SYNTHESIS OF JUVENILE HORMONE BIOANALOGS DERIVED FROM 2-(4-HYDROXYBENZYL)-6-METHYLCYCLOHEXANONE

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A new simple approach to isomeric 2-(4-alkoxybenzyl)-6-methylcyclohexanones and the corresponding alcohols and a subsequent synthesis of compounds imitating the action of the insect juvenile hormones is described. Biological activity of the isomeric juvenile hormone bioanalogs differed considerably when tested on the flesh fly (*Sarcophaga bullata*) and the yellow mealworm (*Tenebrio molitor*).

Key words: Juvenile hormone bioanalogs; 2-(4-Hydroxybenzyl)-6-methylcyclohexanone; *Sarcophaga bullata; Tenebrio molitor*.

Juvenile hormone bioanalogs[1] (juvenoids) derived from 2-(4-hydroxybenzyl)cyclohexanone were invented on a base of a general scheme (Fig. 1) starting from the skeleton of a natural juvenile hormone (e.g. **JH II**) and on a base of many structure–activity studies[2]. All these attempts were motivated by a need of active compounds that would be easier approachable, and thus more convenient for their use as biorational pesticides. An introduction of cycles into the molecule is one of the most often used approaches in designing the active compounds. It led for example to carbamate juvenoids **1**–**4** derived from 2-(4-hydroxybenzyl)cyclohexanone that showed excellent biological activity on a broad spectrum of insect pests[3]. As it follows from Fig. 1 an introduction of a methyl group into position 3″ (for numbering of the products see Fig. 1) of the cyclohexane ring should lead to compounds that would even better suffice the general scheme. Moreover, it has been demonstrated that the substituted oxirane ring with a strictly defined absolute configuration is a site critical in conferring the activity. Therefore, our question was what influence on biological activity will have both the relative and absolute configuration of substituents of the cyclohexane ring. To support our theory on the

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role of the cyclohexane ring, recently, we have reported on remarkably different biological activity of **3** and **4** after their enzymic resolution[4]. Moreover, we have found an essential role of absolute configuration at position 2″, whereas, the absolute configuration at position 1″ of the cyclohexane ring effects the activity much less[4], which is also in good accord with the proposed Fig. 1. The aim of the present work is to find synthetic ways to racemic juvenoids **12**–**15**, to model substrates **5**–**10** for the enzymic resolution and substrates **16**–**20** convenient for a preparation of chiral precursors for a synthesis of optically active **14** and **15**.

Sane and Rao[5] synthesized compounds **5**–**10** via (2*E*)-(4-methoxybenzal)-6-methylcyclohexanone and via a catalytic hydrogenation of 1,6-*trans*-(2*E*)-(4-methoxybenzal)-6-methyl-1-cyclohexanol or its corresponding acetate, respectively. Their method, however, for its relative sluggishness due to many recrystallizations was not convenient for our large scale preparations and, moreover, it does not lead to 1*r*, 2*t*, 6*c*-2-(4-methoxy-

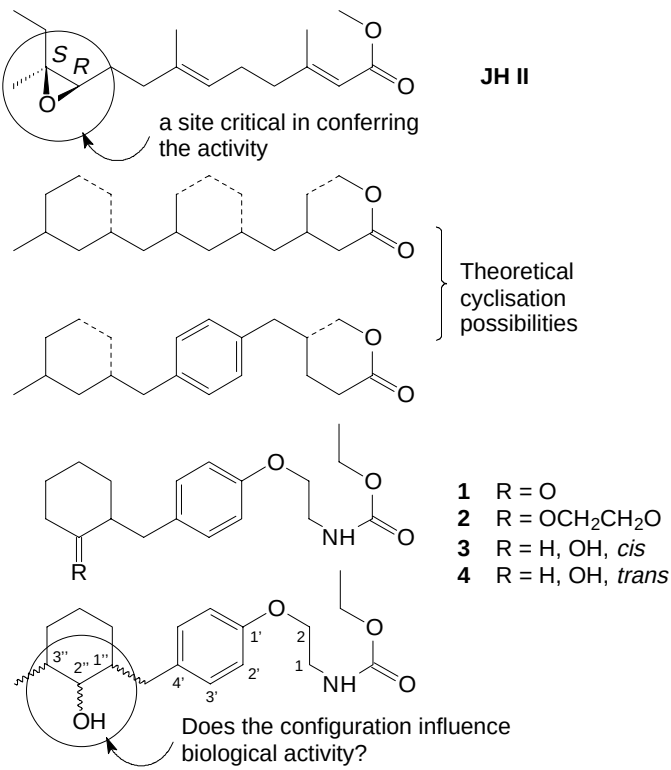
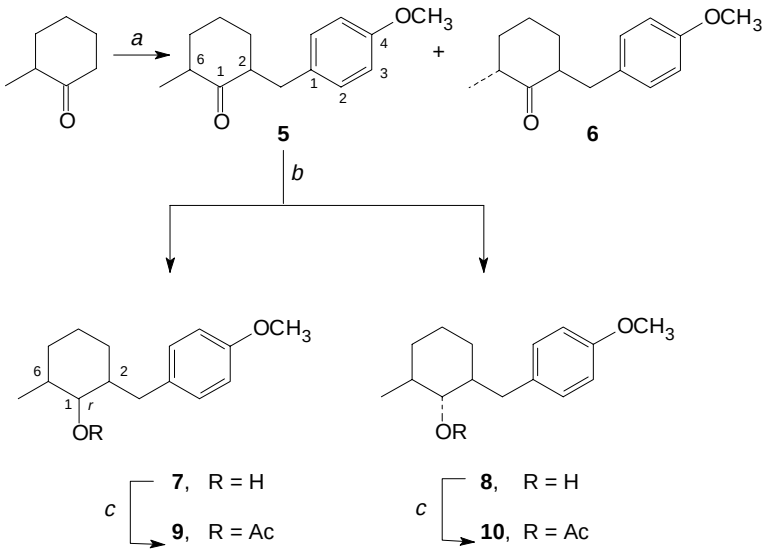


