45. Novel Juvenoids of the 2-(4-Hydroxybenzyl)cyclohexan-1-one Series

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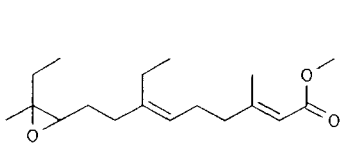
A series of insect juvenile hormone analogs (juvenoids) was synthesized and studied. The basic skeleton of these juvenoids contains three rings and a short aliphatic subunit and bears two or three chiral centers (depending on the appropriate structure; see **6**–**9**). The chiral center located in the 1,2-diphenoxypropane subunit has the configuration (*RS*), (*R*) (**a** series), or (*S*) (**b** series). The juvenoids were subjected to a biological screening, the preliminary results of which are briefly described.

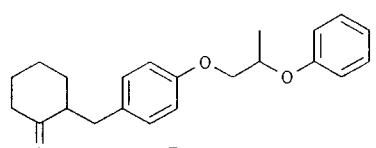
Introduction. – Insects represent the most widespread class of animals on earth. In fact, the majority of insect species is useful from a man's point of view, but many others are serious food competitors with man or carriers of serious deseases. The development of methods to control excessively spreading populations of insect pest is still one of the goals of common research of chemical and biological laboratories all over the world.

A research field focusing on an environmentally safe way of insect-pest control has been based on the discovery of insect juvenile hormones (JH's) [1]. In 1965, *Sláma* and *Williams* [2] described the juvenilizing effect of sheets of paper made from the wood of balsam fir (*Abies balsamea*). Subsequently, the compound responsible for this juvenilizing effect was identified as juvabione [3], the first naturally occurring JH bioanalog (JHA; juvenoid). Since that time, thousands of compounds were synthesized displaying JH activity on a broad variety of insect pests (see, *e.g.*, [4–7]). Moreover, important differences in the biological activity of geometrical isomers of α,β-unsaturated esters [4] [7], positional isomers of 1,2-disubstituted cyclohexane derivatives [4], and even optical isomers of several commercially available juvenoids [5] were described.

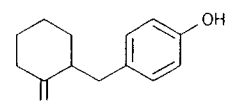
A series of 2-(4-hydroxybenzyl)cyclohexan-1-one derivatives has been studied since 1975 [8] [9]. Among several hundred juvenoids of this series, partial structure-activity studies indicated that *cis*- and *trans*-isomers of juvenoids derived from 2-(4-hydroxybenzyl)cyclohexan-1-ol show different biological-activity values when tested on a large variety of non-related insect species [10]. Several generally applicable findings proved to play an important role in the structure-activity relationship: *a*) the length of the juvenoid molecule (19–24 nm) [4] [7], *b*) the branching of the juvenoid molecule (rings may be introduced to substitute branching in the molecule as shown by **A** and **B** [4] [7]), *c*) *para*-substitution of aromatic rings [4] [7], and *d*) some additional findings [5–7].



A



B



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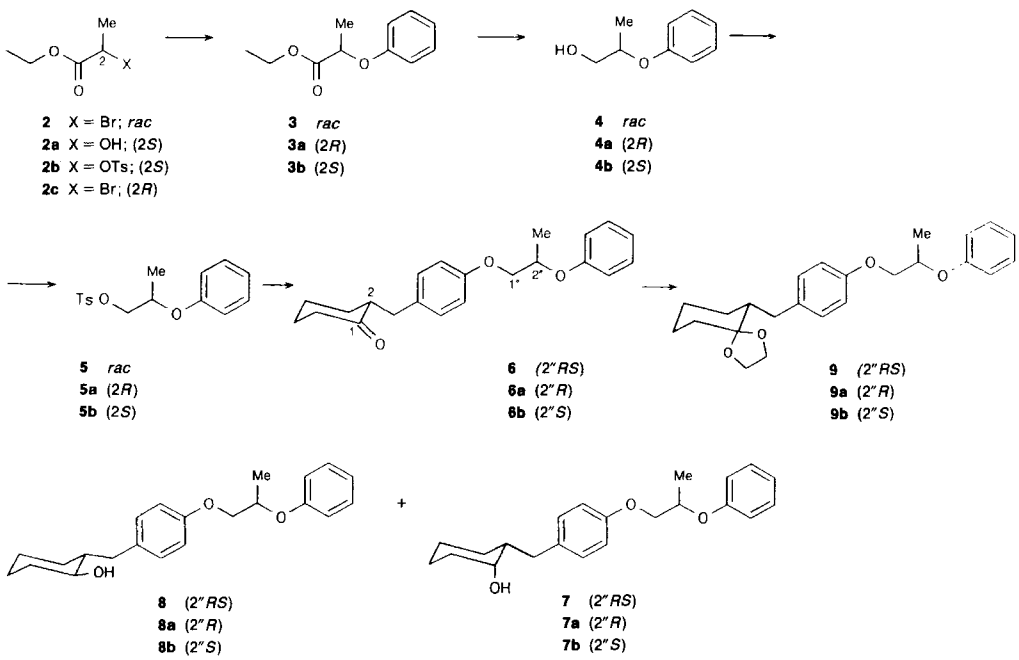
Recently, we focused our attention on the synthesis and investigation of a juvenoid series derived from 2-(4-hydroxybenzyl)cyclohexan-1-one (**1**), containing a terminal phenyl group superimposable with the ester function of JH (*cf.* **A** and **B**). The choice of the principal group R at the cyclohexane moiety of this series (see **B**), *i.e.* a keto, hydroxy, or ethylene-acetal moiety, was based on the formulation of the final product for the biological investigation. The formulation must be straightforward, versatile, and also unconventional, *i.e.* the final product should possibly be used, as a juvenogen [11] [12]. Juvenogens were defined as biochemically activated juvenoid complexes liberating a biologically active juvenoid under the effect of either biotic or abiotic factors [11].

