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Optically active juvenoids derived from 2-substituted cyclopentanol and their biological activity on *Tenebrio molitor*

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Abstract

Optically active juvenoids **1c**–**4c** were synthesised using chiral precursors prepared by biotransformation reactions of suitable substrates. Biological activity of these juvenoids on *Tenebrio molitor* is reported.

1. Introduction

Although the mechanism of insect juvenile hormones (JH) reception has not been elucidated, it is generally accepted that the receptor is chiral. Considerable differences in biological activity observed for the optical isomers of compounds imitating the action of insect JH have been presented.[1] This fact implies that a chiral receptor system (and possibly more than one such site) is involved in the insect JH response. It is supposed that the optically active centre of the juvenoid molecule takes a direct part in, or is very close to the part of the molecule interacting with the receptor site.[2]

In our previous paper[3] we reported on the biological activity of optically active juvenoids derived from 2-substituted cyclohexanol. The biological activity of these compounds was strongly influenced by the spatial arrangement of the cyclohexane ring substituents. Moreover, in the case of the six-membered ring it was shown that biological activity was much more strongly influenced by C(2) configuration (carbon atom bearing the hydroxyl group) than by the C(1) one.

In this paper we wish to report on the preparation and biological activity of optically active juvenoids **1c**–**4c** derived from 2-substituted cyclopentanol (Fig. 1).

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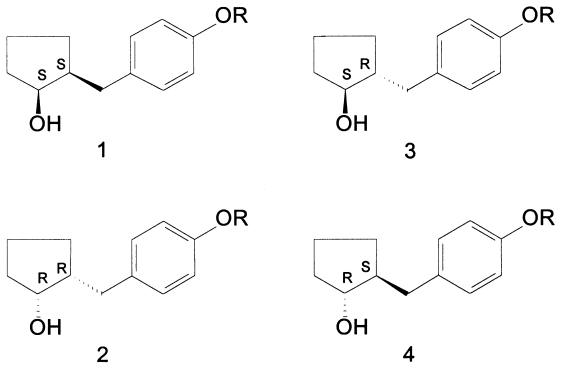


Fig. 1.

2. Results and discussion

Biotransformation was chosen as a technique for the introduction of the chiral information. Substrates **5**–**7** (Fig. 2) used for the biotransformation were prepared (Scheme 1) from 2-(4-hydroxybenzyl)-1-cyclopentanone.[4] A sodium salt of this compound was treated with chloromethyl methyl ether[5] in benzene yielding the racemic substrate **5**. The ketone **5** was reduced by $LiAlH_4$ and a mixture of corresponding isomeric alcohols **8** and **9** was separated on silica gel. An acetylation[6] of the respective isomeric alcohols **8** and **9** yielded the racemic substrates **6** or **7** respectively (Scheme 1).

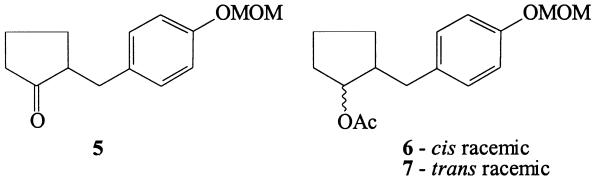


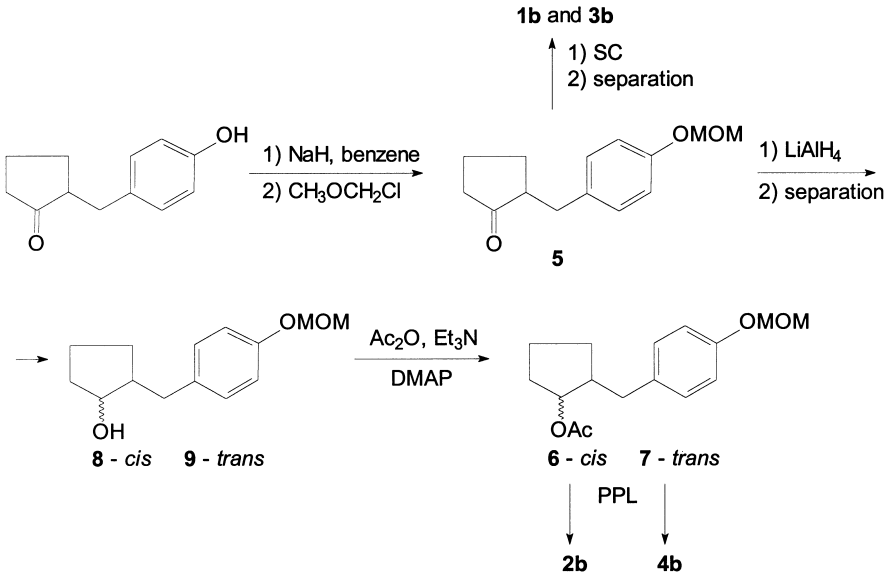
Fig. 2.