FIG. 1
Invention of structure of juvenile hormone bioanalogs

benzyl)-6-methyl-1-cyclohexanol (for numbering of the intermediates see Scheme 1, compound **5**) and its corresponding acetate, it means their method led only to three of the four possible target isomers. The most obvious way to the desired compounds was an alkylation of an enamine of 2-methylcyclohexanone and a separation of the respective isomeric ketones. A reduction of the pure ketones should lead to mixtures of isomeric alcohols differing in the relative configuration of hydroxyl substituent only, which enables a good separation on silica gel.

Stork alkylation[6] of a pyrrolidine enamine of 2-methylcyclohexanone with 4-methoxybenzyl chloride led (Scheme 1) to isomeric ketones **5** and **6** as the main products. After a separation on silica gel the thermodynamically more stable ketone **5** was reduced by lithium aluminum hydride yielding a separable mixture of isomeric alcohols **7** and **8**. After separation these alcohols **7** and **8** were converted to the corresponding acetates **9** and **10**. An attempt to reduce the thermodynamically less stable ketone **6** using lithium aluminum hydride gave an unseparable mixture of isomers.

Synthesis of the racemic juvenoids **12**–**15** (Scheme 2) started from the mixture of isomeric ketones **5** and **6**, that were demethylated using azeotropic hydrobromic acid to a mixture of *cis*, *trans*-2-(4-hydroxybenzyl)-6-methylcyclohexanones (**11**). All attempts to separate this mixture by column chromatography failed due to an extreme tendency



a (i) pyrrolidine, (ii) 4-$MeOC_6H_4CH_2Cl$, (iii) separation/SiO_2

b (i) $LiAlH_4$, (ii) separation/SiO_2, (iii) recrystallization

c Ac_2O, DMAP, Et_3N

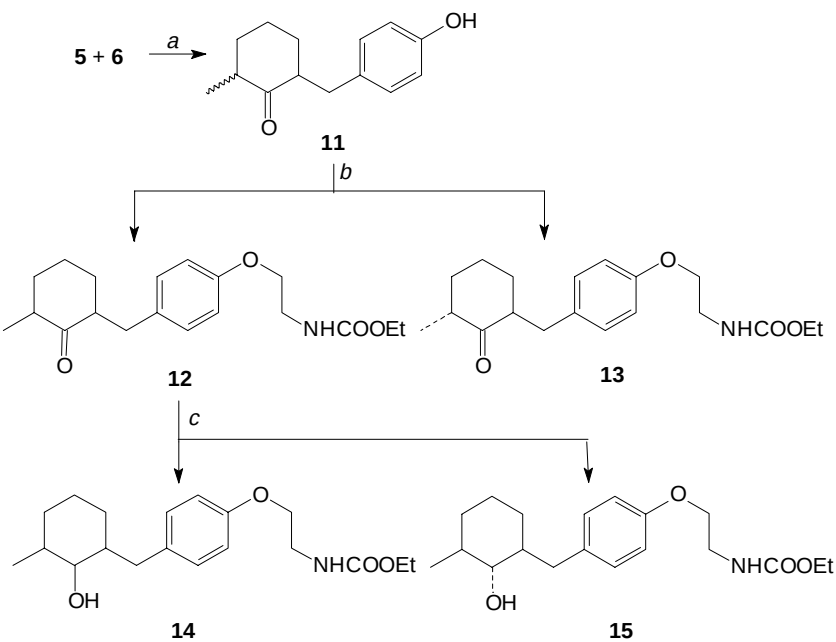
SCHEME 1

of both isomers to crystallize. Therefore, **11** was first alkylated by ethyl 2-bromoethylcarbamate and the obtained mixture was separated on silica gel to yield the respective isomers **12** and **13**. A reduction of **12** by sodium borohydride and a subsequent separation gave compounds **14** and **15**. A reduction of ketone **13** by the complex hydride gave an unseparable mixture of isomers.

The isomeric mixture **11** yielded by a reaction with chloromethyl methyl ether (and a separation from isomeric *trans*-**16**) compound **16** (Scheme 3). A reduction of **16** and a subsequent separation on silica gel gave the isomeric alcohols **17** and **18**, that were finally acetylated to yield acetates **19** and **20**.

All the above mentioned compounds were isolated in high purity and no traces of any isomers were detected (HPLC and ^{1}H NMR). A determination of relative configuration on basis of ^{1}H NMR and IR spectra of the above mentioned compounds will be a subject of an accompanying paper[7].