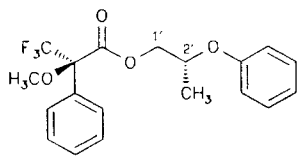
The juvenoids described below have two or three chiral centers. The configuration at C(2) of the cyclohexane moiety is kept racemic (*RS*) in this series, whereas the one of the 1,2-diphenoxypropane subunit is (*R*), (*S*), or (*RS*). The obtained juvenoids were tested for biological activity and the different stereoisomers compared. The results have been published partially [9e] and will be the subject of a future paper.

Results and Discussion. – The 2-(4-hydroxybenzyl)cyclohexan-1-one [8] **1** was used as the key intermediate in the synthesis of the target juvenoids. The second building block was derived from ethyl 2-phenoxypropanoate: ethyl *rac*-2-bromopropanoate (**2**) reacted with phenol in the presence of a strong base to ethyl *rac*-2-phenoxypropanoate (**3**), while ethyl (*S*)-2-hydroxypropanoate (= ethyl L-lactate; **2a**) was transformed *via* its (*S*)-tosyl derivative **2b** to the (*R*)-enantiomer **3a** and *via* the (*R*)-bromo derivative **2c** to the (*S*)-enantiomer **3b** (*Scheme*). Reduction of the ester moiety of **3**, **3a**, and **3b** yielded *rac*-2-phenoxypropan-1-ol **4** and its enantiomers **4a** and **4b**, respectively.

Scheme



The *Mosher* esters (= 3,3,3-trifluoro-2-methoxy-2-phenylpropanoates; MTPA) **10**–**13** of the chiral intermediates **4a** and **4b** allowed determination of the enantiomeric purity and the assignment of the absolute configuration of **4a** and **4b** by HPLC and NMR measurements [13] [14]. Differences in the chemical shifts of the signals of the 2 H–C(1′) (adjacent to the chiral center) of **10**–**13** were used for the assignment of the absolute configuration. Supporting CD data showed opposite $\Delta\varepsilon$ values for **4a** and **4b**, establishing that they were prepared with comparable enantiomeric purity. Spectra of the products originating from **4a** and **4b** were used to confirm the unchanged opposite chirality of these product.



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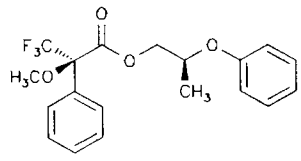

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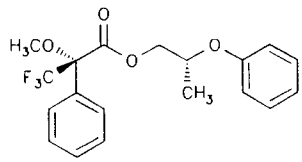

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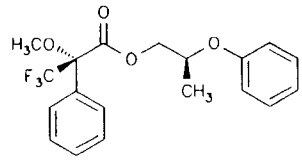

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Racemic alcohol **4** and its enantiomers **4a** and **4b** were tosylated to **5**, **5a**, and **5b**, respectively, which were each reacted with **1** to give ketones **6**, **6a**, and **6b**, respectively. $LiAlH_4$ Reduction of **6**, **6a**, or **6b** yielded the *cis*/*trans*-juvenoids, **7**/**8**, **7a**/**8a**, and **7b**/**8b**, respectively, which could easily be separated by column chromatography on silica gel. The acetals **9**, **9a**, and **9b** were prepared by treatment of **6**, **6a**, and **6b**, respectively, with ethane-1,2-diol under azeotropic conditions.

