Synthesis and Sensory Studies of Umami-Active Scaffolds

by **Michael Backes***, **Susanne Paetz**, **Tobias Vössing**, and **Jakob Peter Ley**

Symrise AG, Mühlenfeldstraße 1, D-37603 Holzminden

The class of 2-isopropyl-5-methylbicyclo[4.1.0]heptane-7-carboxamides, **1**–**4**, has been identified as potent umami-tasting molecules. A scalable synthesis of this challenging scaffold and new sensory insights will be presented. Interestingly, the umami characteristics differ remarkably, depending on constitutional and stereochemical features of the parent scaffold. During our studies, we could identify the carboxamide moiety as a crucial factor to influence the umami intensity of these scaffolds. In addition, the configuration of the cyclopropyl moiety exerts some influence, whereas the absolute configuration of the menthyl scaffold, at least the tested D- and L-configuration, is less important.

Introduction. – After introduction of the concept of umami as a distinctive fifth taste quality triggered by monosodium glutamate (MSG) by *Ikeda* in 1908 [1], it took another 60 years, until *Yamaguchi* could scientifically establish that certain nucleotides (naturally occurring in various food sources) were able to act synergistically to the umami sensation of MSG [2]. Surprisingly, during the next decades only very few new natural umami-tasting compounds with a weaker sensory profile have been identified, which are only of limited use for flavoring purposes [3][4].

Whereas there are no scientifically sound constraints to use MSG in food [5], the public perception of added MSG is nowadays very poor. Hence, the food industry constantly strives to develop new solutions to meet consumer expectations. Due to the identification of the heterodimeric T1R1/T1R3 G protein-coupled receptor as being mainly responsible for the umami perception in the early 2000s [6], a high throughput screening of pharmaceutical compound libraries was started, resulting in amides and related structures showing potent umami activities [7]. Subsequently, the oxalic acid-derived compounds, **A**–**D** (*Fig. 1*), and amide **E** have been registered for the use in food in several countries. In parallel, structure–activity-based concepts led to the identification of several other structural spaces [8][9], resulting in the registration of spilanthol derived amides, **F**–**H**, amide **I**, and the urea derivative **J**.

All of the above mentioned molecules bear some kind of an amide functionality in their core structure. Interestingly, **I** and **J** are the only registered ones so far which possess stereogenic centers. More recently, the dihydrochalcones **K** and **L** have been introduced, which do not follow this general observation [10]. However, they contain a pyridine substructure, which is a very common motive for umami-active scaffolds as well.

Within our sensory screening program directed towards the identification of umami-active scaffolds, we identified diastereoisomeric mixtures of 2-isopropyl-5-

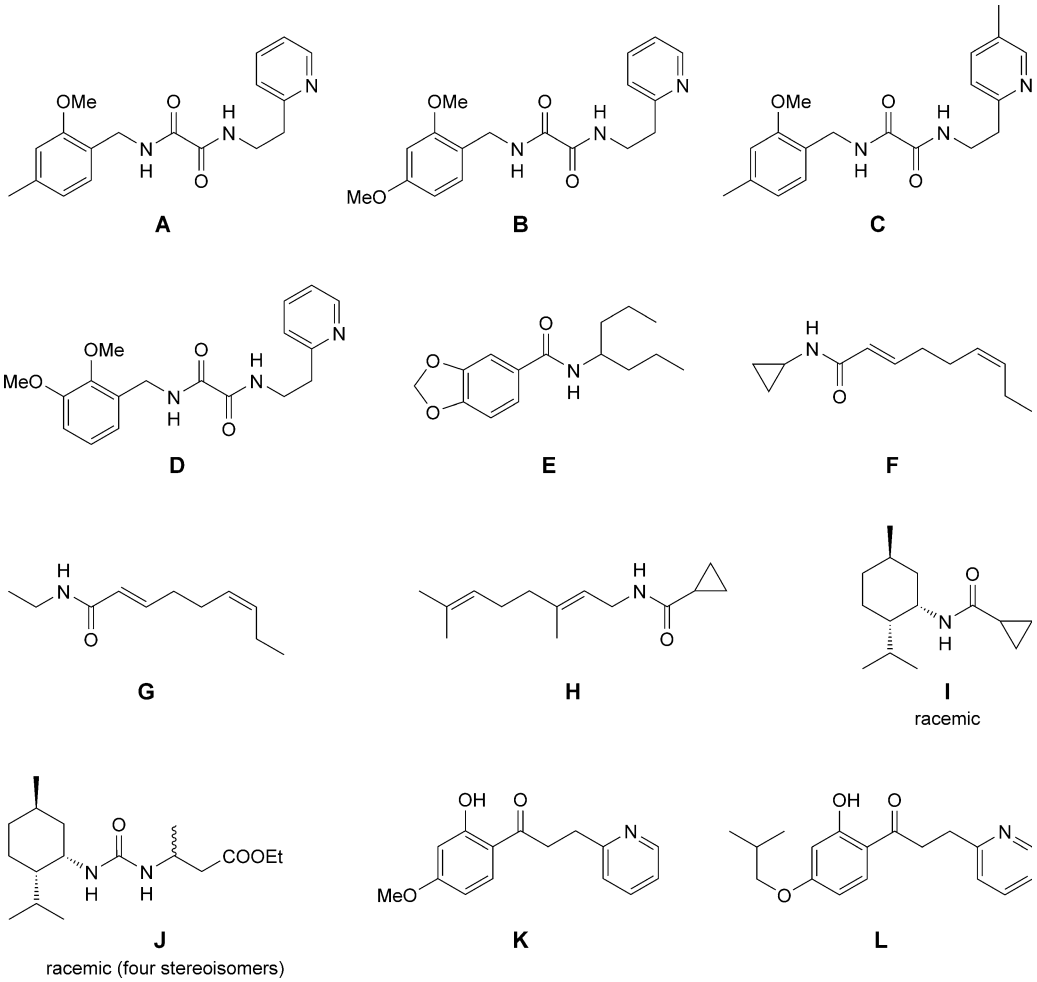


Fig. 1. *Artificial umami compounds currently registered for the use in food*

methylbicyclo[4.1.0]heptane-7-carboxamides, **1** and **2**, as very potent umami-tasting candidates (*Fig. 2*) [11].

We could demonstrate that the amide moiety plays an important role for the umami perception [12]. However, the influence of the configuration of the core structure had not been investigated in detail. For this purpose, a scalable synthetic route to highly enantiomerically enriched 2-isopropyl-5-methylbicyclo[4.1.0]heptane-7-carboxamides **1**–**4** had to be established, envisaging fractional crystallization of the corresponding *N*-methyl carboxamide as the key step for the separation of the diastereoisomeric mixtures obtained from the addition of ethyl diazoacetate ($N_2CHCOOEt$) to *p*-menth-2-ene. Sensory evaluation *via* a descriptive expert panel and a ranking test revealed the influence of the amide moiety and the configuration of the core scaffold for the umami sensation.

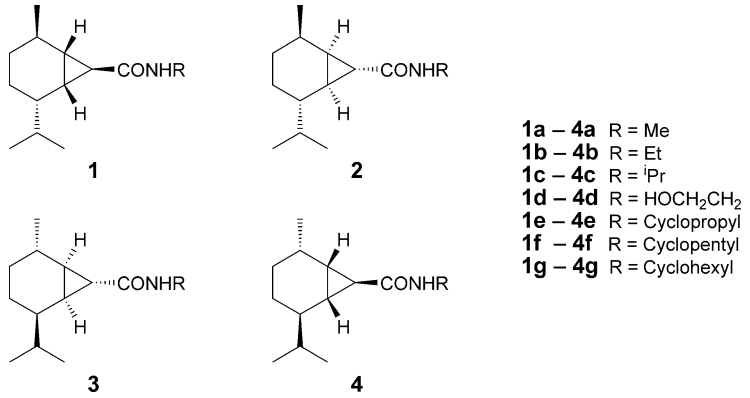
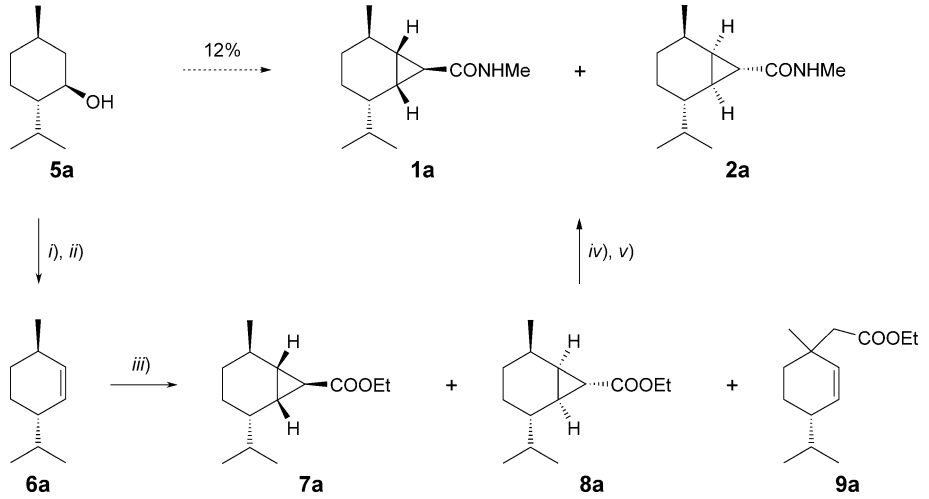


Fig. 2. *Evaluated structures based on the 2-isopropyl-5-methylbicyclo[4.1.0]heptane-7-carboxamide scaffold*

Results and Discussion. – *Synthesis.* An optimized synthetic route to four different stereoisomers of the 2-isopropyl-5-methylbicyclo[4.1.0]-heptane-7-carboxamide scaffolds, **1**–**4**, comprising a linear sequence of ten linear steps could be developed (*Scheme 1*). The synthesis of **1** and **2** starting from L-menthol (**5a**) will be described in detail later, however, the same methods can be applied for the synthesis of the corresponding enantiomeric scaffolds **3** and **4** with D-menthol (**5b**) and (3*R*,6*S*)-*p*-menth-2-ene (**6b**) as starting material, respectively. Although being described in the literature abundantly, the regioselective elimination of L-menthol (**5a**) and its derivatives to (3*S*,6*R*)-*p*-menth-2-ene (**6a**) in larger scale proved to be challenging. Finally, by slightly modifying a literature protocol [13] the elimination of the corresponding *p*-toluenesulfonate employing *t*BuOK in *N*-methylpyrrolidin-2-one at elevated temperatures furnished the desired (3*S*,6*R*)-*p*-menth-2-ene (**6a**) in acceptable yield and purity.

