Practical Synthesis of Optically Pure Menthylamines Starting from Racemic Neomenthol

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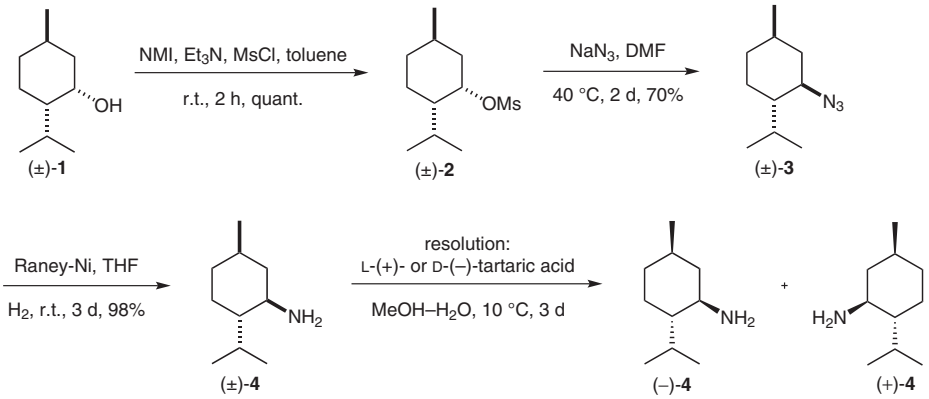
Abstract: A reliable and scalable route to racemic and highly enantiomerically enriched menthylamines exploits the technical product *rac*-neomenthol as the starting material. The elaborated protocol is based on nucleophilic substitution of the hydroxy moiety by azide. Subsequent reduction and resolution with tartaric acid provides the desired optically enriched menthylamines.

Key words: amines, azides, chiral resolution, reduction, terpenoids



Scheme 1

Here, we report a fast synthetic access to optically pure menthylamines starting from racemic neomenthol including a resolution on the final step (Scheme 1). Menthylamines (–)-**4**–**6** are unique α-chiral amines, which exhibit an asymmetric environment in the vicinity of the amino group. Due to the conformational stability of the all-equatorial substituted cyclohexane scaffold a superb transfer of stereogenic information is guaranteed. Recently, this building block has been applied to the construction of supramolecular receptors **7** that allow enantiofacial discrimination of single substrates[1–3] and an efficient binding of caffeine[4] and explosives.[5–7] Epimeric mixtures of optically enriched menthylamine and neomenthylamine have been used in the synthesis of high performance stationary phase like **8** for column chromatography.[8–10] Such a resolution material was employed for the resolution of cerivastatin, a precursor of a formerly top-selling drug.[11] Specific amides of (+)-neomenthylamine [(+)-**6**] turned out to exhibit a strong capacity for umami flavor (Scheme 2).[12]

All pathways for the synthesis of menthylamine take advantage of terpenoic starting materials providing the full carbon skeleton for the desired products. A pathway for the synthesis of menthylamines proceeds from menthol derivatives. Most reactions in the literature start with (–)-menthol (**10**) to obtain the undesired diastereoisomer (+)-neomenthylamine [(+)-**6**] (Scheme 3).

Initially, an efficient leaving group has to be installed, mostly a mesylate [Scheme 3; 1) (a)–(d)].[13–16] In a subsequent nucleophilic substitution reaction the configurationally inverted azide was obtained. Alkali salts usually served as azide sources [Scheme 3; 2) (a), (b)].[13,16] Reduction could be conducted by $CeCl_3$/NaI mixtures[17] or by $LiAlH_4$ to form (+)-neomenthylamine [(+)-**6**].[16] In a Mitsunobu-type transformation employing diisopropyl azodicarboxylate and triphenylphosphine, the substrate **10** reacted with a zinc azide derivative in a one-pot procedure to form the desired azide **12** (Scheme 3).[18]

There is no previous report for the synthesis of (–)-menthylamine starting from neomenthol. Only the mesylation of (+)-neomenthol [(+)-**1**] in pyridine is known (Scheme 4).[19] However, no details about the purity of the