An enzymatic reduction of the substrate **5** in aqueous media (Scheme 1, Tables 1 and 2) using *Saccharomyces cerevisiae*[7] yielded a mixture of diastereomeric alcohols **1b** and **3b** that were separated by column chromatography on silica gel. The chemical yield was improved by dissolving the substrate with a small amount of acetone. An enzymatic hydrolysis of **6** and **7** in aqueous media (Scheme 1, Tables 1 and 2) using porcine pancreatic lipase yielded stereoisomers **2b** or **4b**, respectively. Again, the solubility of the substrates was improved by the addition of a small amount of acetone.

Absolute configuration of the biotransformation products **1b**–**4b** was assigned[8] using ^{1}H and ^{19}F NMR (Table 3) spectra of the corresponding MTPA[9–13] esters.

The enantiomeric excess of the alcohols **1b**–**4b** was determined on the basis of HPLC data of the corresponding MTPA esters (Tables 1 and 4). The MOM protecting group proved to be stable on the HPLC columns. This fact simplified considerably the evaluation of a broad biotransformation screening leading to a selection of optimal biocatalyst and reaction conditions.

Although CD spectra of **1b**–**4b** and **1c**–**4c** were measured, no Cotton effect was found. The analogous six-membered compounds showed very tiny Cotton effects[3] and probably their five-membered analogues



Scheme 1.

Table 1
Biotransformation of substrates **5**–**7**

Substrate	Biocatalyst	Product	AC	Yield (%)	ee (%)
5	SC[a]	**1b**	1*S*, 2*S*	66.6	90.87
		3b	1*S*, 2*R*	16.98	> 99
6	PPL[b]	**2b**	1*R*, 2*R*	11.89	> 99
7	PPL[b]	**4b**	1*R*, 2*S*	10.5	> 99

[a]*Saccharomyces cerevisiae*, [b]Porcine pancreatic lipase

Table 2
Biotransformation conditions

Biocatalyst	*Saccharomyces cerevisiae* (5 g), strain CCY 21-4-63-e	PPL[a] (10 mg), Sigma
Cultivation[10]	48 h at 27±1°C in a liquid malt	-
Biotransformation	7 d at 27±1°C, phosphate buffer pH 7.0 (100 ml)	7 d at room temperature, phosphate buffer pH 7.0 (4.8 ml)
Substrate	**5**, 100 mg (0.40 mmol) in 0.2 ml of acetone	**6**, **7**; 100 mg (0.34 mmol) in 0.2 ml of acetone

[a]Porcine pancreatic lipase

Table 3
^{1}H and ^{19}F NMR data of MTPA esters derived from **1b**–**4b** and the assignment of absolute configuration

Source acid	(*R*)-MTPA		(*S*)-MTPA		(*R*)-MTPA	(*S*)-MTPA	AC
Source alcohol	δ[H-C(6)]	δ[H'-C(6)]	δ[H-C(6)]	δ[H'-C(6)]	δ(CF_3)		
1b	2.41	2.62	2.5	2.71	-67.22	-67.36	1*S*, 2*S*
2b	2.51	2.7	2.41	2.62	-67.36	-67.22	1*R*, 2*R*
3b	2.49	2.74	2.43	2.72	-67.76	-67.84	1*S*, 2*R*
4b	2.42	2.72	2.49	2.74	-67.85	-67.75	1*R*, 2*S*

[a]$CFCl_3$ =0.0 ppm was used as internal reference

Table 4
MTPA esters of alcohols **1b**–**4b**, HPLC data

Source alcohol	AC (major in bold)	MTPA	HPLC area (%)	time (min)	ee (%)
		Saccharomyces cerevisiae			
1b:2b	**1*S*, 2*S*** : 1*R*, 2*R*	*R*	67.25 : 3.503	43.77 & 44.56	90.87
3b:4b	**1*S*, 2*R*** : 1*R*, 2*S*	*R*	73.58 : 0.19	39.71 & 41.02	>99
		Porcine pancreatic lipase			
1b:2b	1*S*, 2*S* : **1*R*, 2*R***	*R*	0.01 : 56.58	43.76 & 44.56	>99
3b:4b	1*S*, 2*R* : **1*R*, 2*S***	*R*	0.02 : 56.56	39.72 & 41.02	>99

