 2 H–C(1)); 5.80 (*m*, H–C(2), H–C(3)); 6.85–7.33 (*m*, 9 arom. H). ^{13}C-NMR: 17.84 (C(4)); 69.26 (C(1)); 115.78 (C(2″)); 117.68 (C(2′)); 120.71 (C(3′)); 122.44 (C(4″)); 126.16 (C(3)); 129.59 (C(3″)); 130.51 (C(2)); 150.24 (C(4′)); 155.05 (C(1′)); 158.48 (C(1″)). MS: 240 (13, M^+), 186 (100), 77 (9). Anal. calc. for $C_{16}H_{16}O_2$: C 79.97, H 6.71; found: C 80.26, H 7.03.

Data of **4a***:* ^{1}H-NMR: 1.43 (*d*, J = 6.4, Me(1)); 4.73 (*q*, J = 6.3, H–C(2)); 5.17 (*dd*, J = 10.1, 1.1, H–C(4) *cis* to H–C(3)); 5.26 (*dd*, J = 16.2, 1.1, H–C(4) *trans* to H–C(3)); 5.92 (*m*, H–C(3)); 6.85–7.33 (*m*, 9 arom. H).

3-Methylbut-2-en-1-yl 4-Phenoxyphenyl Ether (**5**). FC (silica gel, hexane/AcOEt 95:5) yielded **5** (99%). Colorless oil. IR: 3062, 2976, 2914, 2860, 1589, 1504, 1489, 1217, 1006, 871, 840, 752, 690. ^{1}H-NMR: 1.73 (*s*, Me(4)); 1.79 (*s*, Me–C(3)); 4.48 (*d*, J = 6.7, 2 H–C(1)); 5.49 (*m*, H–C(2)); 6.85–7.31 (*m*, 9 arom. H). ^{13}C-NMR: 18.12 (*Me*–C(3)); 25.74 (C(4)); 65.21 (C(1)); 115.65 (C(2″)); 117.59 (C(2′)); 119.75 (C(2)); 120.67 (C(3′)); 122.36 (C(4″)); 129.53 (C(3″)); 137.99 (C(3)); 150.09 (C(4′)); 155.14 (C(1′)); 158.48 (C(1″)). MS: 254 (3, M^+), 186 (100), 77 (15). Anal. calc. for $C_{17}H_{18}O_2$: C 80.28, H 7.13; found: C 80.63, H 7.49.

*4-Phenoxyphenyl (*E*)-3-Phenylprop-2-en-1-yl Ether* (**6**). FC (silica gel, hexane/AcOEt 9:1 afforded pure **6** (28%). White solid. M.p. 104–105° (EtOH). IR: 3058, 3030, 2912, 2862, 1591, 1506, 1490, 1242, 1012, 966, 840, 744.5, 692. ^{1}H-NMR: 4.69 (*dd*, J = 5.7, 1.3, H–C(1)); 6.38 (*dt*, J = 15.9, 5.7, H–C(2)); 6.74 (*d*, J = 16, H–C(3)); 6.90–7.44 (*m*, 9 arom. H). ^{13}C-NMR: 69.21 (C(1)); 115.90 (C(2″)); 117.72 (C(2′)); 120.71 (C(3′)); 122.49 (C(4″)); 124.51 (C(2)); 126.57 (C(2‴)); 127.91 (C(4‴)); 128.59 (C(3‴)); 129.61 (C(3″)); 133.03 (C(3)); 136.46 (C(1‴)); 150.44 (C(4′)); 154.92 (C(1′)); 158.42 (C(1″)). MS: 254 (4, M^+), 117 (100). Anal. calc. for $C_{21}H_{18}O_2$: C 83.14, H 6.31; found: C 83.12, H 6.38.

4-Phenoxyphenyl Prop-2-yn-1-yl Ether (**7**). FC (silica gel, hexane/AcOEt 95:5) yielded pure **7** (63%). Yellow oil. IR: 3296, 3054, 3032, 2949, 2918, 2860, 2129, 1583, 1502, 1489, 1207. ^{1}H-NMR: 2.49 (*t*, *J* = 2.5, H–C(3)); 4.65 (*d*, *J* = 2.4, 2 H–C(1)); 6.92–7.32 (*m*, 9 arom. H). ^{13}C-NMR: 56.42 (C(1)); 75.51 (C(3)); 78.64 (C(2)); 116.18 (C(2″)); 117.91 (C(2′)); 120.54 (C(3′)); 122.66 (C(4″)); 129.64 (C(3″)); 151.14 (C(4′)); 153.77 (C(1′)); 158.21 (C(1″)). MS: 224 (69, M^+), 186 (18), 185 (100), 129 (42), 77 (97), 51 (49), 39 (26). Anal. calc. for $C_{15}H_{12}O_2$: C 80.34, H 5.39; found: C 80.56, H 5.34.