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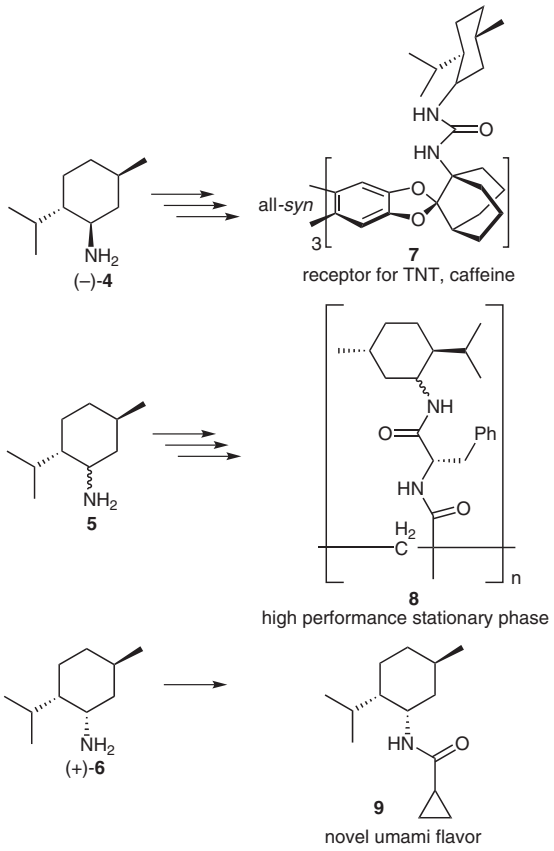
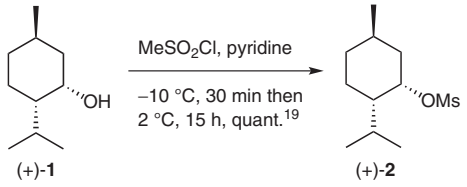


Scheme 2

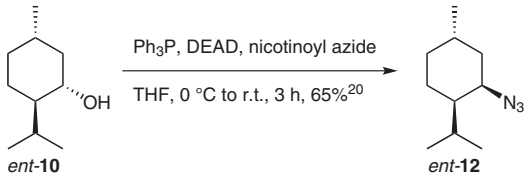
crude product were given and therefore, the conversion was claimed to be quantitative.[19]

Another direct conversion of a menthol derivative to the corresponding azide was reported for (+)-menthol using Mitsunobu conditions (Scheme 5).[20]

Alternatively, menthone could be converted by standard transformations into the corresponding oximes. Preliminary results of the synthesis of menthylamine were published in 1891 by Wallach et al.[21] They reported a Leuckert amination of menthone to obtain the desired menthylamine.[21–23] Detailed investigation of this product in our lab indicated the formation of a mixture of several stereoisomers.[24] Another pathway was a subsequent Bouveault–Blanc-type reduction, which provided the menthylamine in acceptable stereochemistry. However, the original protocol lacked in reproducibility[25] and was



Scheme 4

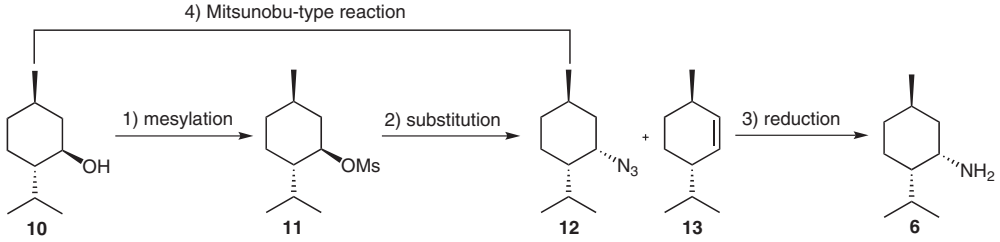


Scheme 5

therefore elaborated into a reliable procedure.[26] The drawback of this method consisted in the required large excess of sodium metal. Consequently, a more sustainable and electroorganic process was developed for the oxime reduction.[27]

Racemic neomenthol [(±)-**1**] is a technical by-product which is obtained in the synthesis of menthol starting from thymol.[28] This particular diastereomer is usually recycled by dehydrogenation/hydrogenation sequences. Consequently, *rac*-neomenthol represents an attractive starting material for the preparation of optically enriched menthylamines. This pathway (Scheme 1) circumvents the separation of menthyl- and neomenthylamines.