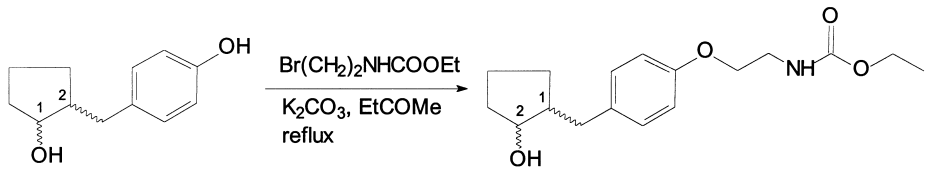
show only immeasurable values. Specific rotations of compounds **1b**–**4b** and **1c**–**4c** are summarised in Table 5.

For the following synthesis of the target optically active juvenoids **1c**–**4c**, chiral precursors **1a**–**4a** prepared by deprotection of **1b**–**4b** were used. The chiral precursors **1a**–**4a** defined by their assigned absolute configuration and enantiomeric excess were alkylated[14] (Scheme 2) using ethyl N-(2-bromoethyl)carbamate[15] in the presence of dry powdered potassium carbonate in refluxing 2-butanone.

Table 5
Specific rotation of alcohols **1b**–**4b** and **1c**–**4c**

Compound	AC	$[\alpha]^{20}_D$	c(g.100 ml^{-1})[a]
1b	1*S*, 2*S*	13.6	0.48
2b	1*R*, 2*R*	-14.08	0.5
3b	1*S*, 2*R*	20.6	0.5
4b	1*R*, 2*S*	-17.35	0.5
1c	1*S*, 2*S*	7.47[b]	0.83
2c	1*R*, 2*R*	-8.33[b]	0.55
3c	1*R*, 2*S*	9.2[b]	1.34
4c	1*S*, 2*R*	-7.39[b]	0.73

[a]($CHCl_3$), [b]24°C



1a (1*S*, 2*S*)
2a (1*R*, 2*R*)
3a (1*S*, 2*R*)
4a (1*R*, 2*S*)

1d (1*S*, 2*S*)
2d (1*R*, 2*R*)
3d (1*R*, 2*S*)
4d (1*S*, 2*R*)

Scheme 2.

The optically active juvenoids **1c**–**4c** were obtained in chemical yields exceeding 87% (when using acetone as a solvent the yields were much lower). The absolute configuration of the asymmetric carbon atoms of the juvenoids **1c**–**4c** corresponds to that of the starting chiral precursors **1a**–**4a**. It should be pointed out that according to the IUPAC nomenclature system, the numbering of the saturated ring of the juvenoids **1c**–**4c** differs from that of compounds **1a**–**4a**. This is due to the side chain directive carbamate moiety of the compounds **1c**–**4c** (Scheme 2). Analogously to our previous work[3] we assume that both the deprotection of **1b**–**4b** and the alkylation of the chiral phenolic precursors **1a**–**4a** did not influence any of the asymmetric carbon atoms, and it is to be expected that the reaction proceeds with retention of both absolute configuration and enantiomeric excess. Moreover, retention of the absolute configuration was confirmed by specific rotation (Table 5) of the juvenoids **1c**–**4c**. To summarise, the optically active juvenoids **1c**–**4c** defined by their assigned absolute configuration of the asymmetric carbon atoms and by their enantiomeric excess were prepared.

The biological assay of compounds **1c**–**4c** and the respective racemates (Table 6) was performed by a standard method described by Sláma et al.[16] The compounds were applied topically on the ventral body part of freshly moulted pupae of the yellow mealworm (*Tenebrio molitor*). The yellow mealworm proved to be a suitable species for a fast and sensitive screening bioassay of compounds showing the juvenilising activity. Biological activity is given in ID_{50} values (an inhibitory dose) that gives a dose of an active compound causing changes of 50% of observed morphological features. In other words, the less the ID_{50} value, the better the activity. For comparison, the biological activity of racemic mixtures of **1c** and **2c** (*cis*-1,2-relative configuration) or **3c** and **4c** (*trans*-1,2-relative configuration), respectively, prepared earlier,[17] was used.