But-2-yn-1-yl 4-Phenoxyphenyl Ether (**8**). FC (silica gel, hexane/AcOEt 95:5) gave pure **8** (33%). Colorless oil. IR: 3041, 2920, 2860, 1589, 1504, 1489, 1242, 1209. ^{1}H-NMR: 1.86 (*t*, *J* = 2.2, Me(4)); 4.62 (*q*, *J* = 2.2, 2 H–C(1)); 6.90–7.33 (*m*, 9 arom. H). ^{13}C-NMR: 13.67 (C(4)); 56.99 (C(1)); 74.11 (C(3)); 83.74 (C(2)); 116.03 (C(2″)); 117.81 (C(2′)); 120.56 (C(3′)); 122.55 (C(4″)); 129.61 (C(3″)); 150.77 (C(4′)); 154.11 (C(1′)); 158.32 (C(1″)). MS: 238 (83, M^+), 185 (100), 77 (20). Anal. calc. for $C_{16}H_{14}O_2$: C 80.65, H 5.92; found: C 81.11, H 6.13.

3-(4-Phenoxyphenoxy)propanol (**11**). To a soln. of **3** (1.036 g, 5.60 mmol) in anh. THF (5 ml) cooled to 0° and kept under N_2, 6.4M diborane in THF (0.70 ml) was added dropwise. The mixture was stirred at r.t. for 1 h. The excess of the reagent was decomposed by careful addition of H_2O. The mixture was warmed to 50°, and 1N NaOH (3.3 ml) was added, followed slowly by 30% H_2O_2 soln. (1.1 ml). The mixture was stirred for 1 h at r.t. Solid K_2CO_3 (4 g) was added and the THF layer separated. The aq. phase was extracted with CH_2Cl_2 (2 × 10 ml), the combined org. layer dried ($MgSO_4$) and evaporated, and the residue purified by FC (silica gel, hexane/AcOEt 7:3): 0.551 mg (46%) of pure **11**. White solid. M.p. 61–62° (from H_2O/EtOH 9:1). IR: 3250, 2900, 2850, 1240, 1060. ^{1}H-NMR: 2.03 (*q*, *J* = 5.8, 2 H–C(2)); 3.86 (*t*, *J* = 5.6, 2 H–C(3)); 4.10 (*t*, *J* = 5.9, 2 H–C(1)); 5.64 (br., OH); 6.84–7.31 (*m*, 9 arom. H). ^{13}C-NMR: 32.05 (C(2)); 60.50 (C(3)); 66.27 (C(1)); 115.54 (C(2″)); 117.66 (C(2′)); 120.77 (C(3′)); 122.47 (C(4″)); 129.61 (C(3″)); 150.37 (C(4′)); 155.05 (C(1′)); 158.42 (C(1″)). MS: 244 (92, M^+), 186 (100), 77 (36). Anal. calc. for $C_{15}H_{16}O_3$: C 73.74, H6.61; found: C 73.92, H 6.77.

Methyl 3-(4-Phenoxyphenoxy)propyl Carbonate (**12**). FC (silica gel, hexane/AcOEt) afforded pure **12** (20%). Colorless oil. IR: 3037, 2959, 1750, 1591, 1506, 1489, 1271, 1221. ^{1}H-NMR: 2.15 (*q*, *J* = 6.2, 2 H–C(2)); 3.78 (*s*, MeO); 4.04 (*t*, *J* = 6.1, 2 H–C(3)); 4.35 (*t*, *J* = 6.3, 2 H–C(1)); 6.84–7.30 (*m*, 9 arom. H). ^{13}C-NMR: 28.76 (C(2)); 54.74 (MeO); 64.54[2]) (C(1)); 64.82[2]) (C(3)); 115.56 (C(2″)); 117.67 (C(2′)); 120.75 (C(3′)); 122.47 (C(4″)); 129.58 (C(3″)); 150.37 (C(4′)); 155.00[3]) (C(1′)); 155.73[3]) (C=O); 158.46 (C(1″)). MS: 254 (12, M^+), 186 (15), 77 (35), 45 (21), 41 (18). Anal. calc. for $C_{17}H_{18}O_5$: C 67.54, H 6.00; found: C 67.90, H 6.36.