The subsequent cyclopropanation employing ethyl diazoacetate resulted in the formation of the expected diastereoisomeric esters **7a** and **8a**, and some undesired by-products. Diethyl malonate and diethyl fumarate both result from the self-condensation of ethyl diazoacetate and by-product **9a** is generated from the insertion of ethyl diazoacetate to H–C(6) of (3*S*,6*R*)-*p*-menth-2-ene (**6a**). Besides the well-established chlorinated solvents, we obtained conversions of nearly 35% (based on ethyl diazoacetate) by using a large excess of **6a** without any additional solvent, employing [$Cu(acac)_2$] as metal source. Interestingly, it was not possible to avoid or even significantly decrease the formation of by-product **9a** by using an additional solvent. The diastereoselectivity of this reaction (6:4 in favor of **7a**) is set by the stereogenic centers present in (3*S*,6*R*)-*p*-menth-2-ene (**6a**). To influence this diastereoselectivity, the use of a chiral L-valine-based bis(oxazoline) ligand with a tartaric acid-derived backbone was investigated [14]. However, no change in diastereoselectivity could be observed, and the yield decreased dramatically. Furthermore, L- and D-menthyl diazoacetate were employed for an auxiliary-based approach [15]. However, the yield dropped significantly, the products were difficult to hydrolyze, and the diastereoiso-

Scheme 1. *Synthesis of* N-*Methylcarboxamides* **1a** *and* **2a** *Starting from* L-*Menthol* (**5a**)

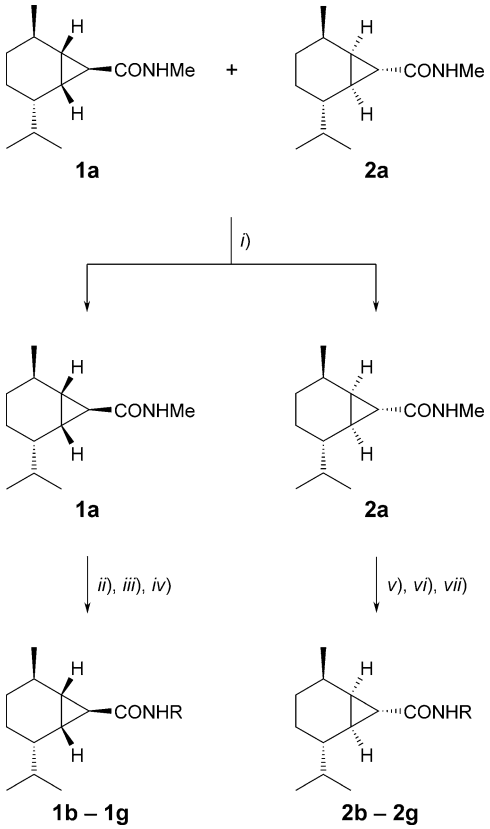


i) TsCl, 3-methylpyridine. *ii*) ^{t}BuOK, NMP (= *N*-methylpyrrolidin-2-one; 66% over two steps). *iii*) $N_2CHCOOEt$, $[Cu(acac)_2]$ (acac, acetylacetonate). *iv*) H_2O_2, HCOOH, NaOH, EtOH. *v*) $MeNH_2$, THF/H_2O (18% over four steps).

meric distribution of the addition products was not affected. In addition, several attempts to separate the diastereoisomers *via* enzymatic resolution or preparative flash chromatography failed. In previous studies, it was found that the corresponding *N*-methyl carboxamides **1a** and **2a**, in contrast to all other synthesized carboxamides, could be separated *via* fractional crystallization. To facilitate this crystallization step, by-product **9a** has to be removed from the mixture. This was achieved by epoxidation of the remaining C=C bond with subsequent ring opening to the corresponding diol, which could easily be separated *via* column chromatography. The obtained pure carboxylic acids **7a** and **8a** were converted to their corresponding acid chlorides with $(COCl)_2$. Subsequent reaction with aqueous $MeNH_2$ under *Schotten–Baumann* conditions led to the desired *N*-methyl carboxamides **1a** and **2a** in 18% over four steps starting from **6a**. The separation of this diastereoisomeric mixture was accomplished by fractional crystallization in acetone, with isomer **1a** being the one to crystallize first (*Scheme 2*).

After concentration of the mother liquor, the second isomer **2a** started to crystallize, the addition of seed crystals obtained *via* preparative HPLC facilitated the crystallization process significantly. In case of the fractional crystallization of the enantiomeric amide mixture **3a**/**4a**, the diastereoisomeric excess (de) of the latter was not as high as expected, which might be the result of not using a seed crystal in this step. The diastereoisomers **1a**, **2a**, and **3a** could be obtained with $\geq$94% de, whereas diastereoisomer **4a** could be obtained with only 68% de. *N*-Methyl carboxamides **1a**–**4a** were hydrolyzed to the corresponding acids, which could be transformed to different carboxamides, **1b**–**1g**, **2b**–**2g**, **3b**–**3g**, and **4b**–**4g**, *via* chlorination and subsequent amidation using variations of the *Schotten–Baumann* reaction.

Scheme 2. *Fractional Crystallization and Synthesis of the Corresponding Diastereoisomerically Enriched Carboxamides* **1a**–**1g** *and* **2a**–**2g**



i) Acetone (48% yield, 93% de regarding **1a**; 37% yield, 93% de regarding **2a**). *ii*) Aq. KOH, $HOCH_2CH_2OH$. *iii*) $(COCl)_2$, NMFA (*N*-methylformanilide), CH_2Cl_2. *iv*) R–NH_2, $NaHCO_3$ (yield 63–78% over three steps, ≥98% de). *v*) aq. KOH, $HOCH_2CH_2OH$. *vi*) $(COCl)_2$, NMFA, CH_2Cl_2. *vii*) R–NH_2, KOH, THF/H_2O (26–80% over three steps, ≥98% de).

Sensory Evaluation. Prior to sensory testing, the safety profile of the corresponding *N*-cyclopentyl carboxamide **1f** as representative example for this group of compounds was evaluated. The LD_{50} value in rats (according to *OECD* guideline 423) was determined to be above 2,000 mg kg^{-1}, and a *Salmonella typhimurium* reverse-mutation assay with and without metabolic activation showed no mutagenic effects. Based on these results, the evaluation of this class of compounds using the sip-and-spit method could be performed. In a first step, all synthesized amides were pre-evaluated by an expert panel for their intrinsic umami activity in a dosage of 5 ppm in a 0.5% salt and a 5% sucrose solution (*Table*).

Interestingly, besides the already described pronounced effect of the different amide residues, the L-menthol (**5a**)-derived scaffolds **1** seem to be preferred. To validate this first impression and to gain more detailed information, three ranking tests

Table. *Sensory Evaluation Regarding the Intrinsic Umami Activity of the 2-Isopropyl-5-methylbicyclo[4.1.0]heptan-7-carboxamides in a 0.5% Salt and 5% Glucose Solution Using the Sip-and-Spit Method* (number of panelists 5–8)

	Scaffold **1**	Scaffold **2**	Scaffold **3**	Scaffold **4**
a	≥93% de[a]) very slightly umami	≥93% de[a])	≥95% de	≥67% de
b	≥99% de umami	≥99% de slightly umami	≥99% de	≥66% de
c	≥99% de umami	≥98% de slightly umami	≥99% de umami	≥68% de
d	≥99% de	≥99% de slightly umami	≥99% de	≥62% de
e	≥99% de	≥99% de	≥99% de	≥64% de
f	≥99% de umami	≥99% de	≥98% de umami	≥66% de umami
g	≥99% de	≥98% de slightly umami	≥98% de umami	≥65% de slightly umami

[a]) de, Diastereoisomeric excess. Can be purified to ≥99% de *via* second crystallization using seed crystals.

(ISO 8587:2006) with a larger trained panel on different aspects of this class of compounds were conducted [16]. It is important to note that this kind of test is used to highlight differences of the tested samples regarding one descriptor. However, no conclusions on the overall intensity or the degree of difference can be drawn. In addition, the class of compounds with the poorest score might only be very slightly active or even show no activity at all. In a first attempt the L-menthol (**5a**)-derived scaffolds **1a**–**1g** showing the most potent umami activities, were selected to evaluate the effect of the amide moieties (*Fig. 3*).

Scaffolds **1a**, **1g**, and **1d** were identified as the least active compounds, followed by **1e** and **1b**, being medium active, and two highly active compounds **1c** and **1f**. This is in accordance with the observations reported earlier stating that the *N*-cyclopentyl carboxamides **1f** and **2f** are very active compounds at levels as low as 300 ppb, and the corresponding *N*-methyl carboxamides **1a** and **2a** have virtually no effect at a dosage of 5 ppm [12]. To further investigate the influence of the configuration, strongly active *N*-cyclopentyl carboxamides **1f**–**4f**, and less active *N*-cyclohexyl carboxamides **1g**–**4g**, were selected. As expected, for both series the same ranking of the scaffolds could be observed (*Fig. 4*).