Juvenoids **14** and **15** were tested on the yellow mealworm (*Tenebrio molitor*) that proved to be a suitable species for a fast and sensitive screening bioassay of compounds



a HBr, Ac_2O; *b* (i) K_2CO_3, MeCOEt, $Br(CH_2)_2NHCOOEt$, (ii) separation/SiO_2

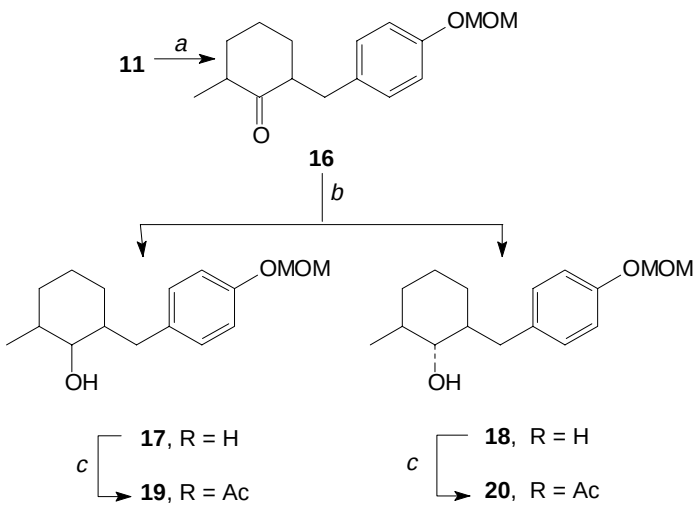
c (i) $NaBH_4$, (ii) separation/SiO_2

SCHEME 2

showing the juvenilizing activity[1] and, moreover, this species is used by many other authors so that comparison is possible. The test was carried out by a standard method described by Sláma et al.[1] . Sterility test on *Sarcophaga bullata* was done on the count of hatched eggs (larvae) and sterile eggs in the uterus. Simultaneously, the distribution of yolk and morphological changes were evaluated. The already mentioned carbamate juvenoids **2**, **3**, and **4** were used as standards. The results of the bioassays are summarized in Table I.

TABLE I
Biological activity of prepared juvenoids **14** and **15** and standards **2**–**4** on selected insect species

Compound	*Sarcophaga bullata* sterilization, %	*Tenebrio molitor* ID_{50}, μg/individual
14	2	$2.0 . 10^{-5}$
15	100	$2.9 . 10^{-6}$
2	42	$2.7 . 10^{-6}$
3	–	$5.3 . 10^{-5}$
4	–	$1.2 . 10^{-4}$



a (i) $ClCH_2OCH_3$, NaH; (ii) separation/SiO_2 (- *trans* - **16**)

b (i) $LiAlH_4$, (ii) separation/SiO_2; *c* Ac_2O, DMAP, Et_3N

SCHEME 3

The introduction of methyl substituent into position 3″ of the cyclohexane ring really led in both cases to an increase of biological activity (cf. Table I**,** *Tenebrio molitor*: **3** versus **14** and **4** versus **15**). A different relative configuration of compounds **14** and **15** causes a difference in biological activity of one order of the magnitude in case of *Tenebrio molitor* and a remarkable difference in sterilization ability on *Sarcophaga bullata*. In both cases isomer **15** is superior when compared to **14**. Biological activity of compound **15** bearing a free alcohol group is only slightly worse or even better than standard compound **2** which is considered to be a very good juvenoid, in spite of the fact, that a polar group present in the molecule usually causes a decrease in activity[1].

To conclude the reported method presents a convenient and quick approach to both isomeric 2-(4-alkoxybenzyl)-6-methylcyclohexanones and after a reduction of the thermodynamically more stable *cis*-isomer using a complex hydride to easily separable mixtures of the corresponding alcohols. The presumed different activity of isomeric compounds **14** and **15** and a possible increase in activity due to an introduction of methyl group into position 3″ of the cyclohexane ring has really been confirmed. These data present an additional proof for the suspected key role of the cyclohexane ring configuration in conferring the biological activity.

EXPERIMENTAL

Melting points (m.p.) were determined on a Kofler hot stage. Infrared spectra (wavenumbers in cm^{-1}) were recorded on a Brucker IFS 88 spectrometer with carbon tetrachloride as the solvent. ^1H NMR spectra were taken on a Varian UNITY-500 (499.8 MHz) spectrometer at 23 °C, in deuteriochloroform and with tetramethylsilane as the internal reference. Chemical shifts are given in ppm (δ-scale), and coupling constants (*J*) are given in Hz. Thin-layer chromatography (TLC) performed on precoated silica gel TLC sheets Silufol and Silufol UV 254. Column chromatography (CC) was performed on silica gel (Gebr. Herrman, Köln–Ehrenfeld). Analytical high-performance liquid chromatography (HPLC) was performed on Sepharon Si silica gel (particle size 5 μm), 3 columns 250 × 4 mm connected in series (light petroleum–ether 1 : 1, 1 ml min^{-1}); detection at 220 and 275 nm, integration at 220 nm. All compounds are racemic, prefix (±) is omitted. Sodium hydride was used as a 50% dispersion in mineral oil.

cis-2-(4-Methoxybenzyl)-6-methylcyclohexanone (**5**) and *trans*-2-(4-Methoxybenzyl)-6-methylcyclohexanone (**6**)