Ethyl 3-(4-Phenoxyphenoxy)propyl Carbonate (**13**). FC (silica gel, hexane/AcOEt) afforded pure **13** (61%). Colorless oil. IR: 3064, 2979, 2931, 1743, 1589, 1504, 1489, 1264, 1219. ^{1}H-NMR: 1.30 (*t*, *J* = 7.1, *Me*CH_2O); 2.16 (*q*, *J* = 6.2, 2 H–C(2)); 4.04 (*t*, *J* = 6.1, 2 H–C(3)); 4.19 (*q*, *J* = 7.2, MeCH_2O); 4.34 (*t*, *J* = 6.3, 2 H–C(1)); 6.84–7.33 (*m*, 9 arom. H). ^{13}C-NMR: 14.23 (*Me*CH_2); 28.76 (C(2)); 63.94 (C(3)); 64.55 (C(1), Me*C*H_2); 115.55 (C(2″)); 117.64 (C(2′)); 120.72 (C(3′)); 122.42 (C(4″)); 129.56 (C(3″)); 150.36 (C(4′)); 155.00[2]) (C(1′)); 155.11[2]) (C=O); 158.43 (C(1″)). MS: 316 (11, M^+), 186 (25), 185 (12), 131 (99), 103 (100), 77 (74). Anal. calc. for $C_{18}H_{20}O_5$: C 68.34, H 6.37; found: C 68.11, H 6.51.

Isobutyl 3-(4-Phenoxyphenoxy)propyl Carbonate (**14**). FC (silica gel, hexane/AcOEt 4:1) gave pure **14** (76%). Colorless oil. IR: 3064, 3043, 2965, 2880, 1747, 1589, 1506, 1489, 1265, 1220. ^{1}H-NMR: 0.95 (*d*, *J* = 6.8, *Me*$_2$CH); 2.00 (*m*, Me$_2$C*H*); 2.16 (*q*, *J* = 6.2, 2 H–C(2)); 3.91 (*d*, *J* = 6.6, Me$_2$CHCH_2); 4.05 (*t*, *J* = 6.1, 2 H–C(3)); 4.34 (*t*, *J* = 6.3, 2 H–C(1)); 6.84–7.29 (*m*, 9 arom. H). ^{13}C-NMR: 19.70 (*Me*$_2$CH); 27.87 (C(2)); 28.88 Me$_2$*C*H); 64.70 (C(3)); 74.01 (C(1)); 74.19 (Me$_2$CH*C*H_2); 115.67 (C(2″)); 117.75 (C(2′)); 120.84 (C(3′)); 122.54 (C(4″)); 129.68 (C(3″)); 150.46 (C(4′)); 155.13[2]) (C(1′)); 155.43[2]) (C=O); 158.55 (C(1″)). MS: 344 (15, M^+), 186 (48), 103 (100), 77 (62). Anal. calc. for $C_{20}H_{24}O_5$: C 69.75, H 7.02; found: C 69.65, H 7.24.

3-(4-Phenoxyphenoxy)propyl Ethylcarbamate (**15**). FC (silica gel, hexane/AcOEt 3:2) afforded pure **15** (99%). Colorless oil. IR: 3340, 3043, 2972, 2933, 2877, 1714, 1699, 1589, 1504, 1489, 1220. ^{1}H-NMR: 1.13 (*t*, *J* = 7.2, *Me*CH_2NH); 2.10 (*q*, *J* = 6.1, 2 H–C(2)); 3.21 (*m*, MeCH_2NH); 4.01 (*t*, *J* = 6.2, 2 H–C(3)); 4.26 (*t*, *J* = 6.3, 2 H–C(1)); 4.62 (*s*, NH); 6.79–7.34 (*m*, 9 arom. H). ^{13}C-NMR: 15.28 (*Me*CH_2); 29.15 (C(2)); 35.90 (Me*C*H_2NH); 61.55 (C(1)); 64.99 (C(3)); 115.55 (C(2″)); 117.64 (C(2′)); 120.75 (C(3′)); 122.44 (C(4″)); 129.59 (C(3″)); 150.28 (C(4′)); 155.14 (C(1′), C=O). MS: 315 (3, M^+), 186 (15), 130 (100), 77 (15), 72 (21). Anal. calc. for $C_{18}H_{21}NO_4$: C 68.55, H 6.71; found: C 68.23, H 6.88.