The biological tests of the juvenoids **7**, **7a**, **7b**, **8**, **8a**, and **8b** with the bugs *Dysdercus cingulatus* (Heteroptera, Pyrrhocoridae) or *Pyrrhocoris apterus* (Heteroptera, Pyrrhocoridae) revealed interesting differences of the *cis*/*trans*-isomers and of diastereoisomers (*cf.* the *Table* for preliminary screaning results). Accordingly, the *cis*-isomers **7**, **7a**, and **7b** generally showed higher biological activity than the corresponding *trans*-isomers **8**, **8a**, and **8b**. The (2″*S*)-diastereoisomers **7b** and **8b** showed higher activity values than the corresponding (2″*R*)-diastereoisomers **7a** and **8a**. In contrast, surprisingly low biological activity was detected for juvenoid ketones **6**, **6a**, and **6b** and juvenoid acetals **9**, **9a**, and **9b**. The ED_{50} values reported in the *Table* indicate the amount of juvenoid causing 50% inhibition of metamorphosis with the species tested. *Pyriproxyfen* (= 1-(4-phenoxyphenoxy)-2-(pyrid-2-yloxy)propane; *Sumitomo*, Japan), showing structural similarity with the juvenoids described in this paper, was used as a reference compound. The biological test consisted in a topical application of an acetone solution of the juvenoid (1–2 µl per individual) onto the surface of the insect body. The juvenilizing effect of the juvenoid was shown by the evoking of the larval-adult intermediate forms.

Table. *Preliminary Results of the Biological Screening of Juvenoids*[a])

cis-Isomer	*Dys.*[b])	*Pyr.*[b])	*trans*-Isomer	*Dys.*[b])	*Pyr.*[b])
7	0.008	0.08	**8**	< 1.0[c])	< 1.0[c])
7a	0.05	0.1	**8a**	1.0	0.1
7b	0.003	0.05	**8b**	0.05	inact.[d])

[a]) For comparison, the ED_{50} values of *Pyriproxyfen* (*Sumitomo*, Japan) were used as reference values; *Dys.*: $ED_{50} = 0.5$, *Pyr.*: $ED_{50} = 0.1$.

[b]) *Dysdercus cingulatus* and *Pyrrhocoris apterus*, ED_{50} values (µg per individual).

[c]) Testing not finished yet.

[d]) Inactive up to a dose of 10 µg per individual.

Experimental Part

General. Ethyl (*S*)-2-hydroxypropanoate (**2a**) was purchased from *Aldrich*; $[\alpha]_D^{20} = -24$ ($c = 8.59$, $CHCl_3$). Column chromatography (CC): silica gel (*Herrmann*, Köln-Ehrenfeld, FRG). TLC: precoated silica gel plates. HPLC: *Hewlett-Packard-HP-1090* instrument, coupled with a *HP-85-B* microcomputer; detection at 220 nm with a UV DAD; integration at 250 nm with a DPU multichannel integrator; 3 columns (each 150 × 3 (i.d.) mm) connected in series, filled with *Separon SGX* (5 µm) as stationary phase; light petroleum ether/Et_2O 95:5 as mobile phase, flow rate 0.5 ml/min. Optical rotations: *Perkin-Elmer-141-M* apparatus. CD spectra ($\Delta\varepsilon$ (λ in nm)): *Jobin-Yvon-Auto-dichrograph-Mark-II* instrument; in MeOH. IR Spectra (in cm^{-1}): *Hewlett-Packard* instrument; in CCl_4. ^{1}H-NMR Spectra: *Varian-Unity-200* spectrometer (in FT mode) at 200.01 MHz; in $CDCl_3$; δ in ppm rel. to Me_4Si (= 0 ppm), J in Hz. ^{13}C-NMR Spectra: *Varian-Unity 5890* spectrometer at 125.70 MHz; in $CDCl_3$; δ in ppm rel. to $CDCl_3$ as internal reference (= 77.00 ppm). GC/MS: anal. *VG-70-250-SE* spectrometer at 70 eV coupled with a *Hewlett-Packard-GC-5890* instrument equipped with a *DB-5* capillary column (30 m × 0.25 mm × 0.25 µm); in *m/z* (rel. %). Elemental analyses: *Perkin-Elmer-240-C* automatic analyzer (C, H, and N) or manual analysis (other elements).