A mixture of 2-methylcyclohexanone (30 g, 0.27 mol) and pyrrolidine (19 g, 0.27 mol) was dissolved in benzene (60 ml), and a catalytic amount of TsOH . H_2O (10 mg, 0.1 mmol) was added. The mixture was refluxed and water removed under azeotropic conditions. The volatiles were evaporated, and the residue was distilled in vacuo to yield *N*-(6-methylcyclohex-1-en-1-yl)pyrrolidine (43.4 g, 98%), b.p. 114 °C/2.0 kPa. To the solution of the enamine (33 g, 0.2 mol) in dioxane (30 ml), 4-methoxybenzyl chloride (34.4 g, 0.22 mol) in dioxane (35 ml) was added. The mixture was refluxed at 120 °C for 5 h, water (50 ml) added, and the mixture heated for an additional 1 h. Dioxane was evaporated, the residue diluted with ether and extracted with ether (10 × 100 ml), the combined extracts washed with 5% aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and water until the mixture was neutral, dried (Na_2SO_4), and evaporated, and the crude mixture of **5** and **6** (HPLC **5**/**6** 2.76 : 1) was

separated by CC (light petroleum–ether 5 : 1). Yield 24.3 g (52%) of **5**, m.p. 58 °C. IR spectrum: 1 713, 1 612, 1 513, 1 301, 1 041. ^{1}H NMR spectrum: 7.13 m, 2 H (2 × arom. H); 6.90 m, 2 H (2 × arom. H); 3.46 s, 3 H (OMe); 3.42 dd, 1 H, *J* = 5.1, 13.9 (1 H of $C_6H_4C\mathbf{H}_2$); 2.51 dd, 1 H, *J* = 8.2, 13.9 (1 H of $C_6H_4C\mathbf{H}_2$); 2.29 m, 1 H (H-2); 2.00 m, 1 H (H-6); 1.92–1.06 m, 6 H (2 × H-3, 2 × H-4, 2 × H-5); 1.13 d, 3 H, *J* = 5.9 (Me-6). Mass spectrum (*m/z*, %): 232 (15, M^+), 216 (8), 121 (100), 91 (8), 77 (8). For $C_{15}H_{20}O_2$ (232.3) calculated: 77.55% C, 8.68% H; found: 77.51% C, 8.67% H. Yield 7.9 g (17%) of **6**. IR spectrum: 1 709, 1 612, 1 513, 1 301, 1 041. ^{1}H NMR spectrum: 7.05 m, 2 H (2 × arom. H); 6.87 m, 2 H (2 × arom. H); 3.44 s, 3 H (OMe); 3.08 dd, 1 H, *J* = 5.7, 13.7 (1 H of $C_6H_4C\mathbf{H}_2$); 2.70 m, 1 H (H-2); 2.57 dd, 1 H, *J* = 9.0, 13.6 (1 H of $C_6H_4C\mathbf{H}_2$); 2.44 m, 1 H (H-6); 1.72–1.22 m, 6 H (2 × H-3, 2 × H-4, 2 × H-5); 1.08 d, 3 H, *J* = 6.8 (Me-6). Mass spectrum (*m/z*, %): 232 (15, M^+), 121 (100), 91 (8), 77 (8). For $C_{15}H_{20}O_2$ (232.3) calculated: 77.55% C, 8.68% H; found: 77.61% C, 8.59% H.

2-*c*-(4-Methoxybenzyl)-6-*c*-methyl-1-*r*-cyclohexanol (**7**) and 2-*t*-(4-Methoxybenzyl)-6-*t*-methyl-1-*r*-cyclohexanol (**8**)

To a stirred suspension of $LiAlH_4$ (4.4 g, 117 mmol) in ether (50 ml), a solution of ketone **5** (9.1 g, 39.2 mmol) in ether (50 ml) was added dropwise. After 4 h of stirring at room temperature (TLC monitoring), a 25% aqueous solution of potassium sodium tartrate tetrahydrate (12.8 ml) was added. The mixture was extracted with ether (4 × 50 ml), the combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated in vacuo. A crude mixture of isomeric alcohols **7** and **8** (HPLC **7**/**8** 1 : 1.2) was separated by CC (light petroleum–ether 1 : 1) and the obtained isomers were recrystallized from light petroleum–ether. Yield 2.7 g (29%) of **7**, m.p. 48 °C (literature[5] gives m.p. 47–48 °C). IR: 3 640, 1 612, 1 512, 1 300, 1 041. ^{1}H NMR spectrum: 7.18 m, 2 H (2 × arom. H); 6.94 m, 2 H (2 × arom. H); 3.47 s, 3 H (OMe); 3.45 dt, 1 H, *J* = 4.9 + 2.5, 2.5 (H-1); 2.79 dd, 1 H, *J* = 8.0, + 13.4 (1 H of $C_6H_4C\mathbf{H}_2$); 2.62 dd, 1 H, *J* = 6.7, 13.4 (1 H of $C_6H_4C\mathbf{H}_2$); 1.73–1.17 m, 8 H (H-2, 2 × H-3, 2 × H-4, 2 × H-5, H-6); 0.90 d, 3 H, *J* = 6.8 (Me-6). Mass spectrum (*m/z*, %): 234 (61, M^+), 216 (53), 160 (32), 134 (89), 121 (100). For $C_{15}H_{22}O_2$ (234.3) calculated: 76.88% C, 9.47% H; found: 76.91% C, 9.41% H. Yield 3.4 g (37 %) of **8**, m.p. 88 °C (literature[5] gives 85 °C). IR spectrum: 3 640, 1 613, 1 511, 1 300, 1 041. ^{1}H NMR spectrum: 7.19 m, 2 H (2 × arom. H); 6.94 m, 2 H (2 × arom. H); 3.46 s, 3 H (OMe); 3.27 dd, 1 H, *J* = 3.7 and 13.4 (1 H of $C_6H_4C\mathbf{H}_2$); 2.73 dt, 1 H, *J* = 5.8 and 9.6 and 9.6 (H-1); 2.39 dd, 1 H, *J* = 9.0 13.2 (1 H of $C_6H_4C\mathbf{H}_2$); 1.61–0.85 m, 8 H (H-2, 2 × H-3, 2 × H-4, 2 × H-5, H-6); 1.07 d, 3 H, *J* = 6.6 (Me-6). Mass spectrum (*m/z*, %): 234 (18, M^+), 216 (19), 160 (10), 134 (61), 121 (100). For $C_{15}H_{22}O_2$ (234.3) calculated: 76.88% C, 9.47% H; found: 76.79% C, 9.39% H.