*(±)-3-(4-Phenoxyphenoxy)propyl Tetrahydro-2*H*-pyran-2-yl Ether* (**16**). To a soln. of **11** (97 mg, 0.39 mmol) and pyridinium toluene-4-sulfonate (15 mg) in CH_2Cl_2 (10 ml), 3,4-dihydro-2*H*-pyran (0.06 ml, 0.59 mmol) was slowly added. The mixture was stirred for 4 h at r.t. The soln. was washed with brine (2 × 20 ml) and H_2O (2 × 20 ml), dried ($MgSO_4$), and evaporated. The residue was purified by FC (silica gel, hexane/AcOEt 4:1): **16** (99 mg,

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[2])[3]) Signal attributions may be interchanged.

77%). Colorless oil. IR: 3045, 2946, 2874, 1593, 1508, 1488, 1225, 1124. ^{1}H-NMR: 1.48–1.79 (*m*, 2 H–C(3‴), 2 H–C(4‴), 2 H–C(5‴)); 2.02 (*q*, *J* = 6.3, 2 H–C(2)); 3.42–3.94 (*m*, 2 H–C(1), 2 H–C(6‴)); 4.02 (*t*, *J* = 6.3, 2 H–C(3)); 4.56 (*dd*, *J* = 2.9, 3.2, H–C(2‴)); 6.81–7.28 (*m*, 9 arom. H). ^{13}C-NMR: 19.60 (C(4‴)); 25.45 (C(5‴)); 29.75 (C(2)); 30.70 (C(3‴)); 62.32 (C(6‴)); 64.01[2]) (C(3)); 65.47[2]) C(1)); 98.95 (C(2‴)); 115.57 (C(2′)); 117.59 (C(2′)); 120.74 (C(3′)); 122.39 (C(4′)); 129.56 (C(3′)); 150.07 (C(4′)); 155.35 (C(1′)); 158.52 (C(1″)). MS: 328 (18, M^+), 186 (75), 143 (42), 85 (93), 77 (60), 69 (100), 41 (32). Anal. calc. for $C_{20}H_{24}O_4 \cdot 1/3$ AcOEt: C 71.62, H 7.51; found: C 71.77, H 7.69.

(RS)-Oxiranemethyl 4-Phenoxyphenyl Ether (**17**). To a soln. of **3** (600 mg, 2.67 mmol) in CH_2Cl_2 (20 ml), 80% 3-chloroperbenzoic acid (595 mg, 2.8 mmol) in CH_2Cl_2 (15 ml) was added dropwise within 30 min. The mixture was stirred at r.t. for 20 h. The org. layer was washed with sat. $NaHCO_3$ soln. (3 × 30 ml) and H_2O (2 × 30 ml), dried ($MgSO_4$), and evaporated. The residue was purified by FC (silica gel, hexane/AcOEt 9:1): 389 mg (61%) of pure **17**. Yellow oil. IR: 3059, 3001, 2924, 1589, 1504, 1489, 1219, 1036, 844, 756, 692, 513. ^{1}H-NMR: 2.77 (*dd*, *J* = 4.9, 2.7, 1 H–C(3‴)); 2.92 (*dd*, *J* = 4.8, 4.2, 1 H–C(3‴)); 3.36 (*m*, H–C(2‴)); 3.96 (*dd*, *J* = 11.1, 5.6, 1 H, ArOCH_2); 4.22 (*dd*, *J* = 11.1, 3.2, 1 H, ArOCH_2); 6.89–7.35 (*m*, 9 arom. H). ^{13}C-NMR: 44.74 (C(3‴)); 50.23 (C(2‴)); 69.45 (ArOCH_2); 115.90 (C(2″)); 117.85 (C(2′)); 120.76 (C(3′)); 122.65 (C(4″)); 129.69 (C(3″)); 154.83 (C(1′)); 158.39 (C(1″)). MS: 242 (100, M^+), 186 (72), 77 (72).