Ethyl rac-*2-Phenoxypropanoate* (**3**). A soln. of phenol (30 mmol) and ethyl *rac*-2-bromopropanoate (**2**, 30 mmol) in butan-2-one (40 ml) was heated under reflux in the presence of anh. K_2CO_3 (6 g) for 4 h. The mixture was then cooled to 0°, diluted with H_2O (40 ml), and extracted with Et_2O. The extract was dried (Na_2SO_4) and evaporated and the residue submitted to CC: 5.54 g (95%) of pure **3**. IR: 1760, 1740, 1602, 1590, 1498, 1243, 694. ^{1}H-NMR: 1.25 (*t*, J = 7.1, *Me*CH_2); 1.62 (*d*, J = 6.8, Me(3)); 4.22 (*q*, J = 7.1, MeCH_2); 4.75 (*q*, J = 6.8, H–C(2)); 6.83–7.02 (*m*, 2 arom. H); 7.22–7.33 (*m*, 3 arom. H). MS: 194 (2, M^+), 185 (5), 181 (15), 149 (5), 107 (13), 91 (100). Anal. calc. for $C_{11}H_{14}O_3$ (194.22): C 68.02, H 7.26; found: C 68.05, H 7.25.

Ethyl (R)-2-Phenoxypropanoate (**3a**). TsCl (65 mmol) was added slowly to a cooled (−20°) and stirred soln. of ethyl (*S*)-2-hydroxypropanoate (**2a**; 63.3 mmol). The mixture was stirred at 0° for 6 h and at r.t. for additional 12 h, then cooled to 0° and poured on ice/5% HCl soln. 1:1 (70 ml). The aq. phase was extracted with AcOEt and the extract dried (Na_2SO_4) and evaporated: 15.2 g (88%) of *ethyl (S)-2-[(tol-4-yl)sulfonyloxy]propanoate* (**2b**), which was used in the next step. $[\alpha]_D^{20} = -33.5$ (c = 0.61, $CHCl_3$). CD: −0.18 (235.5), +0.84 (225.5). IR: 1761, 1745, 1380, 1192, 1180.

As described for **3**, **3a** was prepared from phenol and crude **2b** in 90% yield. CD: +0.49 (276.5), +0.35 (274.5), +0.68 (269.5), +0.52 (265), +0.03 (245.5), +0.87 (228). IR: 1760, 1740, 1602, 1590, 1498, 1243, 694. ^{1}H-NMR: 1.25 (*t*, J = 7.1, *Me*CH_2); 1.62 (*d*, J = 6.8, Me(3)); 4.22 (*q*, J = 7.1, MeCH_2); 4.75 (*q*, J = 6.8, H–C(2)); 6.83–7.02 (*m*, 2 arom. H); 7.22–7.33 (*m*, 3 arom. H). MS: 194 (2, M^+), 185 (5), 181 (15), 149 (5), 107 (13), 91 (100). Anal. calc. for $C_{11}H_{14}O_3$ (194.22): C 68.02, H 7.26; found: C 68.06, H 7.21.

Ethyl (S)-2-Phenoxypropanoate (**3b**). PBr_3 (22.5 mmol) was added dropwise to **2a** (67.7 mmol) cooled to −10° under vigorous stirring. The mixture was stirred for additional 3 h at r.t., and then poured on ice. The aq. phase was extracted with Et_2O, the extract washed with sat. $NaHCO_3$ soln. until neutral, dried (Na_2SO_4), and evaporated, and the residue distilled: 11.5 g (94%) of *ethyl (R)-2-bromopropanoate* (**2c**). B.p. 63–65°/2.9 kPa ([15]: b.p. 84–86°/6.6 kPa). $[\alpha]_D^{20} = +23.9$ (c = 0.43, $CHCl_3$). CD: +1.92 (236.5). IR: 1742.

As described for **3**, **3b** was prepared from phenol and **2c** in 94% yield. CD: −0.65 (277), −0.85 (270.5), −0.70 (264.5), −1.09 (227.5). IR: 1760, 1740, 1602, 1590, 1498, 1243, 694. ^{1}H-NMR: 1.25 (*t*, J = 7.1, *Me*CH_2); 1.62 (*d*, J = 6.8, Me(3)); 4.22 (*q*, J = 7.1, MeCH_2); 4.75 (*q*, J = 6.8, H–C(2)); 6.83–7.02 (*m*, 2 arom. H); 7.22–7.33 (*m*, 3

arom. H). MS: 194 (2, M^{+}), 185 (5), 181 (15), 149 (5), 107 (13), 91 (100). Anal. calc. for $C_{11}H_{14}O_3$ (194.22): C 68.02, H 7.26; found: C 67.98, H 7.30.

rac-, *(R)-, and (S)-2-Phenoxypropan-1-ol* (**4**, **4a**, and **4b**, resp.). A soln. of **3**, **3a**, or **3b** (15.4 mmol) in Et_2O (5 ml) was added dropwise to a cooled (0°) and stirred suspension of $LiAlH_4$ (26.3 mmol) in Et_2O (75 ml). Stirring was continued for additional 3 h at r.t. Then the mixture was worked up according to [16]. The crude product was chromatographed (silica gel): **4**, **4a**, or **4b** in 98–99% yield.