The L-menthyl-derived configuration with the cyclopropa part pointing down, *i.e.*, in **1f** and **1g**, always provided the strongest effect, whereas the L-menthyl-derived configuration with the cyclopropa moiety pointing up, *i.e.*, in **2f** and **2g**, always leads to the less active scaffold. The umami intensity of the corresponding D-menthol (**5b**)-derived scaffolds lies in between. However, in case of the highly active *N*-cyclopentyl carboxamides **3f** and **4f**, the scaffold with the cyclopropa motive pointing down, *i.e.*, **4f**,

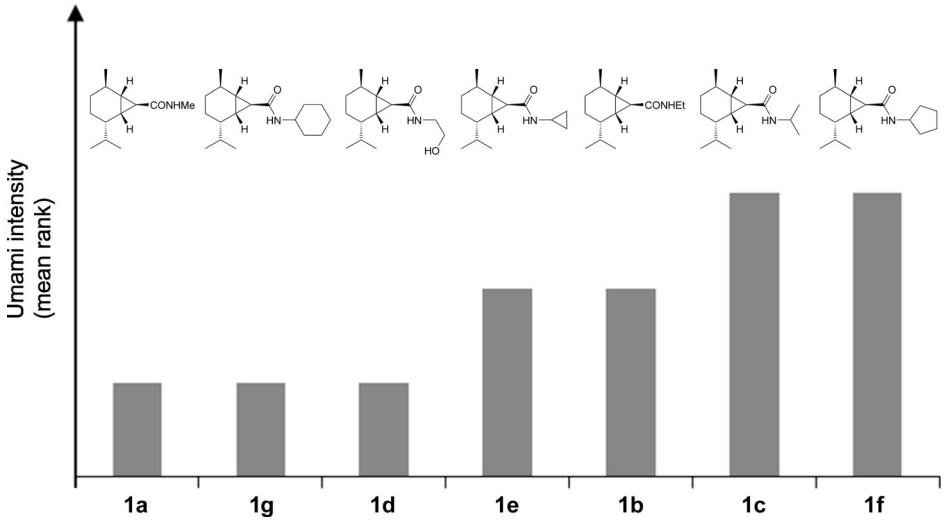


Fig. 3. *Ranking of the carboxamide moieties* **1a**–**1g** *according to their umami intensity employing the ISO 8587:2006 method* (number of panelists 14–18; level of significance for the mean rank (LSD $<10\%$)

shows stronger umami activity, compared to the stereoisomer with the cyclopropa moiety pointing up, *i.e.*, **3f**. In case of the only slightly active *N*-cyclohexyl carboxamides **3g** and **4g**, both compounds are rated equally active. It has to be considered that for the D-menthol-derived scaffolds with the cyclopropa motive pointing down (**4a**–**4g**), only compounds with de values of $\geq 62\%$ were used for the ranking tests. However, even this supports the findings, as the pure compounds with the cyclopropa motive pointing up (*i.e.*, **3a**–**3g**) are weaker in their umami activities.

Conclusions. – In total, 28 different 2-isopropyl-5-methylbicyclo[4.1.0]heptane-7-carboxamides starting from L-menthol (**5a**) and D-menthol (**5b**) have been prepared in yields ranging from 1.1–4.5% following a ten-step synthetic protocol employing fractional crystallization of the corresponding *N*-methyl carboxamides **1a**–**4a** as key step. The umami activities of all compounds have been evaluated, and correlations for structural requirements have been postulated. The amide moiety is the most relevant factor to influence the umami intensity of these scaffolds. In addition, the configuration of the cyclopropa moiety plays a significant role as well, whereas the absolute configuration of the menthyl part, at least the tested D- and L-configuration, is of little importance.

Experimental Part

General. Reagents and solvents were purchased from commercial suppliers (*Acros Organics*, BE-Geel; *Sigma–Aldrich*, DE-Steinheim; *Alfa Aesar GmbH & Co KG*, DE-Karlsruhe) or prepared by *Symrise*, and used without further purification or drying. M.p.: *LICO 500* (*Hach Lange GmbH*, DE-Berlin); uncorrected. Monitoring of the reaction was accomplished by TLC on silica gel GF_{254} plates (SiO_2) with either UV detection or by using a staining reagent consisting of ammonium molybdate,

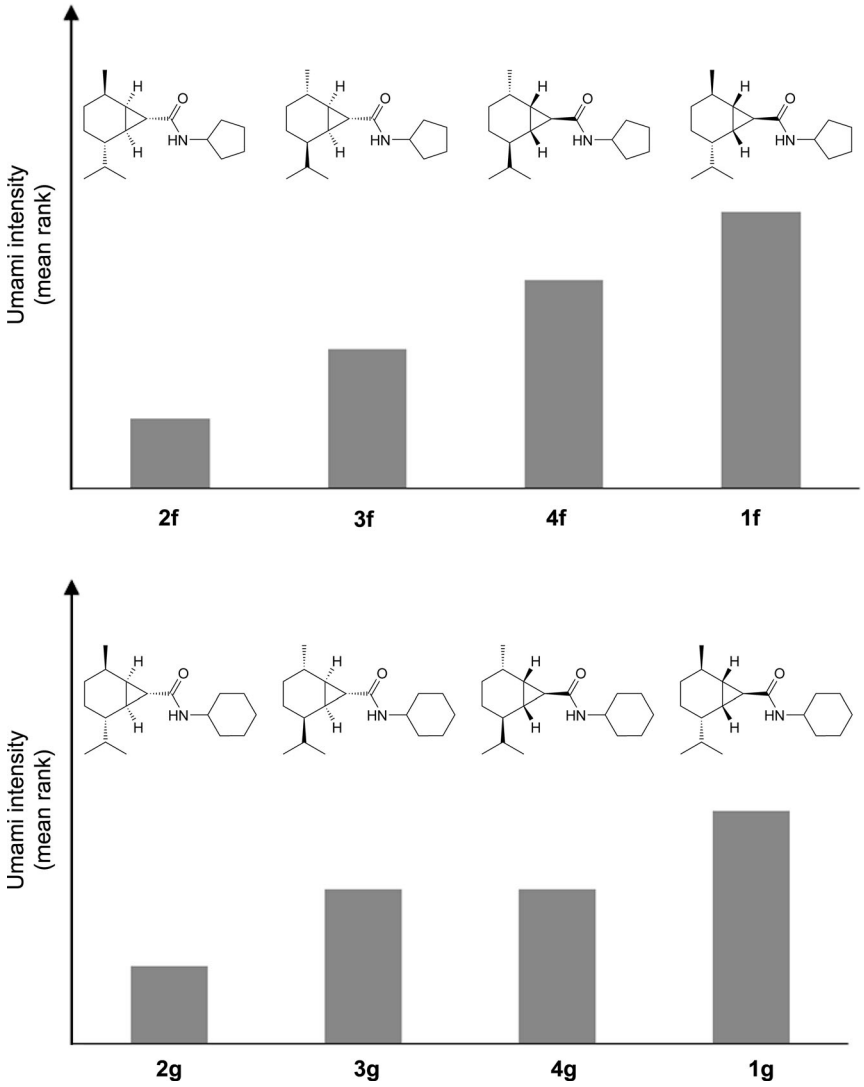


Fig. 4. *Ranking of the* N-*cyclopentyl carboxamides* **1f**–**4f** *and* N-*cyclohexyl carboxamides* **1g**–**4g** *according to their umami intensity employing the ISO 8587:2006 method* (number of panelists 14–18; level of significance for the mean rank (LSD) $<10\%$)

$Ce(SO_4)_2$, and H_2SO_4. Purity and diastereoselectivity were determined using either an *Agilent 6890N* or *Agilent 7890N* system (*Agilent Technologies*, Santa Clara, USA) equipped with *DB-WAX* and *DB-1* columns (length, 20 m; i.d., 0.18 mm; film, 0.18 μm); flow rate, 0.5–3.0 ml min^{-1}; injector split ratio 1:70; 80–250° (rate 12°/s); carrier gas, H_2; detector, FID, 275° (*Agilent Technologies*, Santa Clara, USA). The purity of all reported compounds is $\geq 98.0\%$ according to GC unless otherwise stated. Optical rotations: *Unipol L 1000* (*Schmidt+Haensch GmbH & Co.*, DE-Berlin). ^{1}H- and ^{13}C-NMR spectra: *Varian Mercury Plus* or *Varian Unity Innova* spectrometer (*Varian*, DE-Darmstadt); δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. GC/EI-MS: *Shimadzu GC2010/QP2010* (*Shimadzu Corporation*, Kyoto,

Japan) or *Agilent 6890N* system (*Agilent Technologies*, Santa Clara, USA); 70 eV; detector, quadrupole. HR-EI-MS: coupled system consisting of an *Agilent 7890A* and a *Waters GTC Premier* (*Waters*, DE-Eschborn); 70 eV; detector, TOF.

Chemistry. General Procedure A (*GP A*): *Selected Carboxamides from Corresponding* N-*Methyl Carboxamides.* One equiv. of the corresponding *N*-methyl carboxamide and 10–15 equiv. KOH were stirred at r.t. in $HOCH_2CH_2OH$ (7.5 ml/mmol substrate) for 12 h before heating under reflux for additional 4 h. Subsequently, ice-water (30 ml/mmol substrate) was added, and the aq. phase was washed two times with ^{t}BuOMe (6 ml/mmol substrate). After adjusting the aq. soln. to pH 1 with 1M H_2SO_4, the product was extracted with AcOEt (7.5 ml/mmol substrate). The org. phase was washed two times with H_2O and once with brine before drying (Na_2SO_4). After evaporation of the solvent, the crude carboxylic acid was recrystallized from H_2O/EtOH 2:1 and used in the next step without any further purification.

One equiv. of the corresponding acid and a catalytic amount of *N*-methylformanilide (NMFA) were suspended in CH_2Cl_2 (1 ml/mmol substrate) before 1.1 equiv. $(COCl)_2$ were added slowly to the soln. The mixture was stirred for 1 h at r.t. and additional 30 min at reflux temp. After evaporation of the solvent, the crude product was resolved in THF (2.4 ml/mmol substrate) and slowly added to a mixture of 1.2 equiv. of the corresponding amide dissolved in a mixture of THF (2 ml/mmol substrate), H_2O (2 ml/mmol substrate), and 1.2 equiv. of KOH at r.t. Subsequently, the mixture was heated under reflux for 15 min before adding H_2O (10 ml/mmol substrate) to precipitate the formed carboxamide. The product was separated by filtration, washed with H_2O, and further purified *via* recrystallization from EtOH/H_2O. Finally, the product was dried in a vacuum oven at 75°.