(RS)-1-(4-Phenoxyphenoxy)propan-2-ol (**18**). To a soln. of $LiAlH_4$ (200 mg) in anh. THF (20 ml), **17** (255 mg, 1.05 mmol) in THF (10 ml) under N_2 was added dropwise. The mixture was stirred for 5 h. The reaction was quenched with AcOEt (1.0 ml) and the mixture partitioned between sat. sodium potassium tartrate soln. (100 ml) and CH_2Cl_2 (100 ml). The org. layer was washed with the tartrate soln. (3 × 70 ml) and H_2O (2 × 70 ml), dried and evaporated: 226 mg (88%) of pure **18**. This compound was used in the next step without further purification. M.p. 70–71° (H_2O/EtOH 9:1). IR: 3450, 3102, 3030, 3070, 2974, 2924, 2900, 2871, 1330, 1246, 1103. ^{1}H-NMR: 1.30 (*d*, *J* = 6.4, Me(3)); 2.41 (br., OH); 3.80 (*dd*, *J* = 9.3, 7.7, 1 H–C(1)); 3.95 (*dd*, *J* = 9.3, 3.2, 1 H–C(1)); 4.20 (*m*, H–C(2)); 6.84–7.35 (*m*, 9 arom. H). ^{13}C-NMR: 18.76 (C(3)); 66.30 (C(2)); 73.90 (C(1)); 115.66 (C(2″)); 117.72 (C(2′)); 120.75 (C(3′)); 122.55 (C(4″)); 129.61 (C(3″)); 150.63 (C(4′)); 154.84 (C(1′)); 158.34 (C(1″)). MS: 244 (37, M^+), 186 (100), 77 (25). Anal. calc. for $C_{15}H_{16}O_3$: C 73.75, H 6.60; found: C 73.54, H 6.90.

Methyl (RS)-1-(4-Phenoxyphenoxy)propan-2-yl Carbonate (**19**). FC (silica gel, hexane/AcOEt 4:1) gave pure **19** (46%). Colorless oil. IR: 3041, 2985, 2956, 2875, 1747, 1589, 1504, 1489, 1273, 1219. ^{1}H-NMR: 1.42 (*d*, *J* = 6.4, Me(3)); 3.80 (*s*, MeO); 3.97 (*dd*, *J* = 10.3, 4.7, 1 H–C(1)); 4.05 (*dd*, *J* = 10.2, 5.8, 1 H–C(1)); 5.12 (*m*, H–C(2)); 6.85–7.33 (*m*, 9 arom. H). ^{13}C-NMR: 16.67 (C(3)); 54.71 (MeO); 70.46 (C(2)); 72.93 (C(1)); 115.79 (C(2″)); 117.92 (C(2′)); 120.70 (C(3′)); 122.52 (C(4″)); 129.59 (C(3″)); 154.78[2]) (C(1′)); 155.27[2]) (C=O); 158.37 (C(1″)). MS: 302 (11, M^+), 186 (16), 185 (18), 117 (100), 77 (44). Anal. calc. for $C_{17}H_{18}O_5$: C 67.54, H 6.00; found: C 67.91, H 6.02.

Ethyl (RS)-1-(4-Phenoxyphenoxy)propan-2-yl Carbonate (**20**). FC (silica gel, hexane/AcOEt 3:1) yielded pure **20** (56%). Colorless oil. IR: 3041, 2983, 2937, 2875, 1743, 1589, 1504, 1489, 1265, 1219. ^{1}H-NMR: 1.32 (*t*, *J* = 7.1, *Me*CH_2O); 1.42 (*d*, *J* = 6.4, Me(3)); 3.97 (*dd*, *J* = 10.2, 4.7, 1 H–C(1)); 4.05 (*dd*, *J* = 10.1, 5.8, 1 H–C(1)); 4.21 (*q*, *J* = 7.1, MeCH_2O); 5.11 (*m*, H–C(2)); 6.85–7.33 (*m*, 9 arom. H). ^{13}C-NMR: 14.22 (*Me*CH_2O); 16.71 (C(3)); 63.99 (Me*C*H_2O); 70.51 (C(2)); 72.60 (C(1)); 115.78 (C(2″)); 117.73 (C(2′)); 120.69 (C(3′)); 122.54 (C(4″)); 129.59 (C(3″)); 154.62[2]) (C(1′)); 154.80[2]) (C=O); 158.36 (C(1″)). MS: 316 (7, M^+), 186 (14), 185 (10), 131 (59), 103 (72), 77 (29), 59 (19). Anal. calc. for $C_{18}H_{20}O_5$: C 68.34, H 6.37; found: C 68.44, H 6.21.