4, **4a**, and **4b**: IR: 3610, 1599, 1498, 1244, 1066. ^{1}H-NMR: 1.27 (*d*, *J* = 6.3, Me(3)); 3.70 (*dd*, *J* = 6.1, 11.7, 1 H–C(1)); 3.77 (*dd*, *J* = 4.2, 11.7, 1 H–C(1)); 4.50 (*m*, *J* = 4.2, 6.2, 6.2, H–C(2)); 6.89–7.01 (*m*, 2 arom. H); 7.23–7.35 (*m*, 3 arom. H).

4: Anal. calc. for $C_9H_{12}O_2$ (152.19): C 71.02, H 7.95; found: C 70.9, H 7.99.

4a: CD: −0.26 (278), −0.33 (271). Anal. calc. for $C_9H_{12}O_2$ (152.19): C 71.02, H 7.95; found: C 71.04, H 8.01.

4b: CD: +0.31 (278), +0.34 (271), +0.34 (265.5). Anal. calc. for $C_9H_{12}O_2$ (152.19): C 71.02, H 7.95; found: C 71.05, H 7.93.

rac-, *(R)-, and (S)-2-Phenoxypropyl Toluene-4-sulfonate* (**5**, **5a**, and **5b**, resp.). Toluene-4-sulfonyl chloride (18.9 mmol) was added slowly to a cooled (0°) and stirred soln. of **4**, **4a**, or **4b** (12 mmol) in pyridine (15 ml). Stirring was continued for additional 8 h at r.t. and then the mixture allowed to stand overnight. The mixture was poured on ice/5% HCl soln. 1:1 (50 ml) and extracted with benzene and the extract dried (Na_2SO_4) and evaporated: crude **5**, **5a**, or **5b** in quant. yield.

5, **5a**, and **5b**: IR: 1600, 1590, 1496, 1376, 1241, 1190, 1179. ^{1}H-NMR: 1.30 (*d*, *J* = 6.3, Me(3)); 2.44 (br. *s*, MeC_6H_4); 4.07 (*dd*, *J* = 4.9, 10.5, 1 H–C(1)); 4.17 (*dd*, *J* = 5.9, 10.5, 1 H–C(1)); 4.56 (*m*, H–C(2)); 6.79–6.94 (*m*, 2 arom. H); 7.20–7.36 (*m*, 3 arom. H); 7.22 (*m*, 2 arom. H); 7.78 (*m*, 2 arom. H).

5: Anal. calc. for $C_{16}H_{18}O_4S$ (306.37): C 62.72, H 5.92, S 10.47; found: C 62.63, H 5.99, S 10.56.

5a: CD: −0.26 (278), −0.35 (271.5), +0.17 (238). Anal. calc. for $C_{16}H_{18}O_4S$ (306.37): C 62.72, H 5.92, S 10.47; found: C 62.65, H 5.98, S 10.55.

5b: CD: +0.27 (277), +0.36 (271), +0.30 (266). Anal. calc. for $C_{16}H_{18}O_4S$ (306.37): C 62.72, H 5.92, S 10.47; found: C 62.81, H 5.86, S 10.39.

(2RS,2″RS)-, (2RS,2″R)-, and (2RS,2″S)-2-[4′-(2″-Phenoxypropyloxy)benzyl]cyclohexan-1-one (**6**, **6a**, and **6b**, resp.). Powdered NaOH (0.16 g) was added to a soln. of **1** (3.26 mmol) in DMSO (15 ml) and the mixture vigorously stirred and heated at 110° under N_2 for 1 h. A soln. of crude **5**, **5a**, or **5b** (3.26 mmol) in DMSO (2 ml) was then added dropwise and heating and stirring continued for additional 4 h. After cooling to 0°, the mixture was poured on ice, the aq. phase extracted with Et_2O, the extract dried (Na_2SO_4) and evaporated, and the residue submitted to chromatographic purification: **6**, **6a**, or **6b** in 88–95% yield.