The substitution of the alcohol moiety in (±)-**1** by a nitrogen functionality was challenging since the axially positioned leaving group was prone to elimination processes. For the mesylation step, we tested different bases, K_2CO_3, Et_3N, pyridine, 1-methylimidazole (NMI), and mixtures thereof. Table 1 displays the optimized conditions for the individual reagent mixtures. No reaction occurred employing insoluble bases in 1,4-dioxane (entry 1), or using triethylamine (entry 2) in dichloromethane at ambient conditions. Using pyridine as solvent and base gave significantly more of the desired product (entry 3). The less basic 1-methylimidazole turned out to be beneficial for this transformation. If 1-methylimidazole was applied as reaction medium, the mesylate (±)-**2** was obtained in 89% yield (entry 4). Performing this conversion in THF at lower temperature slowed the reaction rate down, but provid-



Scheme 3 *Reaction conditions:* 1) (a) $MeSO_2Cl$, pyridine, 0 °C;[13] (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 1 h, quant.;[14] (c) $MeSO_2Cl$, NMI, Et_3N, toluene, 20–25 °C, 1 h, 99%;[15] (d) $(MeSO_2)_2O$, pyridine, DMAP, CH_2Cl_2, r.t., 19 h, quant;[16] 2) (a) LiN_3, DMF, 90 °C, 20 h, **12**: 63%, **13**: 11%;[13] (b) NaN_3, DMF, 80 °C, 42 h, **12**: 59%;[16] 3) (a) $CeCl_3 \cdot 7H_2O$, NaI, MeCN, 100 °C, 24 h, 75%;[17] (b) $LiAlH_4$, Et_2O, 40 °C, 2 h, then r.t., 21 h, 51%;[16] 4) $Zn(N_3)_2 \cdot 2Py$, Ph_3P, $N_2(CO_2CHMe_2)$, toluene, r.t., 2 h, 76%.[18]

ed the target compound in excellent yield (entry 5). A mixture of Et_3N and NMI in toluene[15] led to the best result (Table 1, entry 6). These mild conditions suppressed completely the elimination reaction to menth-2-ene. Switching to other leaving functionalities, for example, 4-tolylsulfonate to obtain *rac*-neomenthyl-4-tolylsulfonate [(±)-**14**], gave far inferior results (entry 7).

Table 1 Introduction of Leaving Functionality

Entry	Base	Conditions	Yield (%)[a]
1	K_2CO_3	MsCl, 1,4-dioxane, r.t., 5 d	–
2	Et_3N	MsCl, CH_2Cl_2, r.t., 5 d	–
3	pyridine	MsCl, 0 °C to r.t., 14 h	81[b]
4	NMI	MsCl, 0 °C, 1 h	89[b]
5	NMI	MsCl, THF, –20 °C to r.t., 5 d	95
6	NMI, Et_3N	MsCl, toluene, r.t., 2 h	quant
7	pyridine	TsCl, 0 °C, 70 h	–[c]

[a] Yield of isolated product.
[b] By-product menth-2-ene determined by ^{1}H NMR spectroscopy (5–10%).
[c] Reaction did not go to completion; a mixture of (±)-**1**, **13**, and (±)-**14** (1:1:1) was obtained.