General Procedure B (*GP B*): *Selected Carboxamides from Corresponding* N-*Methyl Carboxamides.* One equiv. of the corresponding *N*-methyl carboxamide and 5 equiv. KOH were heated under reflux in $HOCH_2CH_2OH$ (4 ml/mmol substrate) for 6 h. Subsequently, ice water (12 ml/mmol substrate) was added, and the aq. phase was washed two times with AcOEt (10 ml/mmol substrate). After adjusting the aq. soln. to pH 1 with 1M H_2SO_4, the product was extracted two times with AcOEt (10 ml/mmol substrate). The org. phase was washed (4×) with H_2O before drying (Na_2SO_4). After evaporation of the solvent, the crude carboxylic acid product was used in the next step without any further purification.

One equiv. of the corresponding acid and a cat. amount of NMFA were suspended in CH_2Cl_2 (3–4 ml/mmol substrate) before 1.3 equiv. $(COCl)_2$ were added slowly, and the mixture was stirred for 3 h under reflux. After evaporation of the solvent, the crude product was resolved in acetone (2.5–4.0 ml/mmol substrate) and slowly added to a mixture of 1.5 equiv. of the corresponding amine dissolved in a mixture of aq. 5% $NaHCO_3$ soln. (7–10 ml/mmol substrate) and H_2O (6–8 ml/mmol substrate) at r.t. Subsequently, the mixture was stirred for 70 h, while the resulting carboxamides started to crystallize. The products were separated by filtration, washed with H_2O, and further purified *via* recrystallization from H_2O/acetone. Finally, the products were dried in a vacuum oven at 50°.

General Procedure C (*GP C*): *Selected Carboxamides from Corresponding* N-*Methyl Carboxamides.* One equiv. of the corresponding *N*-methyl carboxamide and 5 equiv. KOH were heated under reflux in $HOCH_2CH_2OH$ (3.5 ml/mmol substrate) for 6 h. Subsequently, ice water (10 ml/mmol substrate) was added, and the aq. phase was washed two times with AcOEt (3 ml/mmol substrate). After adjusting the aq. soln. to pH 1 with 1M H_2SO_4, the product was extracted two times with AcOEt (5 ml/mmol substrate). The org. phase was washed (5×) with H_2O before drying (Na_2SO_4). After evaporation of the solvent, the crude carboxylic acid product was used in the next step without further purification.

One equiv. of the corresponding acid and a cat. amount of NMFA were suspended in CH_2Cl_2 (2.5 ml/mmol substrate) before 1.3 equiv. $(COCl)_2$ were added slowly, and the mixture was stirred for 3 h under reflux. After evaporation of the solvent, the crude product was resolved in acetone (2.5 ml/mmol substrate) and slowly added to a mixture of 2.0 equiv. of the corresponding amine and 2.0 equiv. of $NaHCO_3$ dissolved in H_2O/acetone 1:1 (7.5–14.0 ml/mmol substrate) at r.t. Subsequently, the mixture was stirred for 24 h while some of the resulting carboxamides started to crystallize. After addition of H_2O (15.0 ml/mmol substrate), all carboxamides participated and were separated by filtration, washed with H_2O, and further purified *via* recrystallization from EtOH/H_2O. Finally, the product was dried in a vacuum oven at 50°.

*(3*R*,6*S*)-3-Methyl-6-(1-methylethyl)cyclohexene* (=*(3*S*,6*R*)*-p-*Menth-2-ene*; **6a**). A soln. of 600.0 g (3.8 mol) L-menthol in 500 ml 3-methylpyridine was slowly added to a suspension of 805.2 g (4.2 mol)

TsCl in 500 ml 3-methylpyridine, while maintaining the temp. below 30°. The mixture was stirred for 4 h at r.t. before 365 ml 3-methylpyridine were removed *via* distillation, until the mixture nearly became solid. The residue was dissolved in 3500 ml AcOEt, and the org. phase was extracted two times with 1M H_2SO_4 and once with sat. aq. $NaHCO_3$ soln. After evaporation of the solvent, 1184.4 g of the corresponding L-menthyl *p*-toluenesulfonate were obtained as colorless solid.

A mixture of 1.0 equiv. of the L-menthyl *p*-toluenesulfonate and 1.5 equiv. ^{t}BuOK were suspended in *N*-methylpyrrolidin-2-one (0.5–0.8 ml/mmol substrate), and the mixture was heated at 140° for 3 h. After cooling to 80°, H_2O (0.5 ml/mmol substrate) was added, and the org. phase was separated, subsequently washed with H_2O, and dried (Na_2SO_4). The residue contained 89.6–92.4% of **6a** besides other regioisomers and unreacted L-menthol.

This reaction sequence was repeated several times and in total the reaction of 4.102 kg (26.2 mol) L-*menthol* (**5a**) resulted in 2.745 kg of **6a** (purity 91.2%). Final purification *via* distillation (52–55°/18 mbar) led to 2.460 kg (97.0%, 17.3 mol) **6a** in an overall yield of 66%. $[\alpha]_D^{23} = +149.6$ ($c = 1.0$, EtOH); [17]: $[\alpha]_D^{24} = +115.3$ ($c = 2.2$, benzene).

(3S,6R)-3-Methyl-6-(1-methylethyl)cyclohexene (*=(3R,6S)-2*-p-*menthene* (**6b**)). As described for **6a**, 247.8 g (1.59 mol) D-menthol were converted to the corresponding *p*-toluenesulfonate. The elimination was affected with 2.5 equiv. KOH (85% aq. soln.) in polyethylene glycol 400 (0.5–1.5 ml/mmol substrate) at 130° for 3 h. After workup and final distillation, 100.0 g (95.1%, 0.69 mol) **6b** were obtained in an overall yield of 43%. $[\alpha]_D^{23} = -147.1$ ($c = 1.0$, EtOH); [18]: $[\alpha]_D^{15} = -139.5$ ($c = 2.0$, benzene).

*(1S,2R,5S,6R,7R)- and (1R,2R,5S,6S,7S)-*N*,2-Dimethyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**1a** and **2a**, resp.). A mixture of 2.61 g (10.0 mmol) [$Cu(acac)_2$] and 236.0 g (97.0%, 1.656 mmol) of **6a** was heated to 95° before 100.0 g (90%, 0.79 mol) ethyl diazoacetate were added during 5.5 h maintaining the same temp. After further stirring for 1 h at 95°, the mixture was cooled and filtered over a plug of *Celite*®. After distillation (78–100°/2 mbar), 85.5 g of the corresponding esters, **7a** (41.8%), **8a** (29.2%), and **9a** (15.5%), were obtained, and they were dissolved in 100 ml of HCOOH. Subsequently, 28.3 g (30%, 0.25 mol) of aq. H_2O_2 were slowly added over a period of 2 h keeping the temp. at 70–80°. After the addition, the mixture was stirred for 2 h, before a mixture of HCOOH and H_2O was removed by distillation. The residue was suspended in 200 ml (15%, 0.75 mol) of NaOH, and the mixture was stirred at r.t. for additional 6 h. After addition of 100 ml of H_2O, the aq. phase was washed with ^{t}BuOMe, before it was adjusted to pH 1 by addition of 2M H_2SO_4 and extracted AcOEt (2 × 100 ml). The combined org. phases were washed with H_2O, dried (Na_2SO_4), and, after evaporation, the crude mixture was further purified *via* column chromatography (CC; hexane/^{t}BuOMe 3:1). The resulting 44.0 g and a cat. amount of NMFA were dissolved in 150 ml of CH_2Cl_2 at r.t., before 19.9 ml (235.2 mmol) $(COCl)_2$ were added during 2 h. After the mixture was subsequently heated under reflux for 1 additional h, the solvent was removed, and the residue was dissolved in 50 ml of THF. This soln. was slowly added to a mixture of 56.8 ml (41%, 672.5 mmol) of $MeNH_2$, 100 ml of H_2O, and 300 ml of THF, maintaining the temp. below 25°. Subsequently, the mixture was stirred for 30 min at r.t. and additional 30 min under reflux, before 900 ml of H_2O were added to the hot mixture to effect the complete precipitation of **1a** and **2a**. The suspension was cooled to r.t., and the products were filtered off, washed extensively with H_2O, and dried at 75° in a vacuum oven to yield 30.9 g (58.0% **1a**, 37.8% **2a**; 141.4 mmol) of an off-white solid which corresponded to an overall yield of 18% (based on ethyl diazoacetate) over five steps.

Fractional Crystallization. The mixture **1a**/**2a** was dissolved in 1000 ml of acetone under reflux, and the unsolved material was removed by hot filtration. While slowly cooling to r.t., **1a** started to precipitate, was filtered off after 20 min, and dried to furnish 8.9 g (42.5 mmol) of a colorless solid with a diastereoselectivity of ≥93% and a yield of 48% based on the available amount of the relevant diastereoisomer **1a**. The mother liquor was concentrated at 50° to 600 ml and, after cooling to r.t., **2a** started to precipitate. After filtration and drying, 4.4 g (21.0 mmol) of a colorless solid with a diastereoselectivity of ≥93% and a yield of 37% based on the available amount of the relevant diastereoisomer **2a** could be achieved.

Compound **1a** (≥93% de). M.p. 201.2°. $[\alpha]_D^{23} = +37.0$ ($c = 1.0$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.56 (*tdd*, $J = 13.5, 11.5, 1.9$, 1 H); 0.79 (*m*, 1 H); 0.91 (*d*, $J = 6.7$, 3 H); 0.93 (*d*, $J = 6.7$, 3 H); 1.02 (*t*, $J = 4.5$,

1 H); 1.08 (*d*, *J* = 6.7, 3 H); 1.31 (*ddd*, *J* = 9.3, 4.1, 1.8, 1 H); 1.37 (*dsept.*, *J* = 7.9, 6.7, 1 H); 1.40–1.58 (*m*, 3 H); 1.57–1.67 (*m*, 2 H); 2.28 (*d*, *J* = 4.9, 3 H); 5.48 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.5 (Me); 20.7 (Me); 23.4 (Me); 24.8 (CH_2); 25.5 (CH); 26.0 (CH); 26.5 (Me); 27.5 (CH); 30.4 (CH); 32.7 (CH_2); 33.6 (CH); 39.9 (CH); 174.2 (C=O). GC/EI-MS: 209 (5, $M^{+\bullet}$), 166 (100), 136 (40), 124 (73), 113 (45), 109 (66), 81 (36), 74 (42), 73 (84), 67 (47), 58 (55). HR-MS: 209.1785 ($M^{+\bullet}$, $C_{13}H_{23}NO^+$; calc. 209.1780).