2-*c*-(4-Methoxybenzyl)-6-*c*-methyl-1-*r*-cyclohexanol Acetate (**9**)

Acetic anhydride (0.3 g, 2.9 mmol) was added in several portions to a stirred mixture of the alcohol **7** (0.66 g, 2.8 mmol) and 4-dimethylaminopyridine (1.2 mg, 0.01 mmol) in dry triethylamine (14 ml) at room temperature. After stirring for 5 h, the reaction was poured into a cooled saturated solution of potassium hydrogen carbonate (6 ml). The product was extracted by light petroleum (3 × 20 ml), the combined organic extracts were dried over K_2CO_3 and the solvents were evaporated under reduced pressure. The crude product was purified by CC (light petroleum–ether 5 : 1) affording the pure acetate **9** (0.63 g, 81%); m.p. 51 °C. IR spectrum: 1 738, 1 613, 1 513, 1 300, 1 245, 1 240, 1 041. ^{1}H NMR spectrum: 7.03 m, 2 H (2 × arom. H); 6.81 m, 2 H (2 × arom. H); 5.11 t, 1 H, *J* = 2.2 (H-1); 3.78 s, 3 H (OMe); 2.56 dd, 1 H, *J* = 5.9 and 13.7 (1 H of $C_6H_4C\mathbf{H}_2$); 2.25 dd, 1 H, *J* = 8.6 and 13.7 (1 H of $C_6H_4C\mathbf{H}_2$); 2.14 s, 3 H (OAc); 1.74–1.19 m, 8 H (H-2, 2 × H-3, 2 × H-4, 2 × H-5, H-6); 0.82 d, 3 H, *J* = 6.8 (Me-6). Mass spectrum (*m/z*, %): 276 (47, M^+), 216 (81), 134 (44), 121 (100), 95 (22), 69 (30). For $C_{17}H_{24}O_3$ (276.4) calculated: 73.88% C, 8.75% H; found: 73.92% C, 8.69% H.

2-*t*-(4-Methoxybenzyl)-6-*t*-methyl-1-*t*-cyclohexanol Acetate (**10**)

Acetylation of alcohol **8** (0.66 g, 2.8 mmol) by the same procedure (see presenting experiment) gave 0.51 g (65%) of acetate **10**. IR spectrum: 1 738, 1 613, 1 512, 1 300, 1 244, 1 041. ^{1}H NMR spectrum: 7.03 m, 2 H (2 × arom. H); 6.81 m, 2 H (2 × arom. H); 4.47 t, 1 H, *J* = 10.3 (H-1); 3.78 s, 3 H (OMe); 2.75 dd, 1 H, *J* = 4.0 and 13.7 (1 H of $C_6H_4C\mathbf{H}_2$); 2.16 dd, 1 H, *J* = 9.5 and 13.7 (1 H of $C_6H_4C\mathbf{H}_2$); 2.04 s, 3 H (OAc); 1.76–0.92 m, 8 H (H-2, 2 × H-3, 2 × H-4, 2 × H-5, H-6); 0.87 d, 3 H, *J* = 6.8 (Me-6). Mass spectrum (*m/z*, %): 276 (9, M^+), 216 (30), 134 (78), 121 (100), 95 (10). For $C_{17}H_{24}O_3$ (276.4) calculated: 73.88% C, 8.75% H; found: 73.90% C, 8.67% H.