Since the S_N2 reaction was not preferred on a six-membered carbocycle and the leaving group was preset for the elimination reaction, a very good and low basic nitrogen nucleophile was required. A pronounced solvent effect was anticipated and therefore, aprotic reaction media were tested (Table 2): DMF, DMSO, and NMP (entries 1, 6, 7) gave very similar results, whereas acetone as solvent led to no conversion at all (entry 9). However, DMF seemed to be the superior solvent for the substitution reaction. The azide (±)-**3** was contaminated with 20% of the by-product **13** if the synthesis was performed on large-scale (up to 0.25 mol starting material). In test reactions of 5 mmol scale, only a little elimination process was detected (not exceeding 5%). Remarkably, an excess of 1.5 equivalents NaN_3 seemed to be crucial (entry 1); 3 equivalents offered slightly better results (entry 3). Exposure to an excess of nucleophile gave lower yield and produced an increased amount of elimination product (entries 4, 5).

Table 3 displays possible reagents for the reduction of *rac*-menthyl azide [(±)-**3**]. Neither a mixture of $FeCl_3$ with Zn nor $NaBH_4$ were reactive enough to synthesize the amine (±)-**4** (entries 1, 2). When employing $LiAlH_4$ in THF (±)-**4** was obtained in good yields (entry 4). For a multigram approach of the menthylamine, Raney-Ni in THF turned out to be the method of choice (entry 5). Compared to $LiAlH_4$, the workup with Raney-Ni was more practical and provided better yields.

Finally, the racemic menthylamine (±)-**4** had to be resolved by optically pure acids. The resolution turned out to be more difficult than anticipated. Common resolving

Table 2 Conditions for the S_N2 Reaction

Entry	NaN_3 (equiv)	Conditions	Yield (%)[a]
1	1.5	DMF, 40 °C, 2 d	70[b]
2	2	DMF, 40 °C, 2 d	65[b]
3	3	DMF, 40 °C, 2 d	78[b]
4	4	DMF, 40 °C, 2 d	58[c]
5	5	DMF, 40 °C, 30 h	57[c]
6	1.5	DMSO, 40 °C, 2 d	63[b]
7	1.5	NMP, 40 °C, 2 d	70[b]
8	1.5	DMF, 30 °C, 4 d	63[b]
9	3	acetone, 40 °C, 7 d	–

[a] Yield of isolated product.
[b] By-product menth-2-ene determined by ^{1}H NMR spectroscopy for a 5 mmol scale; ca. 5%. For scaled-up processes (250 mmol); ca. 20%.
[c] By-product menth-2-ene determined by ^{1}H NMR spectroscopy for a 5 mmol synthesis; ca. 20%.

Table 3 Reduction of *rac*-Menthyl Azide

Entry	Reducing agent	Conditions	Yield (%)
1	$FeCl_3$/Zn	EtOH, 0 °C to r.t., 7 d	–
2	$NaBH_4$	EtOH, 0 °C to r.t., 7 d	trace
3	PtO_2, H_2	MeOH, r.t., 4 d	61
4	$LiAlH_4$	THF, 0 °C to r.t., 22 h	92
5	Raney-Ni, H_2	THF, r.t., 3 d	98

agents like (–)-*O*,*O*′-dibenzoyl-L-tartaric acid, L-(–)-malic acid, (+)-camphorsulfonic acid, or Brown's acid gave no resolvable diastereomeric salts. Only L-(+)-tartaric acid separated the enantiomers in low but acceptable yields (Table 4). At first different concentrations of EtOH (entries 1–6) and MeOH solutions (entries 7–12) at different conditions (temperature and water content) were studied. Best results were achieved with a 1.25 mmol/mL concentration in MeOH, which contained 5% water (entry 10). The crystallization had to be conducted at 10 °C.

With these conditions in hand it should be possible to use L-(+)- and D-(–)-tartaric acid in an alternate way making both antipodes accessible in high optical purity and enhanced efficiency (Figure 1). Starting the resolution of the enantiomers with L-(+)-tartaric acid, (–)-menthylamine formed a crystalline salt with the chiral acid. The salt was dissolved in NaOH and extracted with *tert*-butyl methyl ether to obtain the desired amine (13%, >95% ee). The filtrate, which was enriched with (+)-menthylamine, was isolated and formed a diastereomeric salt with D-(–)-tartaric acid. After a two-fold crystallization with D-(–)-tartaric acid of this enriched filtrate and the mentioned workup, (+)-menthylamine was obtained in good yields and high optical purity (27%, >95% ee, 2 steps). Further-