Compound **2a** (≥ 93% de). M.p. 156.8°. $[\alpha]_D^{23} = +63.4$ (*c* = 1.0, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.52 (*tdd*, *J* = 13.4, 11.9, 2.2, 1 H); 0.90 (*m*, 1 H); 0.91 (*d*, *J* = 6.8, 3 H); 0.93 (*d*, *J* = 6.8, 3 H); 0.96 (*d*, *J* = 6.6, 3 H); 0.99 (*t*, *J* = 4.4, 1 H); 1.24 (*dtd*, *J* = 12.6, 5.4, 2.1, 1 H); 1.36–1.54 (*m*, 3 H); 1.58 (*dt*, *J* = 9.3, 5.2, 4.4, 1 H); 1.66 (*dsept.*, *J* = 6.8, 5.4, 1 H); 1.90 (*m*, 1 H); 2.82 (*d*, *J* = 4.9, 3 H); 5.58 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.3 (Me); 19.9 (Me); 21.4 (Me); 25.27 (CH); 25.29 (CH); 26.2 (CH_2); 26.5 (Me); 28.3 (CH); 28.81 (CH_2); 28.82 (CH); 33.3 (CH); 41.9 (CH); 174.4 (C=O). GC/EI-MS: 209 (11, $M^{+\bullet}$), 166 (100), 136 (15), 124 (70), 109 (29), 95 (24), 93 (15), 81 (31), 73 (39), 67 (19), 58 (28). HR-MS: 209.1771 ($M^{+\bullet}$, $C_{13}H_{23}NO^+$; calc. 209.1780).

*(1*R*,2*S*,5*R*,6*S*,7*S*)- and (1*S*,2*S*,5*R*,6*R*,7*R*)-*N*,2-Dimethyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**3a** and **4a**, resp.). A mixture of 2.60 g (8.4 mmol) $[Cu(acac)_2]$, 98.0 g (95.1%, 0.67 mol) of **6b**, and 100 ml of PhCl was heated up to 95°, before 100.0 g (85%, 0.745 mol) ethyl diazoacetate were added during 7 h maintaining the same temp. After further stirring for 1 h at 95°, the mixture was cooled and filtered over a plug of *Celite*®. After distillation (78–100°/2 mbar), 97.5 g of the corresponding esters **7b** (41.8%), **8b** (29.4%), and **9b** (15.3%) were obtained and dissolved in 100 ml of HCOOH. Subsequently, 28.3 g (30%, 0.25 mol) of aq. H_2O_2 were slowly added over a period of 2 h keeping the temp. at 70–80°. After the addition, the mixture was stirred for 2 h, before a mixture of HCOOH and H_2O was removed by distillation. The residue was suspended in 270 ml (15%, 1.0 mol) of NaOH and stirred at r.t. for additional 6 h. After addition of 100 ml of H_2O, the aq. phase was washed with ^{t}BuOMe before being adjusted to pH 1 by the addition of 2M H_2SO_4 and extracted two times with ^{t}BuOMe. The combined org. phases were washed with H_2O, dried (Na_2SO_4), and, after evaporation, the crude mixture was further purified *via* CC (hexane/^{t}BuOMe 3 : 1). The resulting 55.0 g and a cat. amount of NMFA were dissolved in 250 ml of CH_2Cl_2 at r.t., before 25.7 ml (0.3 mol) $(COCl)_2$ were added during 1 h. After the mixture was stirred for 1 h at r.t. and subsequently refluxed for 1 h, the solvent was removed, and the residue was dissolved in 100 ml of acetone. This soln. was slowly added to a mixture of 76.0 ml (41%, 0.9 mol) of $MeNH_2$, 350 ml of H_2O, and 100 ml of acetone maintaining the temp. below 10°. Subsequently, the mixture was stirred for 1 h at r.t. and 1 h under reflux, before 200 ml of H_2O were added to the hot mixture to effect the complete precipitation of **3a** and **4a**. The suspension was cooled to r.t., and the products were filtered off, washed extensively with H_2O, and dried at 75° in a vacuum oven to yield 36.2 g (56.4% **3a**, 41.7% **4a**; 169.6 mmol) of an off-white solid which corresponded to an overall yield of 25% (based on **6b**) over five steps.

Fractional Crystallization. The mixture **3a**/**4a** was dissolved in 1200 ml of acetone under reflux, unsolved material was removed by hot filtration, and the mixture was slowly cooled to r.t. Amide **3a** started to precipitate, was filtered off after 20 min, and dried to give 11.0 g (52.5 mmol) of a colorless solid with a diastereoselectivity of ≥ 94% and a yield of 52% based on the available amount of the relevant diastereoisomer **3a**. The mother liquor was concentrated to dryness, and the residue was recrystallized from H_2O/EtOH 2 : 1. After filtration and drying, 17.2 g (82.2 mmol) of a colorless solid with a diastereoselectivity of ≥ 67% and a yield of 95% based on the available amount of the relevant diastereoisomer **4a** could be achieved.

Compound **3a** (≥ 95% de). $[\alpha]_D^{23} = -31.6$ (*c* = 0.9, EtOH). The spectroscopic data corresponded to those of **1a**.

Compound **4a** (≥ 66% de). $[\alpha]_D^{23} = -62.1$ (*c* = 1.0, EtOH). The spectroscopic data corresponded to those of enantiomer **2a**.

*(1*S*,2*R*,5*S*,6*R*,7*R*)-*N*-Ethyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**1b**). According to *GP A*, 2.15 g (10.3 mmol) of **1a** were reacted with 0.82 ml (70%, 10.2 mmol) of aq. $EtNH_2$. After crystallization from EtOH/H_2O (2 : 1), 1.46 g (6.5 mmol, 63%) of **1b** were obtained as colorless solid (≥ 99% de). M.p. 195.4°. $[\alpha]_D^{23} = +31.4$ (*c* = 1.0, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.56 (*tdd*, *J* = 13.4, 11.6, 1.9, 1 H); 0.79 (*m*, 1 H); 0.91 (*d*, *J* = 6.6, 3 H); 0.94 (*d*, *J* = 6.7, 3 H); 1.00 (*t*, *J* = 4.5, 1 H); 1.09 (*d*, *J* = 6.7, 3 H); 1.14 (*t*, *J* = 7.3, 3 H); 1.31 (*ddd*, *J* = 9.2, 4.2, 1.9, 1 H); 1.37 (*dsept.*, *J* = 7.9, 6.7,

1 H); 1.44–1.55 (*m*, 3 H); 1.57–1.64 (*m*, 2 H); 3.30 (*dq*, *J* = 7.3, 5.6, 2 H); 5.41 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.1 (Me); 20.5 (Me); 20.7 (Me); 23.4 (Me); 24.8 (CH_2); 25.6 (CH); 26.1 (CH); 27.4 (CH); 30.4 (CH); 32.7 (CH_2); 33.6 (CH); 34.5 (CH_2); 39.9 (CH); 173.4 (C=O). GC/EI-MS: 223 (7, $M^{+\bullet}$), 180 (78), 138 (52), 109 (58), 88 (39), 87 (100), 81 (28), 72 (45), 67 (33), 55 (28), 29 (33). HR-MS: 223.1935 ($M^{+\bullet}$, $C_{14}H_{25}NO^+$; calc. 223.1936).

*(1*R,*2*R,*5*S,*6*S,*7*S*)*-N-*Ethyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**2b**). According to *GP B*, 0.86 g (4.1 mmol) of **2a** were reacted with 0.39 g (70%, 6.1 mmol) aq. $EtNH_2$. After crystallization from H_2O/acetone (4 : 5), 0.73 g (3.2 mmol, 80%) of **2b** were obtained as colorless solid (≥ 99% de). M.p. 144°. $[\alpha]_D^{23} = +54.9$ (*c* = 1.0, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.52 (*tdd*, *J* = 13.5, 11.9, 2.2, 1 H); 0.90 (*m*, 1 H); 0.91 (*d*, *J* = 6.8, 3 H); 0.93 (*d*, *J* = 6.8, 3 H); 0.95 (*m*, 1 H); 0.97 (*d*, *J* = 6.5, 3 H); 1.15 (*t*, *J* = 7.3, 3 H); 1.25 (*dtd*, *J* = 12.7, 5.4, 2.1, 1 H); 1.35–1.54 (*m*, 3 H); 1.57 (*m*, 1 H); 1.66 (*m*, 1 H); 1.90 (*m*, 1 H); 3.18–3.42 (*m*, 2 H); 5.41 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.9 (Me); 19.2 (Me); 19.9 (Me); 21.4 (Me); 25.2 (CH); 25.3 (CH); 26.1 (CH_2); 28.2 (CH); 28.67 (CH); 28.74 (CH_2); 33.2 (CH); 34.4 (CH_2); 41.8 (CH); 173.6 (C=O). GC/EI-MS: 223 (13, $M^{+\bullet}$), 180 (100), 138 (72), 109 (32), 95 (25), 88 (16), 87 (52), 81 (29), 72 (25), 67 (18), 55 (16). HR-MS: 223.1936 ($M^{+\bullet}$, $C_{14}H_{25}NO^+$; calc. 223.1936).

*(1*R,*2*S,*5*R,*6*S,*7*S*)*-N-*Ethyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**3b**). According to *GP B*, 1.50 g (7.2 mmol) of **3a** were reacted with 0.58 g (70%, 9.0 mmol) of aq. $EtNH_2$. After crystallization from H_2O/acetone (5 : 9), 0.97 g (4.3 mmol, 59%) of **3b** could be obtained as colorless solid (≥ 99% de). $[\alpha]_D^{23} = -27.6$ (*c* = 1.0, EtOH). The spectroscopic data corresponded to those of **1b**.