Ethyl *cis*-*N*-{2-{4-[(3-Methyl-2-oxocyclohex-1-yl)methyl]phenoxy}ethyl}carbamate (**12**) and
Ethyl *trans*-*N*-{2-{4-[(3-Methyl-2-oxocyclohex-1-yl)methyl]phenoxy}ethyl}carbamate (**13**)

To the crude mixture of isomeric ketones **5** and **6** (50 g, 215.2 mmol) in acetic anhydride (100 ml), 48% aqueous HBr (80 ml) was added at room temperature. After 12 h of refluxing , the mixture was cooled, water (200 ml) added, the mixture neutralized by addition of powdered $CaCO_3$ (233 g), and the precipitate filtered off and washed with water and ether. The aqueous layer was extracted with ether (5 × 100 ml), the combined organic extracts dried (Na_2SO_4), and evaporated, and the mixture was recrystallized from light petroleum–ether to yield the isomeric mixture **11** (30.7 g, 65%). Dry powdered potassium carbonate (2.62 g, 19.0 mmol) and ethyl *N*-(2-bromoethyl)carbamate (0.67 g, 3.4 mmol) were added to a solution of **11** (0.37 g, 1.7 mmol) in 2-butanone (20 ml), the mixture was refluxed for 8 h, then cooled and filtered. The solid was washed with ether, and then the filtrate was washed with water and dried ($MgSO_4$). The volatiles were evaporated under reduced pressure to yield a crude mixture of **12** and **13** (HPLC **12**/**13** 1 : 1.83). The mixture was separated by CC (light petroleum–ether 3 : 1) to give pure **12** (0.16 g, 29%). IR spectrum: 3 464, 1 727, 1 715, 1 612, 1 509. ^{1}H NMR spectrum: 7.07 m, 2 H (arom. H); 6.79 m, 2 H (arom. H); 5.16 br s, 1 H (NH); 4.12 br q, 2 H, *J* = 6.9 ($OC\mathbf{H}_2CH_3$); 4.00 t, 2 H, *J* = 5.1 (2 × H-2); 3.56 br q, 2 H, *J* = 5.1 (2 × H-1); 3.14 dd, 1 H, *J* = 5.1 and 14.2 (1 H of $C_6H_4C\mathbf{H}_2$); 2.50 m, 1 H (H-1″); 2.41 m, 1 H (H-3″); 2.34 dd, 1 H, *J* = 8.3 and 14.2 (1 H of $C_6H_4C\mathbf{H}_2$); 2.12–1.26 m, 6 H (2 × H-4″, 2 × H-5″, 2 × H-6″); 1.24 t, 3 H, *J* = 6.9 ($OCH_2C\mathbf{H}_3$); 1.02 d, 3 H, *J* = 6.4 (Me-3″). Mass spectrum (*m/z*, %): 333 (6, M^+), 216 (5), 176 (5), 116 (100), 88 (52). For $C_{19}H_{27}NO_4$ (333.4) calculated: 68.44% C, 8.16% H, 4.20% N; found: 68.48% C, 8.20% H, 4.15% N. Yield of **13** 0.31 g (56%). IR spectrum: 3 465, 1 726, 1 712, 1 612, 1 509. ^{1}H NMR spectrum: 7.06 m, 2 H (2 × arom. H); 6.80 m, 2 H (2 × arom. H); 5.11 br s, 1 H (NH); 4.12 br q, 2 H, *J* = 7.1 ($OC\mathbf{H}_2CH_3$); 4.00 t, 2 H, *J* = 5.1 (2 × H-2); 3.57 br q, 2 H, *J* = 5.4 (2 × H-1); 3.00 dd, 1 H, *J* = 5.4 and 13.7 (1 H of $C_6H_4C\mathbf{H}_2$); 2.67 m, 1 H (H-1″); 2.62 m, 1 H (H-3″); 2.58 dd, 1 H, *J* = 8.3 and 14.2 (1 H of $C_6H_4C\mathbf{H}_2$); 2.02–1.50 m, 6 H (2 × H-4″, 2 × H-5″, 2 × H-6″); 1.24 t, 3 H, *J* = 7.1 ($OCH_2C\mathbf{H}_3$); 1.09 d, 3 H, *J* = 6.4 (Me-3″). Mass spectrum (*m/z*, %): 333 (6, M^+), 287 (6), 244 (6), 176 (19), 116 (100), 88 (45). For $C_{19}H_{27}NO_4$ (333.4) calculated: 68.44% C, 8.16% H, 4.20% N; found: 68.35% C, 8.19% H, 4.21% N.

Ethyl *N*-{2-{4-[(2-*r*-Hydroxy-3-*c*-methylcyclohex-1-*c*-yl)methyl]phenoxy}ethyl}carbamate (**14**) and
Ethyl *N*-{2-{4-[(2-*t*-Hydroxy-3-*t*-methylcyclohex-1-*t*-yl)methyl]phenoxy}ethyl}carbamate (**15**)

To a solution of ketone **12** (1.97 g, 5.9 mmol) in methanol (100 ml), $NaBH_4$ (1.11 g, 29.5 mmol) was added at 0 °C under stirring (TLC monitoring). The mixture was diluted with brine (100 ml) and extracted with ether (5 × 100 ml), the combined organic layer dried (Na_2SO_4) and evaporated and the obtained isomeric mixture of **14** and **15** (HPLC **14**/**15** 1.3 : 1) was separated by CC (light petroleum–ether 1 : 1); yield of pure **14** 0.77 g (39%). IR spectrum: 3 640, 3 465, 1 727, 1 612, 1 509, 1 448. ^{1}H NMR spectrum: 7.10 m, 2 H (2 × arom. H); 6.81 m, 2 H (2 × arom. H); 5.13 br t, 1 H, *J* = 5.4