Table 6
Biological activity of optically active juvenoids **1c**–**4c** in comparison with the racemic forms

Compound	ID_{50} (μg/pupa)
1c	0.000 001 9
1c and **2c** (racemic)	0.000 17
2c	0.000 075
3c	0.000 000 65
3c and **4c** (racemic)	0.000 083
4c	0.000 001 2

Results of the bioassays are summarised in Table 6. The (1*R*,2*S*)-stereoisomer **3c** generally shows the

best activity when compared with the other stereoisomers **1c**, **2c**, **4c**, and the racemic compounds **1c**/**2c** and **3c**/**4c**. The differences in biological activity of the respective stereoisomers **1c**–**4c** show clearly that the cyclopentane ring (the spatial arrangement of its substituents on C(1) and C(2), respectively) plays a role in molecular recognition in the interaction of these juvenoids with the receptor site(s). The receptor decides clearly in favour of juvenoids **1c** and **3c** with the (*S*)-absolute configuration of C(2). On the other hand, the absolute configuration of C(1) seems to influence the biological activity (Table 6) much less, a phenomenon which also occurs in the case of the cyclohexane analogues.[3] To conclude, even though we did not work with optically pure compounds (ee of compounds **1c**–**4c** was in the range 90–>99%), we have found considerable differences in biological activity of the particular stereoisomers **1c**–**4c**. (*S*)-Absolute configuration of C(2) is essential for high biological activity, whereas the configuration of carbon atom C(1) does not influence biological activity of these compounds decidedly.

3. Experimental

The ^{1}H NMR spectra were recorded on a Varian UNITY-200 spectrometer at 200.06 MHz frequency in deuteriochloroform, using tetramethylsilane as an internal reference. The ^{13}C NMR spectra were recorded on a Varian UNITY-500 spectrometer at 125.7 MHz frequency in deuteriochloroform, using the central line of the solvent as an internal reference (δ=77.0 ppm). The ^{19}F NMR spectra were recorded on a Varian UNITY-200 spectrometer at 188.15 MHz in deuteriochloroform, with a capillary containing hexafluorobenzene as an external reference (δ=−162.9 ppm), unless stated otherwise. The IR spectra were recorded on a Perkin–Elmer 580 instrument in tetrachloromethane, unless stated otherwise. HPLC analyses were carried out on a Knauer instrument. Detection was carried out at 220, 230, 240, 265 nm wavelength by means of an ultraviolet deuterium lamp; integration was carried out at 220 nm. A column 250×4 (i.d.) mm, filled with Separon SGX (particle size 7 mm) as stationary phase, was used for the analysis. Light petroleum (40–68°C fraction) with 3% ether was used as mobile phase, flow rate 1.4 (*cis*) or 1.2 (*trans* samples) ml min^{-1}, respectively. Column chromatography was carried out on silica gel (Gebr. Herrman, Köln–Ehrenfeld). Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The CD spectra were obtained from a Jobin Yvon Mark V instrument in methanol. Microanalyses were performed using a Perkin–Elmer 240 C elemental analyser.

*3.1. 2-(4-Methoxymethoxybenzyl)-1-cyclopentanone, **5***

To a stirred suspension of NaH (3.94 g, 81.8 mmol, 50% disp. in mineral oil) in dry benzene (50 ml), a solution of 2-(4-hydroxybenzyl)-1-cyclopentanone (22.0 g, 0.126 mol) in dry benzene (50 ml) was added under Ar, and the mixture was refluxed for 1 h. The mixture was cooled to 0°C and chloromethyl methyl ether (30.64 g, 0.379 mmol) was added. The mixture was stirred for 9 h at 0°C. Water (50 ml) was added and the mixture was extracted with diethyl ether (3×100 ml), washed with NaOH/H_2O 5% solution (50 ml), with water (2×100 ml), and the organic layer was dried over $MgSO_4$. The volatiles were evaporated in vacuo and the residue (475 mg) was purified by column chromatography on silica gel (100 g) to yield pure **5** (12.4 g, 41.9%). IR: 2959, 2933, 1742, 1712, 1511, 1236, 1200, 1176, 1154, 1081, 1017, 1012, 925 cm^{-1}; ^{1}H NMR: δ 7.08 (m, 2H), 6.95 (m, 2H), 5.15 (s, 2H), 3.47 (s, 3H), 3.07 (dd, *J*=13.9, 4.2, 1H), 2.51 (dd, *J*=13.9, 9.3, 1H), 2.34–2.08 (m, 2H), 2.32–1.51 (m, 7H); ^{13}C NMR: δ 220.2 (C-1), 51.1 (C-2), 29.1 (C-3), 20.5 (C-4), 38.2 (C-5), 34.8 (C-6), 133.4 (C-7), 129.9 (C-8,8′), 116.3 (C-9,9′), 155.7 (C-10), 94.6 (C-11), 55.9 (C-12); MS: m/z 234 (M^+, 35), 151 (30), 121 (29), 107 (5), 81 (3), 77 (3), 55 (3), 45 (100). Anal. calcd for $C_{14}H_{18}O_3$ (234.28): C, 71.82; H, 7.74. Found: C, 71.87; H, 7.77.