*(1*S,*2*S,*5*R,*6*R,*7*R*)*-N-*Ethyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**4b**). According to *GP C*, 1.67 g (8.0 mmol) of **4a** were reacted with 0.84 g (70% in H_2O, 13.0 mmol) of $EtNH_2$. After crystallization from EtOH/H_2O 2 : 5, 0.77 g (purity 97.8%; 3.4 mmol, 43%) of **4b** could be obtained as colorless solid (≥ 66% de). $[\alpha]_D^{23} = -38.2$ (*c* = 1.1, EtOH). The spectroscopic data corresponded to those of **2b**.

*(1*S,*2*R,*5*S,*6*R,*7*R*)*-2-Methyl-*N,*5-bis(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**1c**). According to *GP A*, 2.15 g (10.3 mmol) of **1a** were reacted with 0.88 ml (10.2 mmol) of ^{i}PrNH$_2$. After crystallization from EtOH/H_2O (2 : 1), 1.83 g (7.7 mmol, 75%) of **1c** could be obtained as colorless solid (≥ 99% de). M.p. 198.3°. $[\alpha]_D^{23} = +30.2$ (*c* = 1.0, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.55 (*tdd*, *J* = 13.4, 11.6, 1.8, 1 H); 0.79 (*m*, 1 H); 0.91 (*d*, *J* = 6.6, 3 H); 0.93 (*d*, *J* = 6.6, 3 H); 0.97 (*t*, *J* = 4.5, 1 H); 1.09 (*d*, *J* = 6.7, 3 H); 1.14 (*d*, *J* = 6.5, 3 H); 1.16 (*d*, *J* = 6.5, 3 H); 1.31 (*ddd*, *J* = 9.2, 4.2, 2.0, 1 H); 1.36 (*dsept.*, *J* = 7.9, 6.7, 1 H); 1.43–1.55 (*m*, 3 H); 1.56–1.65 (*m*, 2 H); 4.09 (*dsept.*, *J* = 8.0, 6.6, 1 H); 5.26 (*d*, *J* = 7.0, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.5 (Me); 20.6 (Me); 22.9 (Me); 23.1 (Me); 23.4 (Me); 24.9 (CH_2); 25.6 (CH); 26.1 (CH); 27.2 (CH); 30.4 (CH); 32.7 (CH_2); 33.7 (CH); 39.9 (CH); 41.4 (CH); 172.6 (C=O). GC/EI-MS: 237 (12, $M^{+\bullet}$), 194 (84), 152 (55), 109 (55), 102 (34), 101 (100), 95 (34), 86 (45), 67 (30), 43 (65), 41 (30). HR-MS: 237.2076 ($M^{+\bullet}$, $C_{15}H_{27}NO^+$; calc. 237.2093).

*(1*R,*2*R,*5*S,*6*S,*7*S*)*-2-Methyl-*N,*5-bis(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**2c**). According to *GP B*, 0.86 g (4.1 mmol) of **2a** were reacted with 0.35 g (5.9 mmol) of ^{i}PrNH$_2$. After crystallization from H_2O/acetone (1 : 10), 0.57 g (2.4 mmol, 59%) of **2c** could be obtained as colorless solid (≥ 98% de). M.p. 160°. $[\alpha]_D^{23} = +47.7$ (*c* = 1.0, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.52 (*tdd*, *J* = 13.6, 12.0, 2.0, 1 H); 0.84–0.95 (*m*, 2 H); 0.91 (*d*, *J* = 6.8, 3 H); 0.93 (*d*, *J* = 6.8, 3 H); 0.96 (*d*, *J* = 6.6, 3 H); 1.14 (*d*, *J* = 6.6, 3 H); 1.15 (*d*, *J* = 6.6, 3 H); 1.25 (*m*, 1 H); 1.34–1.45 (*m*, 2 H); 1.49 (*m*, 1 H); 1. 56 (*m*, 1 H); 1.67 (*dsept.*, *J* = 6.7, 5.9, 1 H); 1.90 (*m*, 1 H); 4.07 (*dsept.*, *J* = 8.0, 6.5, 1 H); 5.27 (*d*, *J* = 7.8, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.2 (Me); 19.9 (Me); 21.4 (Me); 23.0 (Me); 23.1 (Me); 25.3 (CH); 25.5 (CH); 26.1 (CH_2); 28.3 (CH); 28.6 (CH); 28.8 (CH_2); 33.3 (CH); 41.4 (CH); 41.9 (CH); 172.8 (C=O). GC/EI-MS: 237 (17, $M^{+\bullet}$), 194 (100), 152 (68), 109 (32), 101 (47), 95 (29), 86 (23), 81 (26), 55 (18), 43 (30), 41 (20). HR-MS: 237.2073 ($M^{+\bullet}$, $C_{15}H_{27}NO^+$; calc. 237.2093).

*(1*R,*2*S,*5*R,*6*S,*7*S*)*-2-Methyl-*N,*5-bis(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**3c**). According to *GP B*, 1.50 g (7.2 mmol) of **3a** were reacted with 0.53 g (9.0 mmol) of ^{i}PrNH$_2$. After crystallization from H_2O/acetone 5 : 11, 0.89 g (3.8 mmol, 53%) of **3c** could be obtained as colorless solid (≥ 99% de). $[\alpha]_D^{23} = -20.0$ (*c* = 1.0, EtOH). The spectroscopic data corresponded to those of **1c**.

*(1S,2S,5R,6R,7R)-2-Methyl-*N*,5-bis(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**4c**). According to *GP C*, 1.67 g (8.0 mmol) of **4a** were reacted with 0.77 g (13.0 mmol) of $^{i}PrNH_2$. After crystallization from EtOH/H_2O (1:2), 0.61 g (purity 97.6%; 2.5 mmol, 31%) of **4c** could be obtained as colorless solid (≥66% de). $[\alpha]_D^{23} = -35.1$ ($c = 0.8$, EtOH). The spectroscopic data corresponded to those of enantiomer **2c**.

*(1S,2R,5S,6R,7R)-*N*-(2-Hydroxyethyl)-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**1d**). According to *GP A*, 2.15 g (10.3 mmol) of **1a** were reacted with 0.61 ml (10.2 mmol) of $HOCH_2CH_2NH_2$. After crystallization from EtOH/H_2O 4:3, 1.35 g (5.6 mmol, 54%) of **1d** were obtained as colorless solid (≥99% de). M.p. 194°. $[\alpha]_D^{23} = +22.5$ ($c = 1.0$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.57 (*tdd*, $J = 13.3, 11.6, 2.0$, 1 H); 0.79 (*m*, 1 H); 0.92 (*d*, $J = 6.6$, 3 H); 0.94 (*d*, $J = 6.7$, 3 H); 1.08 (*t*, $J = 4.5$, 1 H); 1.09 (*d*, $J = 6.7$, 3 H); 1.33 (*m*, 1 H); 1.37 (*m*, $J = 7.9, 6.7$, 1 H); 1.44–1.57 (*m*, 3 H); 1.58–1.68 (*m*, 2 H); 2.83 (br. *s*, 1 H); 3.44 (*m*, 2 H); 3.73, (*t*, $J = 4.4$, 2 H); 5.98 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.5 (Me); 20.7 (Me); 23.4 (Me); 24.7 (CH_2); 25.8 (CH); 26.1 (CH); 27.9 (CH); 30.3 (CH); 32.6 (CH_2); 33.6 (CH); 39.9 (CH); 42.9 (CH_2); 63.1 (CH_2); 172.6 (C=O). GC/EI-MS: 239 (5, $M^{+\cdot}$), 196 (63), 154 (40), 135 (49), 109 (47), 103 (100), 95 (48), 85 (37), 81 (42), 67 (36), 55 (48). HR-MS: 239.1881 ($M^{+\cdot}$, $C_{14}H_{25}NO_2^+$; calc. 239.1885).

*(1R,2R,5S,6S,7S)-*N*-(2-Hydroxyethyl)-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**2d**). According to *GP B*, 1.30 g (6.2 mmol) of **2a** were reacted with 0.55 g (9.0 mmol) of $HOCH_2CH_2NH_2$. After crystallization from H_2O/acetone 6:2, 0.37 g (1.6 mmol, 26%) of **2d** could be obtained as colorless solid (≥99% de). M.p. 134°. $[\alpha]_D^{23} = +48.4$ ($c = 1.0$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.53 (*tdd*, $J = 13.0, 12.1, 2.2$, 1 H); 0.90 (*m*, 1 H); 0.92 (*d*, $J = 6.7$, 3 H); 0.93 (*d*, $J = 6.7$, 3 H); 0.98 (*d*, $J = 6.6$, 3 H); 1.03 (*t*, $J = 4.4$, 1 H); 1.27 (*m*, 1 H); 1.46–1.49 (*m*, 2 H); 1.51 (*m*, 1 H); 1.60 (*m*, 1 H); 1.67 (*dsept.*, $J = 6.9, 5.7$, 1 H); 1.91 (*m*, 1 H); 2.80 (br. *s*, 1 H); 3.43 (*m*, 2 H); 3.74 (*t*, $J = 4.9$, 2 H); 5.92 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.2 (Me); 19.9 (Me); 21.4 (Me); 25.2 (CH); 25.8 (CH); 26.0 (CH_2); 28.3 (CH); 28.7 (CH_2); 29.3 (CH); 33.3 (CH); 41.8 (CH); 43.0 (CH_2); 63.1 (CH_2); 175.3 (C=O). GC/EI-MS: 239 (14, $M^{+\cdot}$), 196 (100), 154 (68), 136 (35), 135 (38), 109 (36), 103 (46), 95 (48), 93 (32), 81 (42), 55 (30). HR-MS: 239.1887 ($M^{+\cdot}$, $C_{14}H_{25}NO_2^+$; calc. 239.1885).