6, **6a**, and **6b**: IR: 1713, 1653, 1613, 1601, 1589, 1513, 1495, 1237. ^{1}H-NMR: 1.25–1.90 (*m*, CH_2(3), CH_2(4), CH_2(5)); 1.44 (*d*, *J* = 6.1, Me(3″)); 2.04 (*m*, H–C(2)); 2.21–2.69 (*m*, CH_2(6)); 2.36 (*dd*, *J* = 8.4, 13.5, 1 H, $C_6H_4CH_2$); 3.15 (*dd*, *J* = 4.4, 13.5, 1 H, $C_6H_4CH_2$); 3.97 (*dd*, *J* = 5.4, 9.5, 1 H–C(1″)); 4.20 (*dd*, *J* = 5.4, 9.5, 1 H–C(1″)); 4.73 (*m*, H–C(2″)); 6.82 (*m*, 2 arom. H); 6.92–6.99 (*m*, 2 arom. H); 7.06 (*m*, 2 arom, H); 7.22–7.33 (*m*, 3 arom. H). ^{13}C-NMR: 17.24 (*q*); 25.00 (*t*); 28.01 (*t*); 33.32 (*t*); 34.53 (*t*); 42.12 (*t*); 52.62 (*d*); 70.87 (*t*); 72.37 (*d*); 114.48 (*d*); 116.11 (*d*); 121.07 (*d*); 129.48 (*d*); 130.02 (*d*); 132.70 (*s*); 157.02 (*s*); 157.77 (*s*); 212.61 (*s*). MS: 338 (100, M^{+}), 241 (75), 147 (75), 135 (77), 121 (29), 107 (95), 94 (15), 77 (35).

6: Anal. calc. for $C_{22}H_{26}O_3$ (338.43): C 78.07, H 7.74; found: C 78.10, H 7.71.

6a: CD: −0.47 (278), −0.59 (271), +0.42 (235). Anal. calc. for $C_{22}H_{26}O_3$ (338.43): C 78.07, H 7.74; found: C 78.05, H 7.75.

6b: CD: +0.59 (278), +0.68 (270.5), +0.56 (266.5). Anal. calc. for $C_{22}H_{26}O_3$ (338.43): C 78.07, H 7.74; found: C 78.12, H 7.69.

(1RS,2RS,2″RS)-, (1RS,2RS,2″R)-, (1RS,2RS,2″S)-, (1RS,2RS,2″RS)-, (1RS,2RS,2″R)-, and (1RS,2RS,2″S)-2-[4′-(2″-Phenoxypropyloxy)benzyl]cyclohexan-1-ol (**7**, **7a**, **7b**, **8**, **8a**, and **8b**, resp.). A soln. of **6**, **6a**, or **6b** (3.25 mmol) in Et_2O (5 ml) was added dropwise to a cooled (0°) and stirred suspension of $LiAlH_4$ (13 mmol) in Et_2O (50 ml). Stirring was continued at r.t. for additional 3 h. After workup according to [16], the *cis*- and *trans*-isomers were separated by CC: 38–42% of *cis*-isomer **7**, **7a**, or **7b** and 51–54% of *trans*-isomer **8**, **8a**, or **8b**.

7, **7a**, and **7b**: IR: 3629, 1612, 1601, 1589, 1513, 1495, 1236, 1049, 975. ^{1}H-NMR: 0.77–1.83 (*m*, H–C(2), CH_2(3), CH_2(4), CH_2(5), CH_2(6)); 1.44 (*d*, *J* = 6.3, Me(3″)); 2.47 (*dd*, *J* = 7.6, 13.7, 1 H, $C_6H_4CH_2$); 2.65 (*dd*, *J* = 7.3, 13.7, 1 H, $C_6H_4CH_2$); 3.78 (*dt*, *J* = 2.4, 2.4, 4.0, H–C(1)); 3.98 (*dd*, *J* = 5.3, 9.8, 1 H–C(1″)); 4.15 (*dd*, *J* = 5.3, 9.8, 1 H–C(1″)); 4.73 (*m*, *J* = 5.8, 5.8, 5.8, 5.8, 5.8, H–C(2″)); 6.83 (*m*, 2 arom. H); 6.93–6.99 (*m*, 2 arom. H); 7.10 (*m*, 2 arom. H); 7.23–7.34 (*m*, 3 arom. H). ^{13}C-NMR: 17.28 (*q*); 20.33 (*t*); 25.30 (*t*); 26.35 (*t*); 33.27 (*t*);

37.76 (*t*); 43.67 (*d*); 68.48 (*d*); 70.89 (*t*); 72.40 (*d*); 114.45 (*d*); 116.13 (*d*); 121.08 (*d*); 129.50 (*d*); 129.99 (*d*); 133.39 (*s*); 156.90 (*s*); 157.80 (*s*). MS: 340 (100, M^{+}), 322 (35), 241 (30), 229 (10), 207 (7), 188 (38), 147 (36), 135 (80), 107 (86), 94 (18), 77 (36).