3.2. cis- *and* trans-*2-(4-Methoxymethoxybenzyl)-1-cyclopentanol,* ***8*** *and* ***9***

To a cooled (0°C) and stirred suspension of $LiAlH_4$ (2.66 g, 70.96 mmol) in dry diethyl ether (100 ml) ketone **5** (8.31 g, 35.48 mmol) in dry diethyl ether (100 ml) was added dropwise. After 7 h of stirring, potassium sodium tartrate tetrahydrate 25% aq. solution (10.8 ml) was added. The mixture was extracted with diethyl ether (4×100 ml), the combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The crude mixture of isomeric alcohols (9 g) was separated by column chromatography on silica gel (100 g) to give 1.35 g (16.1%) of pure **8** and 4.20 g (50.0%) of pure **9**. **8**: IR: 2957, 2934, 1511, 1232, 1198, 1175, 1154, 1081, 1018, 1013, 924 cm^{-1}; ^1H NMR: δ 7.14 (m, 2H), 6.96 (m, 2H), 5.15 (s, 2H), 4.08 (dt, *J*=2×1.5, 4.4, 1H), 3.48 (s, 3H), 2.75 (dd, *J*=13.8, 7.8, 1H), 2.63 (dd, *J*=13.8, 7.8, 1H), 1.97 (m, 1H), 1.88–1.44 (m, 6H); ^{13}C NMR: δ 74.4 (C-1), 34.9 (C-2), 28.7 (C-3), 21.8 (C-4), 34.6 (C-5), 47.7 (C-6), 135.3 (C-7), 129.6 (C-8,8′), 116.2 (C-9,9′), 155.4 (C-10), 94.6 (C-11), 55.9 (C-12); MS: m/z 236 (M^+, 22), 218 (10), 188 (13), 151 (14), 121 (20), 107 (10), 91 (6), 77 (5), 45 (100). Anal. calcd for $C_{14}H_{20}O_3$ (236.30): C, 71.16; H, 8.53. Found: C, 71.12; H, 8.51. **9**: IR: 2956, 2931, 2898, 1233, 1511, 1233, 1199, 1176, 1154, 1081, 1018, 1012, 924 cm^{-1}; ^1H NMR: δ 7.11 (m, 2H), 6.96 (m, 2H), 5.15 (s, 2H), 3.90 (dt, *J*=2×5.6, 6.8, 1H), 3.48 (s, 3H), 2.69 (dd, *J*=13.7, 6.8, 1H), 2.49 (dd, *J*=13.7, 8.3, 1H), 1.99 (m, 1H), 1.88–1.20 (m, 6H); ^{13}C NMR: δ 78.5 (C-1), 38.9 (C-2), 29.8 (C-3), 21.5 (C-4), 34.2 (C-5), 50.0 (C-6), 134.5 (C-7), 129.7 (C-8,8′), 116.3 (C-9,9′), 155.5 (C-10), 94.6 (C-11), 55.9 (C-12); MS: m/z 236 (M^+, 34), 218 (2), 206 (2), 188 (3), 174 (4), 151 (14), 121 (30), 107 (18), 91 (5), 77 (4), 45 (100). Anal. calcd for $C_{14}H_{20}O_3$ (236.30): C, 71.16; H, 8.53. Found: C, 71.12; H, 8.50.