(NH); 4.12 q, 2 H, J = 7.1 ($OC\mathbf{H}_2CH_3$); 4.01 t, 2 H, J = 5.1 (2 × H-2); 3.57 br q, 2 H, J = 5.4 (2 × H-1); 3.48 m, 1 H (H-2″); 2.66 dd, 1 H, J = 8.3 and 13.6 (1 H of $C_6H_4C\mathbf{H}_2$); 2.51 dd, 1 H, J = 7.1 and 13.6 (1 H of $C_6H_4C\mathbf{H}_2$); 1.74–1.20 m, 1 H (H-1″, H-3″, 2 × H-4″, 2 × H-5″, 2 × H-6″); 1.24 t, 3 H, J = 7.1 ($OCH_2C\mathbf{H}_3$); 0.92 d, 3 H, J = 6.8 (Me-3″). Mass spectrum (*m/z*, %): 335 (3, M^+), 176 (6), 116 (100), 107 (30), 88 (47). For $C_{19}H_{29}NO_4$ (335.4) calculated: 68.03% C, 8.71% H, 4.18% N; found: 68.05% C, 8.80% H, 4.20% N. Yield 0.20 g (10%) of **15**. IR spectrum: 3 640, 3 465, 1 727, 1 612, 1 509, 1 446. ^{1}H NMR spectrum: 7.09 m, 2 H (2 × arom. H); 6.80 m, 2 H (2 × arom. H); 5.16 br t, 1 H, J = 5.4 (NH); 4.12 q, 2 H, J = 7.1 ($OC\mathbf{H}_2CH_3$); 4.00 t, 2 H, J = 5.1 (H-2); 3.57 br q, 2 H, J = 5.1 (H-1); 3.10 dd, 1 H, J = 3.9 and 13.6 (1 H of $C_6H_4C\mathbf{H}_2$); 2.84 t, 1 H, J = 9.8 (H-2″); 2.32 dd, 1 H, J = 8.9 and 13.6 (1 H of $C_6H_4C\mathbf{H}_2$); 1.74–0.86 m, 8 H (H-1″, H-3″, 2 × H-4″, 2 × H-5″, 2 × H-6″); 1.24 t, 3 H, J = 7.1 ($OCH_2C\mathbf{H}_3$); 1.02 d, 3 H, J = 6.4 (Me-3″). Mass spectrum (*m/z*, %): 335 (5, M^+), 176 (6), 116 (100), 88 (44). For $C_{19}H_{29}NO_4$ (335.4) calculated: 68.03% C, 8.71% H, 4.18% N; found: 68.00% C, 8.72% H, 4.19% N.

cis-2-(4-Methoxymethoxybenzyl)-6-methylcyclohexanone (**16**)

A solution of the isomeric mixture **11** (14.1 g, 64.7 mmol) in dry benzene (142 ml) was added to a stirred suspension of sodium hydride (3.5 g, 72.8 mmol) in dry benzene (100 ml) under nitrogen and the mixture was refluxed for 1 h. The mixture was cooled to 0 °C, chloromethyl methyl ether (15.7 g, 194.1 mmol) was added, and the mixture was stirred for 9 h at 0 °C. Water (50 ml) was added and the mixture was extracted with ether (3 × 100 ml), washed with a 5% aqueous solution of NaOH (50 ml), with water (2 × 100 ml), and the organic layer was dried ($MgSO_4$). The volatiles were evaporated in vacuo, and the crude **16** was separated from its respective *trans*-isomer by CC (light petroleum–ether 5 : 1) to yield pure **16** (8.20 g, 49%). IR spectrum: 1 713, 1 612, 1 511, 1 154, 1 081, 1 012. ^{1}H NMR spectrum: 7.07 m, 2 H (2 × arom. H); 6.94 m, 2 H (2 × arom. H); 5.14 s, 2 H (OCH_2); 3.47 s, 3 H (OMe); 3.16 dd, 1 H, J = 5.1 and 14.0 (1 H of $C_6H_4C\mathbf{H}_2$); 2.50 m, 1 H (H-2); 2.41 m, 1 H (H-6); 2.34 dd, 1 H, J = 8.2 and 14.0 (1 H of $C_6H_4C\mathbf{H}_2$); 2.12–1.26 m, 6 H (2 × H-3, 2 × H-4, 2 × H-5); 1.02 d, 3 H, J = 5.9 (Me-6). Mass spectrum (*m/z*, %): 262 (32, M^+), 151 (49), 121 (34), 91 (5), 77 (5), 45 (100). For $C_{16}H_{22}O_3$ (262.3) calculated: 73.24% C, 8.45% H; found: 73.31% C, 8.40% H.