7: Anal. calc. for $C_{22}H_{28}O_3$ (340.40): C 77.62, H 8.29; found: C 77.67, H 8.26.

7a: CD: −0.33 (278), −0.44 (271), −0.36 (267.5). Anal. calc. for $C_{22}H_{28}O_3$ (340.40): C 77.62, H 8.29; found: C 77.64, H 8.32.

7b: CD: +0.55 (278), +0.69 (272), +0.57 (265.5). Anal. calc. for $C_{22}H_{28}O_3$ (340.40): C 77.62, H 8.29; found: C 77.58, H 8.31.

8, **8a**, and **8b**: IR: 3623, 1612, 1601, 1589, 1511, 1495, 1236, 1052. ^{1}H-NMR: 0.77–1.75 (*m*, H–C(2), CH_2(3), CH_2(4), CH_2(5), CH_2(6)); 1.44 (*d*, *J* = 6.3, Me(3″)); 2.32 (*dd*, *J* = 9.0, 13.7, 1 H, $C_6H_4CH_2$); 3.07 (*dd*, *J* = 3.9, 13.7, 1 H, $C_6H_4CH_2$); 3.28 (*dt*, *J* = 4.4, 9.8, 9.8, H–C(1)); 3.98 (*dd*, *J* = 5.4, 9.8, 1 H–C(1″)); 4.16 (*dd*, *J* = 5.4, 9.8, 1 H–C(1″)); 4.74 (*m*, *J* = 5.9, 5.9, 5.9, 5.9, 5.9, H–C(2″)); 6.83 (*m*, 2 arom. H); 6.92–6.99 (*m*, 2 arom. H); 7.09 (*m*, 2 arom. H); 7.23–7.34 (*m*, 3 arom. H). ^{13}C-NMR: 17.28 (*q*); 24.89 (*t*); 25.43 (*t*); 29.97 (*t*); 35.81 (*t*); 38.03 (*t*); 47.08 (*d*); 74.46 (*d*); 70.87 (*t*); 72.40 (*d*); 114.39 (*d*); 116.13 (*d*); 121.07 (*d*); 129.49 (*d*); 130.28 (*d*); 133.04 (*s*); 156.91 (*s*); 157.80 (*s*). MS: 340 (100, M^{+}), 322 (49), 281 (12), 241 (30), 228 (11), 207 (30), 188 (49), 147 (53), 135 (88), 121 (37), 107 (98), 94 (28), 77 (45).

8: Anal. calc. for $C_{22}H_{28}O_3$ (340.40): C 77.62, H 8.29; found: C 77.65, H 8.33.

8a: CD: −0.21 (278), −0.28 (271), −0.21 (266). Anal. calc. for $C_{22}H_{28}O_3$ (340.40): C 77.62, H 8.29; found: C 77.57, H 8.24.

8b: CD: +0.53 (278), +0.64 (271.5), +0.54 (265.5). Anal. calc. for $C_{22}H_{28}O_3$ (340.40): C 77.62, H 8.29; found: C 77.64, H 8.27.

*(2*RS*,2″*RS*)-, (2*RS*,2″*R*)-, (2*RS*,2″*S*)-2-[4′-(2″-Phenoxypropyloxy)benzyl]cyclohexan-1-one Ethylene Acetal* (**9**, **9a**, and **9b**, resp.). To a soln. of **6**, **6a**, or **6b** (6.5 mmol) in benzene (60 ml), ethane-1,2-diol was added and the mixture refluxed under azeotropic conditions for 5 h. Then it was cooled to 0° and diluted with H_2O (20 ml), the aq. phase extracted with Et_2O, the combined org. phase dried (Na_2SO_4) and evaporated, and the residue purified by short CC: **9**, **9a**, or **9b** in quant. yield.