3.3. cis- *and* trans-*2-(4-Methoxymethoxybenzyl)-1-acetoxycyclopentane,* ***6*** *and* ***7***

To a stirred mixture of the *cis*-alcohol **8** (0.438 g, 1.9 mmol) and 4-dimethylaminopyridine (1.2 mg, 0.01 mmol) in dry triethylamine (14 ml), acetic anhydride (0.272 ml, 2.88 mmol) was added through a septum in portions and at room temperature. After 5 h of stirring, the reaction mixture was poured into a cooled saturated potassium bicarbonate solution (6 ml). The mixture was extracted with light petroleum (3×20 ml), the combined organic extracts were dried over potassium carbonate and the solvents were evaporated under reduced pressure. The crude product (0.6 g) was purified by column chromatography on silica gel (50 g) affording the pure acetate **6** (0.410 g, 78.8%). IR: 2956, 2933, 2897, 2875, 1736, 1612, 1511, 1450, 1441, 1373, 1311, 1239, 1199, 1176, 1154, 1081, 1032, 1017, 1012, 924 cm^{-1}; ^1H NMR: δ 7.05 (m, 2H), 6.94 (m, 2H), 5.14 (s, 2H), 5.08 (dt, *J*=1.9, 2×5.1, 1H), 3.47 (s, 3H), 2.75 (dd, *J*=6.8, 13.7, 1H), 2.52 (dd, *J*=8.6, 13.7, 1H), 2.09 (m, 1H), 2.07 (s, 3H), 1.95–1.44 (m, 6H); ^{13}C NMR: δ 77.7 (C-1), 34.6 (C-2), 29.5 (C-3), 21.9 (C-4), 32.4 (C-5), 46.3 (C-6), 134.8 (C-7), 129.5 (C-8,8′), 116.2 (C-9,9′), 155.4 (C-10), 94.6 (C-11), 55.9 (C-12), 170.8 (C-13), 21.3 (C-14); MS: m/z 278 (M^+, 21), 218 (46), 188 (20), 151 (7), 121 (14), 107 (13), 45 (100). Anal. calcd for $C_{16}H_{22}O_4$ (278.34): C, 69.04; H, 7.97. Found: C, 69.01; H, 7.94. The same procedure was used for the preparation of *trans*-acetate **7** starting from the corresponding alcohol **9** (0.765 g, 3.24 mmol). The reaction yielded **7** (0.889 g, 98.7%). IR: 2957, 2933, 2897, 2877, 1734, 1613, 1511, 1442, 1376, 1363, 1254, 1199, 1176, 1154, 1081, 1018, 1012, 924 cm^{-1}; ^1H NMR: δ 7.07 (m, 2H), 6.94 (m, 2H), 5.15 (s, 2H), 4.83 (ddd, *J*=4.4, 5.2, 7.32, 1H), 3.47 (s, 3H), 2.76 (dd, *J*=6.1, 13.8, 1H), 2.44 (dd, *J*=9.1, 13.8, 1H), 2.20 (m, 1H), 1.96 (s, 3H), 1.83–1.22 (m, 6H); ^{13}C NMR: δ 80.6 (C-1), 38.4 (C-2), 29.5 (C-3), 22.1 (C-4), 31.6 (C-5), 46.9 (C-6), 134.1 (C-7), 129.8 (C-8,8′), 116.1 (C-9,9′), 155.5 (C-10), 94.6 (C-11), 55.9 (C-12), 171.0 (C-13), 21.2 (C-14); MS: m/z 278 (M^+, 18), 218 (51), 188 (18), 151 (9), 121 (14), 107 (14), 45 (100). Anal. calcd for $C_{16}H_{22}O_4$ (278.34): C, 69.04; H, 7.97. Found: C, 69.03; H, 7.98.

3.4. cis-*(1S,2S)*-, cis-*(1R,2R)*-, trans-*(1S,2R)*- *and* trans-*(1R,2S)*-*2-(4-Methoxymethoxybenzyl)-1-cyclopentanol,* ***1b–4b***

The optically active alcohols **1b**–**4b** were obtained by biotransformation reactions of substrates **5**–**7**. The biotransformation reactions are described in Table 2 in detail. Specific rotation of the respective alcohols **1b**–**4b** are summarised in Table 5. Chemical yields of the biotransformations are summarised in Table 1. IR, ^{1}H NMR, ^{13}C NMR spectra, MS and microanalyses of stereoisomers **1b** and **2b** or **3b** and **4b** were in good accord with data found for the racemic alcohols **8** or **9**, respectively.