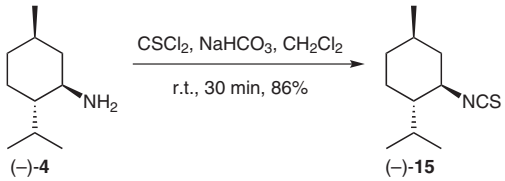
Table 4 Resolution with L-(+)-Tartaric Acid[a]

Entry	Solvent (c [mmol/mL])	H_2O (%)	Temp (°C)	Time (d)	$[\alpha]_D^{20}$	Yield (%)[b]
1	EtOH (0.5)	–	r.t.	6	–33.8	10
2	EtOH (0.5)	2.5	r.t.	6	–28.2	13
3	EtOH (0.5)	–	10	1	– 1.3	29
4	EtOH (1.0)	–	r.t.	1	– 6.6	42
5	EtOH (1.5)	–	r.t.	1	– 4.0	48
6	EtOH (2.0)	–	r.t.	1	– 3.7	49
7	MeOH (1.25)	2.5	r.t.	8	–20.3	23
8	MeOH (1.25)	5	r.t.	3	–36.1	10
9	MeOH (1.25)	7.5	r.t.	8	–23.8	17
10	MeOH (1.25)	5	10	3	–36.5	13
11	MeOH (1.5)	5	10	6	–26.9	7
12	MeOH (2.0)	5	10	6	–27.3	9

[a] Optical rotation of liberated amine from crystallized diastereomeric salt is given.
[b] Yields of isolated products.

more, the filtrates were recycled for further resolutions so that no menthylamine was wasted. The sequential resolution strategy allowed a fast access to significant amounts of both antipodes. Since the manipulations were easy to perform, a scale up was readily achieved.

The optically enriched menthylamines had to be attached on scaffolds to exploit their unique stereodirecting capabilities as previously mentioned for the supramolecular receptors.[5–7] For this purpose the isocyanates had been prepared and reported.[26] We also synthesized the (–)-menthyl isothiocyanate by reacting (–)-menthylamine [(–)-**4**] with thiophosgene in a biphasic mixture of CH_2Cl_2 and aqueous sodium bicarbonate (Scheme 6).[29] The isothiocyanate (–)-**15** might also find application as building block in supramolecular chemistry or organocatalysis.



Scheme 6

In conclusion, a fast and reliable procedure to optically enriched menthylamine was elaborated. The method exploited as starting material a technical by-product *rac*-neomenthol. For an efficient installation of the amino moiety, the elimination reaction was suppressed by using 1-methylimidazole. Application of these elaborated reaction conditions essentially avoided by-products. After reduction with Raney-nickel in a hydrogen atmosphere, resolution was achieved by the formation of diastereomeric salts with tartaric acid. Crystallization from aqueous methanol provided essentially enantiopure menthylamine salt.

After one recrystallization, (–)-menthylamine and (+)-menthylamine were obtained in 13% and 44% yield with an enantiomeric excess of >95% ee and 81% ee, respectively. With this procedure (–)-menthylamine and its antipode are readily available. The protocols are scalable and