*(1R,2S,5R,6S,7S)-*N*-(2-Hydroxyethyl)-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**3d**). According to *GP B*, 2.00 g (9.6 mmol) of **3a** were reacted with 0.73 g (12.0 mmol) of $HOCH_2CH_2NH_2$. After crystallization from H_2O/acetone 10:11, 0.60 g (2.5 mmol, 26%) of ethanolamide **3d** could be obtained as colorless solid (≥99% de). $[\alpha]_D^{23} = -20.5$ ($c = 1.0$, EtOH). The spectroscopic data corresponded to those of **1d**.

*(1S,2S,5R,6R,7R)-*N*-(2-Hydroxyethyl)-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**4d**). According to *GP C*, 1.67 g (8.0 mmol) of **4a** were reacted with 0.79 g (13.0 mmol) of $HOCH_2CH_2NH_2$. After crystallization from EtOH/H_2O 1:2, 0.75 g (purity 97.4%; 3.1 mmol, 39%) of **4d** could be obtained as colorless solid (≥62% de). $[\alpha]_D^{23} = -37.5$ ($c = 0.8$, EtOH). The spectroscopic data corresponded to those of **2d**.

*(1S,2R,5S,6R,7R)-*N*-Cyclopropyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**1e**). According to *GP A*, 2.15 g (10.3 mmol) of **1a** were reacted with 0.71 ml (10.2 mmol) of cyclopropylamine. After crystallization from EtOH/H_2O 3:1, 1.69 g (7.1 mmol, 69%) of **1e** could be obtained as colorless solid (≥99% de). M.p. 227°. $[\alpha]_D^{23} = +26.7$ ($c = 1.0$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.43–0.66 (*m*, 3 H); 0.70–0.87 (*m*, 3 H); 0.90 (*d*, $J = 6.6$, 3 H); 0.93 (*d*, $J = 6.7$, 3 H); 1.08 (*d*, $J = 6.7$, 3 H); 1.11 (*m*, 1 H); 1.27–1.42 (*m*, 2 H); 1.42–1.56 (*m*, 3 H); 1.56–1.66 (*m*, 2 H); 2.72 (*dddd*, $J = 10.9, 7.0, 3.8, 3.0$, 1 H); 5.66 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 6.67 (CH_2); 6.73 (CH_2); 20.5 (Me); 20.7 (Me); 22.8 (CH); 23.4 (Me); 24.8 (CH_2); 25.8 (CH); 25.9 (CH); 27.6 (CH); 30.4 (CH); 32.6 (CH_2); 33.6 (CH); 39.9 (CH); 174.9 (C=O). GC/EI-MS: 235 (18, $M^{+\cdot}$), 135 (56), 95 (100), 93 (79), 81 (59), 69 (29), 67 (24), 57 (27), 55 (47), 43 (29), 41 (36). HR-MS: 235.1925 ($M^{+\cdot}$, $C_{15}H_{25}NO^+$; calc. 235.1936).

*(1R,2R,5S,6S,7S)-*N*-Cyclopropyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**2e**). According to *GP B*, 0.86 g (4.1 mmol) of **2a** were reacted with 0.34 g (6.0 mmol) cyclopropylamine. After crystallization from H_2O/acetone 4:7, 0.48 g (2.0 mmol, 49%) of **2e** could be obtained as colorless solid (≥98% de). M.p. 185°. $[\alpha]_D^{23} = +46.9$ ($c = 1.0$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.43–0.59 (*m*, 3 H); 0.69–0.98 (*m*, 4 H); 0.91 (*d*, $J = 6.7$, 3 H); 0.93 (*d*, $J = 6.8$, 3 H); 0.95 (*d*, $J = 6.6$, 3 H); 1.23 (*m*, 1 H); 1.36–1.64 (*m*, 4 H); 1.66 (*m*, 1 H); 1.90 (*m*, 1 H); 2.72 (*m*, 1 H); 5.69 (*s*, 1 H). ^{13}C-NMR (100 MHz,

$CDCl_3$): 6.6 (CH_2); 6.7 (CH_2); 19.2 (Me); 19.9 (Me); 21.4 (Me); 22.8 (CH); 25.2 (CH); 25.6 (CH); 26.1 (CH_2); 28.3 (CH); 28.8 (CH_2); 29.0 (CH); 33.3 (CH); 41.9 (CH); 175.1 (C=O). GC/EI-MS: 235 (35, $M^{+\bullet}$), 179 (51), 135 (56), 109 (28), 95 (100), 93 (67), 81 (54), 69 (30), 55 (41), 41 (28). HR-MS: 235.1934 ($M^{+\bullet}$, $C_{15}H_{25}NO^+$; calc. 235.1936).

*(1*R,*2*S,*5*R,*6*S,*7*S*)*-N-*Cyclopropyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**3e**). According to *GP B*, 1.50 g (7.2 mmol) of **3a** were reacted with 0.51 g (9.0 mmol) of cyclopropylamine. After crystallization from H_2O/acetone 5:11, 1.01 g (4.3 mmol, 60%) of **3e** could be obtained as colorless solid (≥99% de). $[\alpha]_D^{23} = -22.5$ ($c = 1.0$, EtOH). The spectroscopic data corresponded to those of **1e**.

*(1*S,*2*S,*5*R,*6*R,*7*R*)*-N-*Cyclopropyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**4e**). According to *GP C*, 1.67 g (8.0 mmol) of **4a** were reacted with 0.77 g (13.0 mmol) of cyclopropylamine. After crystallization from EtOH/H_2O 1:2, 0.59 g (purity 97.5%; 2.5 mmol, 40%) of **4e** could be obtained as colorless solid (≥63% de). $[\alpha]_D^{23} = -38.1$ ($c = 0.8$, EtOH). The spectroscopic data corresponded to those of **2e**.

*(1*S,*2*R,*5*S,*6*R,*7*R*)*-N-*Cyclopentyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**1f**). According to *GP A*, 2.15 g (10.3 mmol) of **1a** were reacted with 1.01 ml (10.2 mmol) of cyclopentylamine. After crystallization from EtOH/H_2O 5:2, 2.04 g (7.7 mmol, 75%) of **1f** could be obtained as colorless solid (≥99% de). M.p. 200°. $[\alpha]_D^{23} = +29.7$ ($c = 1.0$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.55 (*tdd*, $J = 13.4, 11.5, 1.8$, 1 H); 0.79 (*m*, 1 H); 0.91 (*d*, $J = 6.6$, 3 H); 0.93 (*d*, $J = 6.6$, 3 H); 0.98 (*t*, $J = 4.5$, 1 H); 1.09 (*d*, $J = 6.8$, 3 H); 1.31 (*m*, 1 H); 1.34–1.42 (*m*, 3 H); 1.44–1.71 (*m*, 9 H); 1.99 (*m*, 2 H); 4.22 (*m*, 1 H); 5.42 (*d*, $J = 7.1$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.5 (Me); 20.6 (Me); 23.4 (Me); 23.7 (CH_2); 23.8 (CH_2); 24.8 (CH_2); 25.6 (CH); 26.1 (CH); 27.3 (CH); 30.4 (CH); 32.7 (CH_2); 33.2 (CH_2); 33.5 (CH_2); 33.7 (CH); 39.9 (CH); 51.3 (CH); 173.1 (C=O). GC/EI-MS: 263 (17, $M^{+\bullet}$), 220 (100), 178 (45), 127 (98), 109 (51), 95 (39), 69 (58), 67 (33), 60 (67), 55 (37), 41 (41). HR-MS: 263.2244 ($M^{+\bullet}$, $C_{17}H_{29}NO^+$; calc. 263.2249).

*(1*R,*2*R,*5*S,*6*S,*7*S*)*-N-*Cyclopentyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**2f**). According to *GP B*, 0.75 g (3.6 mmol) of **2a** were reacted with 0.45 g (5.3 mmol) of cyclopentylamine. After crystallization from H_2O/acetone 4:7, 0.67 g (2.5 mmol, 69%) of **2f** could be obtained as colorless solid (≥98% de). M.p. 164°. $[\alpha]_D^{23} = +42.6$ ($c = 1.0$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.52 (*tdd*, $J = 13.5, 11.9, 2.0$, 1 H); 0.88 (*m*, 1 H); 0.91 (*d*, $J = 6.8$, 3 H); 0.93 (*d*, $J = 6.8$, 3 H); 0.93 (*m*, 1 H); 0.96 (*d*, $J = 6.6$, 3 H); 1.25 (*m*, 1 H); 1.31–1.45 (*m*, 3 H); 1.49 (*m*, 1 H); 1.53–1.72 (*m*, 7 H); 1.89 (*m*, 1 H); 1.99 (*m*, 2 H); 4.20 (*m*, 1 H); 5.49 (*d*, $J = 7.1$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.2 (Me); 19.9 (Me); 21.4 (Me); 23.8 (2 CH_2); 25.3 (CH); 25.5 (CH); 26.1 (CH_2); 28.3 (CH); 28.7 (CH); 28.8 (CH_2); 33.26 (CH); 33.33 (CH_2); 33.4 (CH_2); 41.9 (CH); 51.2 (CH); 173.2 (C=O). GC/EI-MS: 263 (18, $M^{+\bullet}$), 220 (100), 178 (55), 127 (35), 109 (26), 95 (30), 81 (24), 69 (34), 67 (20), 55 (22), 41 (24). HR-MS: 263.2230 ($M^{+\bullet}$, $C_{17}H_{29}NO^+$; calc. 263.2249).

*(1*R,*2*S,*5*R,*6*S,*7*S*)*-N-*Cyclopentyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**3f**). According to *GP B*, 1.50 g (7.2 mmol) of **3a** were reacted with 0.77 g (9.0 mmol) of cyclopentylamine. After crystallization from H_2O/acetone 5:11, 1.12 g (4.3 mmol, 60%) of **3f** could be obtained as colorless solid (≥98% de). $[\alpha]_D^{23} = -29.3$ ($c = 1.0$, EtOH). The spectroscopic data corresponded to those of **1f**.