3.5. *MTPA esters of alcohols* ***1b–4b***

A general procedure used for the preparation of the MTPA esters in a milligram scale starting from the chloride of MTPA has already been described in detail.[16] The characterisation of the MTPA esters by spectral data is summarised in Table 3. The HPLC determination of optical purity of the alcohols **1b**–**4b** using the corresponding MTPA esters is presented in Table 4.

3.6. *(1S,2S)*-cis-, *(1R,2R)*-cis-, *(1R,2S)*-trans- *and (1S,2R)*-trans-*Ethyl* N-*{2-[4-(2-hydroxy-1-cyclopentylmethyl)phenoxy]ethyl}carbamate,* ***1c–4c***

After deprotection of **1b**–**4b** by conc. HCl in a benzene:ethanol (1:1) solution, the respective chiral precursor **1a**–**4a** (0.6 mmol) defined by its assigned absolute configuration and optical purity (Table 6) was dissolved in 2-butanone (15 ml). Dry powdered potassium carbonate (1 g) and ethyl N-(2-bromoethyl)carbamate (1 g, 5.0 mmol) were added, and the mixture was refluxed for 16 h. The mixture was cooled and filtered. The solid was washed with diethyl ether (30 ml) and the filtrate was washed with water (10 ml) and dried over $MgSO_4$. The volatiles were evaporated under reduced pressure and the residue was purified by column chromatography on silica gel. The chromatography yielded the compound **1c** (99.1%), **2c** (86.8%), **3c** (91.6%) or **4c** (89.4%). Specific rotations of **1c**–**4c** are summarised in Table 5. The following data are common for both **1c** and **2c**. IR (CCl_4): 3617, 3465, 1728, 1521, 1244, 1112, 987 cm^{-1}; ^{1}H NMR: δ 7.14 (m, 2H), 6.81 (m, 2H), 5.12 (br. s, 1H), 4.13 (q, *J*=7.3, 2H), 4.07 (m, 1H), 4.01 (t, *J*=5.1, 2H), 3.57 (br. q, *J*=5.4, 1H), 2.79 (dd, *J*=7.8, 13.7, 1H), 2.61 (dd, *J*=7.6, 13.7, 1H), 1.62–1.38 (m, 7H), 1.24 (t, *J*=7.3, 3H); ^{13}C NMR: δ 74.3 (C-1), 47.8 (C-2), 28.7 (C-3), 21.8 (C-4), 34.5 (C-5), 34.8 (C-6), 134.5 (C-7), 129.6 (C-8,8′), 114.3 (C-9,9′), 156.6 (C-10), 67.0 (C-11), 40.5 (C-12), 156.7 (C-13), 60.9 (C-14), 14.6 (C-15); MS: m/z 307 (M^+, 10), 116 (100), 107 (16), 88 (44). Anal. calcd for $C_{17}H_{25}O_4N$ (307.38): C, 66.42; H, 8.20; N, 4.56. Found for **1c**: C, 66.39; H, 8.15; N, 4.49; and for **2c**: C, 66.37; H, 8.22; N, 4.51. The following data are common for both **3c** and **4c**. IR (CCl_4): 3611, 3470, 1731, 1523, 1249, 1112, 1071 cm^{-1}; ^{1}H NMR: δ 7.14 (m, 2H), 6.81 (m, 2H), 5.16 (bs, 1H), 4.12 (q, *J*=7.2, 2H), 4.01 (t, *J*=5.4, 2H), 3.88 (bq, *J*=3×6.9, 1H), 3.56 (br. q, *J*=5.3, 2H), 2.70 (dd, *J*=6.9, 13.7, 1H), 2.47 (dd, *J*=8.1, 13.7, 1H), 1.86–1.40 (m, 7H), 1.25 (t, *J*=7.2, 3H); ^{13}C NMR: δ 78.4 (C-1), 49.9 (C-2), 29.7 (C-3), 21.4 (C-4), 34.2 (C-5), 38.8 (C-6), 133.7 (C-7), 129.8 (C-8,8′), 114.4 (C-9,9′), 156.7 (C-10), 67.0 (C-11), 40.5 (C-12), 156.7 (C-13), 60.9 (C-14), 14.6 (C-15); MS: m/z 307 (M^+, 8), 116 (100), 107 (18), 88 (40). Anal. calcd for $C_{17}H_{25}O_4N$ (307.38): C, 66.42; H, 8.20; N, 4.56. Found for **3c**: C, 66.38; H, 8.26; N, 4.57; and for **4c**: C, 66.39; H, 8.22; N, 4.51.

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