2-*c*-(4-Methoxymethoxybenzyl)-6-*c*-methyl-1-*r*-cyclohexanol (**17**) and 2-*t*-(4-Methoxymethoxybenzyl)-6-*t*-methyl-1-*r*-cyclohexanol (**18**)

Ketone **16** (7.0 g, 26.6 mmol) was reduced by the same procedure as the reduction of ketone **5** to yield a mixture of isomeric alcohols **17** and **18** (HPLC **17**/**18** 1.23 : 1) that were separated by CC (light petroleum–ether 3 : 1). Yield of pure **17** 3.48 g, (49%). IR spectrum: 3 638, 1 612, 1 511, 1 153, 1 080, 1 013. ^{1}H NMR spectrum: 7.10 m, 2 H (2 × arom. H); 6.96 m, 2 H (2 × arom. H); 5.15 s, 2 H (OCH_2); 3.49 br t, 1 H, J = 2.4 (H-1); 3.48 s, 3 H (OMe); 2.66 dd, 1 H, J = 8.2 and 13.5 (1 H of $C_6H_4C\mathbf{H}_2$); 2.52 dd, 1 H, J = 7.0 and 13.5 (1 H of $C_6H_4C\mathbf{H}_2$); 1.71–1.20 m, 8 H (H-2, 2 × H-3, 2 × H-4, 2 × H-5, H-6); 0.92 d, 3 H, J = 6.7 (Me-6). Mass spectrum (*m/z*, %): 264 (26, M^+), 246 (14), 151 (18), 121 (22), 45 (100). For $C_{16}H_{24}O_3$ (264.4) calculated: 72.69% C, 9.15% H; found: 72.60% C, 9.11% H. Yield 3.12 g, (44%) of **18**. IR spectrum: 3 638, 1 612, 1 446, 1 153, 1 080, 1 013. ^{1}H NMR spectrum: 7.09 m, 2 H (2 × arom. H); 6.95 m, 2 H (2 × arom. H); 5.15 s, 2 H (OCH_2); 3.48 s, 3 H (OMe); 3.11 dd, 1 H, J = 3.9 and 13.5 (1 H of $C_6H_4C\mathbf{H}_2$); 2.85 t, 1 H, J = 9.7 (H-1); 2.31 dd, 1 H, J = 9.0 and 13.5 (1 H of $C_6H_4C\mathbf{H}_2$); 1.69–1.32 m, 8 H (H-2, 2 × H-3, 2 × H-4, 2 × H-5, H-6); 1.02 d, 3 H, J = 6.8 (Me-6). Mass spectrum (*m/z*, %): 264 (20, M^+), 246 (10), 151 (15), 121 (21), 45 (100). For $C_{16}H_{24}O_3$ (264.4) calculated: 72.69% C, 9.15% H; found: 72.61% C, 9.21% H.

2-*c*-(4-Methoxymethoxybenzyl)-6-*c*-methyl-1-*r*-cyclohexanol Acetate (**19**)

Acetate **19** was prepared from alcohols **17** (0.94 g, 3.5 mmol) in the same manner as acetate **9** from alcohol **7**. Yield of acetate **19** 1.0 g (92%). IR spectrum: 1 738, 1 612, 1 511, 1 237, 1 153, 1 080, 1 014. ^{1}H NMR spectrum: 7.03 m, 2 H (2 × arom. H); 6.94 m, 2 H (2 × arom. H); 5.15 d, 1 H, J = 6.8 (1 H of OCH_2); 5.14 d, 1H, J = 6.8 (1 H of OCH_2); 5.12 t, 1 H, J = 2.4 (H-1); 3.48 s, 3 H (OMe); 2.57 dd, 1 H, J = 5.7 and 13.7 (1 H of $C_6H_4C\mathbf{H}_2$); 2.25 dd, 1 H, J = 8.6 and 13.8 (1 H of $C_6H_4C\mathbf{H}_2$); 2.14 s, 3 H (OAc); 1.73–1.64 m, 2 H (H-2, H-6); 1.62–1.18 m, 6 H (2 × H-3, 2 × H-4, 2 × H-5); 0.82 d, 3 H, J = 6.7 (Me-6). Mass spectrum (*m/z*, %): 306 (14, M^+), 246 (33), 151 (14), 121 (15), 45 (100). For $C_{18}H_{26}O_4$ (306.4) calculated: 70.56% C, 8.55% H; found: 70.42% C, 8.59% H.

2-*t*-(4-Methoxymethoxybenzyl)-6-*t*-methyl-1-*r*-cyclohexanol Acetate (**20**)

Acetate **20** was prepared from alcohol **18** (0.78 g, 3.0 mmol) by the same procedure as acetate **9** from alcohol **7**. Yield 0.78 g (86%). IR spectrum: 1 736, 1 612, 1 511, 1 241, 1 154, 1 080, 1 013. ^{1}H NMR spectrum: 7.03 m, 2 H (2 × arom. H); 6.94 m, 2 H (2 × arom. H); 5.14 s, 2 H (OCH_2); 4.47 t, 1 H, J = 10.1 (H-1); 3.47 s, 3 H (OMe); 2.75 dd, 1 H, J = 4.0 and 13.8 (1 H of $C_6H_4C\mathbf{H}_2$); 2.17 dd, 1 H, J = 9.5 and 13.7 (1 H of $C_6H_4C\mathbf{H}_2$); 2.03 s, 3 H (OAc); 1.75–1.49 m, 2 H (H-2, H-6); 1.75–1.49 m and 1.24–0.90 m, 6 H (2 × H-3, 2 × H-4, 2 × H-5); 0.87 d, 3 H, J = 6.4 (Me-6). Mass spectrum (*m/z*, %): 306 (13, M^+), 246 (29), 151 (13), 121 (16), 45 (100). For $C_{18}H_{26}O_4$ (306.4) calculated: 70.56% C, 8.55% H; found: 70.52% C, 8.61% H.

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