*(1*S,*2*S,*5*R,*6*R,*7*R*)*-N-*Cyclopentyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**4f**). According to *GP C*, 1.67 g (8.0 mmol) of **4a** were reacted with 0.77 g (13.0 mmol) of cyclopentylamine. After crystallization from EtOH/H_2O 1:2, 0.40 g (1.5 mmol, 19%) of **4f** could be obtained as colorless solid (≥66% de). $[\alpha]_D^{23} = -40.4$ ($c = 0.8$, EtOH). The spectroscopic data corresponded to those of **2f**.

*(1*S,*2*R,*5*S,*6*R,*7*R*)*-N-*Cyclohexyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**1g**). According to *GP A*, 2.15 g (10.3 mmol) of **1a** were reacted with 1.17 ml (10.2 mmol) of cyclohexylamine. After crystallization from EtOH/H_2O 5:2, 2.24 g (8.0 mmol, 78%) of **1c** could be obtained as colorless solid (≥99% de). M.p. 220°. $[\alpha]_D^{23} = +22.6$ ($c = 1.0$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.55 (*m*, 1 H); 0.79 (*m*, 1 H); 0.91 (*d*, $J = 6.6$, 3 H); 0.93 (*d*, $J = 6.6$, 3 H); 0.98 (*t*, $J = 4.5$, 1 H); 1.09 (*d*, $J = 6.8$, 3 H); 1.05–1.21 (*m*, 3 H); 1.28–1.42 (*m*, 4 H); 1.45–1.74 (*m*, 8 H); 1.91 (*m*, 2 H); 3.77 (*m*, 1 H); 5.35 (*d*, $J = 7.9$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.56 (Me); 20.58 (Me); 23.4 (Me); 24.87

(CH_2); 24.91 (CH_2); 25.0 (CH_2); 25.6 (CH_2); 25.6 (CH); 26.2 (CH); 27.2 (CH); 30.4 (CH); 32.7 (CH_2); 33.4 (CH_2); 33.6 (CH_2); 33.7 (CH); 39.9 (CH); 48.2 (CH); 172.5 (C=O). GC/EI-MS: 277 (20, $M^{+\bullet}$), 234 (100), 192 (37), 141 (88), 109 (45), 95 (38), 83 (48), 81 (31), 60 (66), 55 (69), 41 (32). HR-MS: 277.2403 ($M^{+\bullet}$, $C_{18}H_{31}NO^+$; calc. 277.2406).

*(1*R*,2*R*,5*S*,6*S*,7*S*)*-N-*Cyclohexyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**2g**). According to *GP B*, 0.75 g (3.6 mmol) of **2a** were reacted with 0.52 g (5.3 mmol) of cyclohexylamine. After crystallization from H_2O/acetone 4:7, 0.49 g (1.8 mmol, 50%) of **2g** could be obtained as colorless solid (≥98% de). M.p. 196.4°. $[\alpha]_D^{23} = +41.9$ ($c = 1.0$, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.52 (*m*, 1 H); 0.86–0.98 (*m*, 2 H); 0.91 (*d*, *J* = 6.7, 3 H); 0.93 (*d*, *J* = 6.7, 3 H); 0.96 (*d*, *J* = 6.6, 3 H); 1.06–1.28 (*m*, 3 H); 1.29–1.45 (*m*, 3 H); 1.45–1.75 (*m*, 8 H); 1.84–1.98 (*m*, 3 H); 3.75 (*m*, 1 H); 5.35 (*d*, *J* = 7.9, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.2 (Me); 19.9 (Me); 21.4 (Me); 25.0 (2 CH_2); 25.3 (CH); 25.58 (CH); 25.62 (CH_2); 26.1 (CH_2); 28.3 (CH); 28.7 (CH); 28.9 (CH_2); 33.3 (CH); 33.4 (CH_2); 33.5 (CH_2); 41.9 (CH); 48.2 (CH); 172.7 (C=O). GC/EI-MS: 277 (21, $M^{+\bullet}$), 234 (100), 192 (48), 141 (32), 109 (24), 95 (30), 83 (24), 81 (24), 55 (34), 41 (19). HR-MS: 277.2405 ($M^{+\bullet}$, $C_{18}H_{31}NO^+$; calc. 277.2406).

*(1*R*,2*S*,5*R*,6*S*,7*S*)*-N-*Cyclohexyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**3g**). According to *GP B*, 1.50 g (7.2 mmol) of **3a** were reacted with 0.89 g (9.0 mmol) of cyclohexylamine. After crystallization from H_2O/acetone 5:15, 1.22 g (4.4 mmol, 61%) of **3g** could be obtained as colorless solid (≥98% de). $[\alpha]_D^{23} = -18.9$ ($c = 1.0$, EtOH). The spectroscopic data corresponded to those of **1g**.

*(1*S*,2*S*,5*R*,6*R*,7*R*)*-N-*Cyclohexyl-2-methyl-5-(1-methylethyl)bicyclo[4.1.0]heptane-7-carboxamide* (**4g**). According to *GP C*, 1.67 g (8.0 mmol) of **4a** were reacted with 0.77 g (13.0 mmol) of cyclohexylamine. After crystallization from EtOH/H_2O 1:2, 0.39 g (1.4 mmol, 18%) of **4g** could be obtained as colorless solid (≥64% de). $[\alpha]_D^{23} = -28.0$ ($c = 1.1$, EtOH). The spectroscopic data corresponded to those of **2g**.

Sensory Analysis. Sensory tests were carried out with healthy and trained panelists without known taste disorders. Panelists were fully informed about procedure and intention of the project and had given written consent. They were advised not to swallow the samples, and samples were tested using the sip-and-spit method. The samples were tested in sensory panel rooms under standardized conditions, and they were given blind and randomized. For the preparation of the test solns., *Vittel*® water was used. The panelists had participated earlier at regular intervals in sensory work and were, therefore, familiar with the techniques applied.

Pre-Evaluation. A number of 5–8 trained panelists received each compound in a dosage of 5 ppm in a 0.5% salt and a 5.0% sugar soln., and was asked to describe the sample and give a qualitative statement for the umami intensity. No additional reference (*e.g.*, MSG) was presented during the session.

Ranking Test (ISO 8587:2006). A panel of 14–18 trained panelists received at least three samples containing a 0.5% salt soln. plus 5 ppm of the corresponding test compounds. The panelist were asked to rank the samples according to the descriptor umami. The rank sums were determined, and statistical comparisons were made employing least significant difference (LSD) *post hoc* test, and the level of significance for the mean rank was set to <10%. This test could be used to determine differences between the samples, but not to quantify the degree of difference.

REFERENCES

[1] K. Ikeda, *Chem. Senses* **2002**, *27*, 847.
[2] S. Yamaguchi, *J. Food Sci.* **1967**, *32*, 473.
[3] C. Winkel, A. de Klerk, J. Visser, E. de Rijke, J. Bakker, T. Koenig, H. Renes, *Chem. Biodiversity* **2008**, *5*, 1195.
[4] M. Behrens, W. Meyerhof, C. Hellfritsch, T. Hofmann, *Angew. Chem.* **2011**, *123*, 2268.
[5] K. Beyreuther, H. K. Biesalski, J. D. Fernstrom, P. Grimm, W. P. Hammes, U. Heinemann, O. Kempski, P. Stehle, H. Steinhart, R. Walker, *Eur. J. Clin. Nutr.* **2007**, *61*, 304.
[6] F. Zhang, B. Klebansky, R. M. Fine, H. Xu, A. Pronin, H. Liu, C. Tachdjian, X. Li, *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 20930.

[7] C. Tachdjian, A. P. Patron, S. L. Adamski-Werner, F. Bakir, Q. Chen, V. Darmohusodo, S. T. Hobson, X. Li, M. Qi, D. H. Rogers, M. Rinnova, G. Servant, X.-Q. Tang, M. Zoller, M. Wallace, A. Xing, K. Gubernator, *Senomyx Inc.*, PCT Int. Appl. WO 2005 041 684, 2005.
[8] M. L. Dewis, M. E. Huber, M. V. Cossette, D. O. Agyemang, *International Flavors & Fragrances Inc.*, U.S. Pat. 7,361,376, 2008; M. L. Dewis, G. Conklin, T. Pei, *International Flavors & Fragrances Inc.*, U.S. Pat. 7,427,421, 2008.
[9] J. Looft, T. Vössing, J. Ley, M. Backes, M. Blings, *Symrise GmbH & Co. KG*, U.S. Pat. 7,919,133, 2011; J. P. Ley, H. Oertling, M. Backes, T. Vössing, *Symrise AG*, EP 2,135,516, 2012.
[10] Y. Wang, A. Daniher, A. de Klerk, C. Winkel, *Givaudan SA*, PCT Int. Appl. WO 2011 004 016, 2011.
[11] J. Looft, T. Vössing, M. Backes, *Symrise AG*, U.S. Pat. 8,487,133, 2013.
[12] M. Backes, J. P. Ley, S. Paetz, J. Looft, T. Vössing, F. Stähler, C. Bartram, W. Meyerhof, G. Krammer, in 'Advances and Challenges in Flavor Chemistry & Biology, Proceedings of the 9th Wartburg Symposium, Eisenach', Eds. T. Hofmann, W. Meyerhof, P. Schieberle, Deutsche Forschungsanstalt für Lebensmittelchemie, Freising, 2011, p. 75.
[13] Z. Rykowski, H. Orszanska, *Roczniki Chemii Ann. Soc. Chim. Polonorum* **1976**, *50*, 1901.
[14] Y. Imai, W. Zhang, T. Kida, Y. Nakatsuji, I. Ikeda, *Tetrahedron: Asymmetry* **1996**, *7*, 2453; E. Schulz, *Top. Organomet. Chem.* **2005**, *15*, 93.
[15] J. E. Baldwin, C. G. Carter, *J. Am. Chem. Soc.* **1982**, *104*, 1362.
[16] ISO 8587:2006, http://www.iso.org.
[17] K. Gollnick, G. Schade, *Tetrahedron* **1966**, *22*, 123.
[18] N. L. McNiven, J. Read, *J. Chem. Soc.* **1952**, 153.

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