9, **9a**, and **9b**: IR: 1612, 1601, 1589, 1513, 1495, 1237, 1156, 1088, 1052, 926. ^{1}H-NMR: 1.04–1.74 (*m*, H–C(2), CH_2(3), CH_2(4), CH_2(5), CH_2(6)); 1.44 (*d*, *J* = 5.8, Me(3″)); 2.20 (*dd*, *J* = 11.0, 13.7, 1 H, $C_6H_4CH_2$); 2.98 (*dd*, *J* = 3.9, 13.7, 1 H, $C_6H_4CH_2$); 3.97 (*dd*, *J* = 5.4, 9.8, 1 H–C(1″)); 3.97–4.02 (*m*, OCH_2CH_2O); 4.15 (*dd*, *J* = 5.4, 9.8, 1 H–C(1″)); 4.73 (*m*, *J* = 5.6, 5.6, 5.6, 5.6, 5.6, H–C(2″)); 6.82 (*m*, 2 arom. H); 6.91–6.99 (*m*, 2 arom. H); 7.07 (*m*, 2 arom. H); 7.22–7.34 (*m*, 3 arom. H). ^{13}C-NMR: 17.29 (*q*); 23.96 (*t*); 24.64 (*t*); 28.43 (*t*); 33.61 (*t*); 34.90 (*t*); 46.95 (*d*); 64.82 (*t*); 64.89 (*t*); 70.87 (*t*); 72.40 (*d*); 110.66 (*s*); 114.36 (*d*); 116.13 (*d*); 121.06 (*d*); 129.48 (*d*); 130.13 (*d*); 133.81 (*s*); 156.78 (*s*); 157.80 (*s*). MS: 382 (48, M^{+}), 339 (18), 320 (4), 281 (5), 254 (63), 207 (19), 135 (25), 121 (12), 107 (30), 99 (100), 77 (23).

9: Anal. calc. for $C_{24}H_{30}O_4$ (382.48): C 75.36, H 7.91; found: C 75.30, H 7.94.

9a: CD: −0.38 (278), −0.52 (271.5), −0.43 (268.5). Anal. calc. for $C_{24}H_{30}O_4$ (382.48): C 75.36, H 7.91; found: C 75.40, H 7.95.

9b: CD: +0.44 (277.5), +0.54 (269.5), +0.55 (266). Anal. calc. for $C_{24}H_{30}O_4$ (382.48): C 75.36, H 7.91; found: C 75.31, H 7.89.

3,3,3-Trifluoro-2-methoxy-2-phenylpropanoates (MTPA) **10**–**13**. MTPA chloride (5.7 mg, 0.023 mmol) in dry benzene (0.2 ml) was added to a soln. of **4a** or **4b** (0.023 mmol) and 4-(dimethylamino)pyridine (2.7 mg, 0.023 mmol) in dry pyridine (0.1 ml). The mixture was stirred at r.t. for 7 h. Usual workup and purification by CC afforded the MTPA's in 90–95% yields.

10: CD: −0.28 (278), −0.38 (270), −0.42 (267), −0.38 (261.5), +2.22 (229.5). ^{1}H-NMR: 1.33 (*d*, *J* = 6.4, Me(3′)); 3.51 (*q*, *J* = 1.2, MeO); 4.34 (*dd*, *J* = 3.8, 11.4, 1 H–C(1′)); 4.56 (*dd*, *J* = 6.9, 11.4, 1 H–C(1′)); 4.65 (*m*, *J* = 3.8, 6.5, 6.5, 6.5, 6.9, H–C(2′)); 6.84–7.56 (*m*, 10 arom. H).

11: CD: −0.12 (277), −0.17 (271.5), +0.09 (261.5), −0.003 (257.5), −1.49 (233). ^{1}H-NMR: 1.33 (*d*, *J* = 6.4, Me(3′)); 3.52 (*q*, *J* = 1.2, MeO); 4.44 (*dd*, *J* = 4.1, 11.4, 1 H–C(1′)); 4.48 (*dd*, *J* = 5.8, 11.4, 1 H–C(1′)); 4.65 (*m*, H–C(2′)); 6.84–7.56 (*m*, 10 arom. H).

12: CD: +0.24 (277.5), +0.31 (271), +0.17 (265), +1.80 (229.5). ^{1}H-NMR: 1.33 (*d*, *J* = 6.3, Me(3′)); 3.52 (*q*, *J* = 1.2, MeO); 4.44 (*dd*, *J* = 4.3, 11.4, 1 H–C(1′)); 4.48 (*dd*, *J* = 6.1, 11.4, 1 H–C(1′)); 4.65 (*m*, *J* = 4.3, 6.1, 6.3, 6.3, 6.3, 1 H–C(2′)); 6.84–7.56 (*m*, 10 arom. H).

13: CD: +0.47 (277.5), +0.60 (270), +0.59 (267), +0.51 (261.5), −1.80 (229.5). ^{1}H-NMR: 1.33 (*d*, *J* = 6.4, Me(3′)); 3.52 (*q*, *J* = 1.2, MeO); 4.34 (*dd*, *J* = 3.9, 11.4, 1 H–C(1′)); 4.56 (*dd*, *J* = 6.9, 11.4, 1 H–C(1′)); 4.65 (*m*, *J* = 3.9, 6.4, 6.4 6.4, 6.9, H–C(2′)); 6.84–7.56 (*m*, 10 arom. H).

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