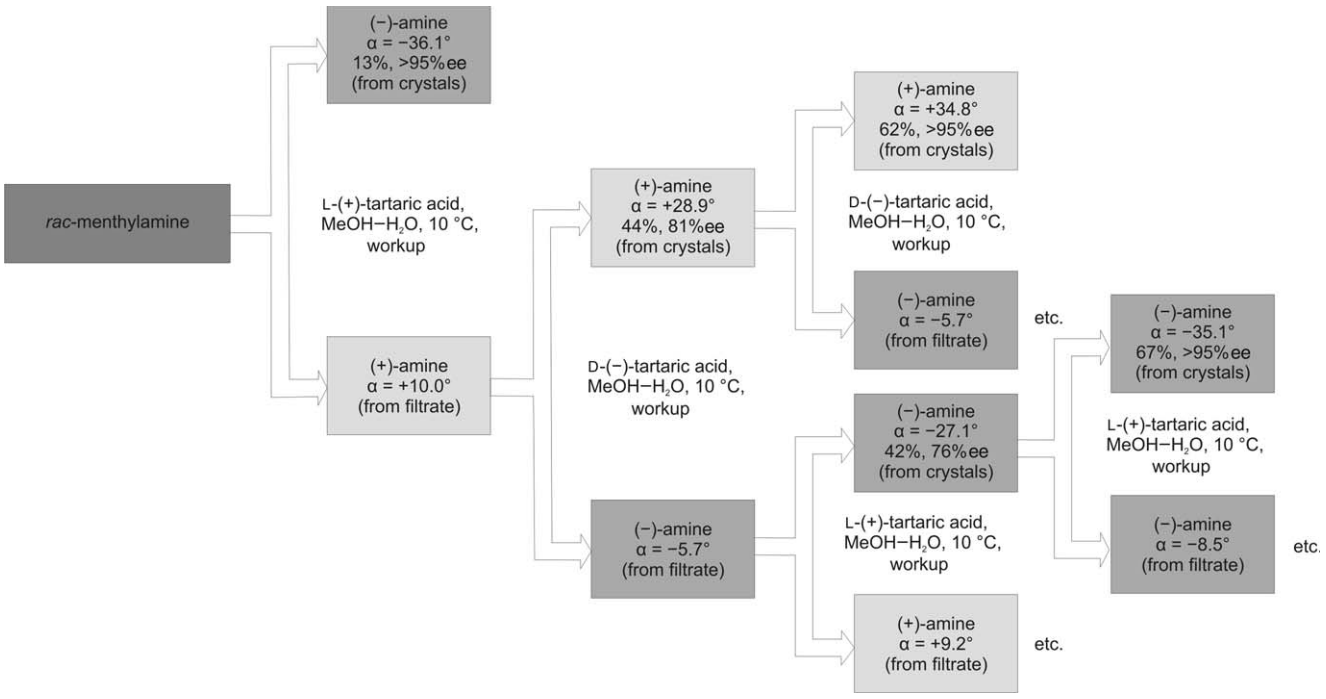


Figure 1 Flow chart depicting the resolution process of menthylamine with tartaric acid

will allow a broad application of these unique optically pure amines.

All reagents used were of analytical grade. Solvents for extractions were technical grade and distilled prior to use. Column chromatography was performed on silica gel (particle size 63–200 μm, Acros Organics BVBA, Geel, Belgium) using mixtures of cyclohexane and EtOAc as eluents. TLC was done on silica gel 60 F_{254} on glass (Merck KGaA, Darmstadt). GC analysis was obtained on a GC-2010 of Shimadzu, Japan with a HP 5 column of Agilent Technologies, USA, (length: 30 m, bore diameter: 0.25 mm, thickness of coating: 0.25 μm). ^{1}H NMR spectra were recorded at 25 °C on Bruker DPX 300 or 400 instruments (Analytische Messtechnik Karlsruhe, Germany). Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS as internal standard or traces of $CHCl_3$ in the deuterated solvent. IR spectra were measured on a Bruker Ifs 28 spectrometer and reported in cm^{-1}. Mass spectra were obtained on a MAT95XL (Finnigan, Bremen, Germany) employing EI. Optical rotations were measured using a polarimeter P-2000 of Jasco, Labor- und Datentechnik GmbH, Gross-Umstadt, in a 10 cm cell at ambient conditions.

rac-Neomenthyl Methanesulfonate [(±)-2]