Isobutyl (RS)-1-(4-Phenoxyphenoxy)propan-2-yl Carbonate (**21**). FC (silica gel, hexane/AcOEt 85:15) afforded pure **21** (86%). Colorless oil. IR: 3043, 2965, 2876, 1747, 1589, 1506, 1489, 1248. ^{1}H-NMR: 0.95 (*d*, *J* = 6.8, *Me*$_2$CH); 1.42 (*d*, *J* = 6.5, Me(3)); 1.96 (*m*, Me$_2$C*H*); 3.94 (*d*, *J* = 6.7, Me$_2$CHCH_2); 3.99 (*m* (*AB*), 2 H–C(1)); 5.12 (*m*, 1 H–C(2)); 6.85–7.32 (*m*, 9 arom. H). ^{13}C-NMR: 16.66 (C(3)); 18.86 (*Me*$_2$CH); 27.76 (Me$_2$*C*H); 70.46 (C(2)); 72.55 (C(1)); 74.06 (Me$_2$CHCH_2); 115.74 (C(2″)); 117.67 (C(2′)); 120.65 (C(3′)); 122.47 (C(4″)); 129.55 (C(3″)); 150.60 (C(4′)); 154.76[2]) (C(1′)); 154.83[2]) (C=O); 158.32 (C(1″)). MS: 344 (8, M^+), 186 (45), 185 (29), 103 (100), 77 (45), 57 (40), 41 (25). Anal. calc. for $C_{20}H_{24}O_5$: C 69.75, H 7.02; found: C 69.51, H 6.96.

(RS)-1-(4-Phenoxyphenoxy)propan-2-yl Ethylcarbamate (**22**). FC (silica gel, hexane/AcOEt 3:2) yielded pure **22** (73%). White solid. M.p. 63–64°. IR: 3321, 3064, 2978, 2937, 2883, 1689, 1544, 1504, 1269, 1234. ^{1}H-NMR: 1.15 (*t*, *J* = 7.2, *Me*CH_2NH); 1.38 (*d*, *J* = 6.5, Me(3)); 3.24 (*m*, MeCH_2NH); 3.97 (*m* (*AB*), 2 H–C(1)); 4.66 (*s*, NH); 5.16 (*m*, H–C(2)); 6.87–7.34 (*m*, 9 arom. H). ^{13}C-NMR: 15.21 (*Me*CH_2); 16.98 (C(3)); 35.88 (Me*C*H_2NH); 69.10 (C(2)); 70.97 (C(1)); 115.78 (C(2″)); 117.69 (C(2′)); 120.71 (C(3′)); 122.50 (C(4″)); 129.59 (C(3″)); 150.51 (C(4′)); 155.03 (C(1′)); 158.40 (C(1″)). MS: 315 (2, M^+), 244 (26), 186 (81), 130 (100), 77 (31).

(RS)-1-(4-Phenoxyphenoxy)propan-2-yl Tetrahydro-2H-pyran-2-yl Ether (**23**). As described for **16**, with **18** (66 mg, 0.27 mmol), pyridinium toluene-4-sulfonate (15 mg), CH_2Cl_2 (5 ml), and 3,4-dihydro-2*H*-pyran (0.04 ml, 0.40 mmol): diastereoisomer mixture **23** (1:1; 60%). Colorless oil. IR: 3041, 2939, 2869, 1589, 1504, 1489, 1222, 1033, 993. ^{1}H-NMR: 1.27 (*d*, *J* = 6.1, Me(3)); 1.34 (*d*, *J* = 6.5, Me(3)); 1.40–1.75 (*m*, 2 H–C(3‴), 2 H–C(4‴),

2 H–C(5‴)); 3.40–4.20 (*m*, 2 H–C(1), H–C(2), 2 H–C(6‴)); 4.95 (*m*, H–C(2‴)); 6.90–7.29 (*m*, 9 arom. H). ^{13}C-NMR: 16.75, 18.58 (C(3)); 19.42, 19.72 (C(4‴)); 25.44 (C(5‴)); 30.67, 30.92 (C(3‴)); 62.20, 62.69 (C(6‴)); 70.28, 71.37 (C(2)); 72.25, 72.42 (C(1)); 96.56, 98.89 (C(2″)); 115.65 (C(2″)); 117.57 (C(2′)); 120.69 (C(3′)); 122.37 (C(4″)); 129.53 (C(3″)); 150.13 (C(4′)); 155.21 (C(1′)). MS: 328 (16, M^+), 186 (67), 143 (20), 85 (100), 77 (20). Anal. calc. for $C_{20}H_{24}O_4$: C 73.15, H 7.37; found: C 73.06, H 7.47.

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