To a solution of *rac*-neomenthol [(±)-**1**; 40.0 g, 0.25 mol], Et_3N (32.0 mL, 0.38 mol), and 1-methylimidazole (30.0 mL, 0.38 mol) in toluene (250 mL) was added $MeSO_2Cl$ (29.4 mL, 0.38 mol) dissolved in toluene (400 mL) dropwise over 15 min. After stirring the mixture for 2 h at r.t., H_2O (200 mL) was added. The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (2 × 200 mL). The combined organic layers were washed with sat. aq NH_4Cl (500 mL) and brine (500 mL), dried ($MgSO_4$) and the solvent was removed in vacuo to afford a colorless oil (59.5 g, quant), which turned to be analytically pure.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.14 (s, 1 H, 3-H), 3.00 (s, 3 H, 11-H), 2.17 (dq, *J* = 3.5, 14.6 Hz, 1 H, 2-H), 1.70 (m, 3 H, 5-H, 6-H, 8-H), 1.48 (m, 1 H, 1-H), 1.25 (m, 1 H, 5-H), 1.09 (m, 1 H, 2-H), 1.01 (m, 1 H, 4-H), 0.97 (d, *J* = 6.6 Hz, 3 H, 10-H), 0.91 (d, *J* = 6.5 Hz, 3 H, 7-H), 0.89 (m, 4 H, 9-H, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 81.3 (C-3), 47.5 (C-4), 40.2 (C-2), 39.2 (C-11), 34.4 (C-6), 28.8 (C-1), 26.0 (C-8), 24.2 (C-5), 22.0 (C-7), 20.7 (C-10), 20.6 (C-9).

MS (EI, 70 eV): *m*/*z* (%) = 138.1 (62, $[M - HOMs]^+$), 123.1 (32, $[M - HOMs - CH_3]^+$), 95.0 (100, $[C_7H_{11}]^+$), 81.0 (68, $[C_6H_9]^+$).

rac-Menthyl Azide [(±)-3]

Mesylate (±)-**2** (61.0 g, 0.26 mol) was dissolved in DMF (200 mL) and NaN_3 (25.4 g, 0.39 mol) was added. The suspension was stirred for 2 d at 40 °C. After this time, GC analysis showed complete conversion. The mixture was poured onto ice and extracted with *tert*-butyl methyl ether (3 × 150 mL). The combined organic layers were washed with H_2O (3 × 200 mL) and brine (200 mL), and dried ($MgSO_4$). Evaporation of the solvent in vacuo afforded the menthyl azide (32.8 g, 70%) as a pale yellow liquid, which was used without further purification (NMR spectra showed the presence of 20% menth-2-ene). Analytically pure azide was obtained by removal of menth-2-ene by solvent distillation. ***Caution!*** This should only be carried out in small quantities because of potential explosions.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.05 (ddd, *J* = 4.1, 11.2, 11.2 Hz, 1 H, 3-H), 2.10 (m, 2 H, 2-H, 8-H), 1.68 (m, 2 H, 5-H, 6-H), 1.43 (m, 1 H, 1-H), 1.16 (m, 1 H, 4-H), 1.09 (m, 1 H, 2-H), 1.02 (m, 1 H, 5-H), 0.94 (d, *J* = 6.6 Hz, 3 H, 10-H), 0.91 (d, *J* = 7.0 Hz, 3 H, 7-H), 0.83 (m, 1 H, 6-H), 0.79 (d, *J* = 6.9 Hz, 3 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.5 (C-3), 47.2 (C-4), 40.4 (C-2), 34.2 (C-6), 31.9 (C-1), 26.9 (C-8), 23.6 (C-5), 22.0 (C-7), 20.8 (C-10), 15.9 (C-9).

MS (EI, 70 eV): *m*/*z* (%) = 138.1 (72, $[M - HN_3]^+$), 123.1 (30, $[M - HN_3 - CH_3]^+$), 95.0 (100, $[C_7H_{11}]^+$), 81.0 (78, $[C_6H_9]^+$).

rac-Menthylamine [(±)-4]

Raney-Ni: Raney-nickel was synthesized from Al/Ni alloy (25.4 g alloy, 46.4 g NaOH, 250 mL H_2O) and was stored under H_2O. For the reaction, the slurry was washed and decanted several times with THF.

Reduction with Raney-Ni: A flask was charged with *rac*-menthyl azide [(±)-**3**; 32.4 g, 0.18 mol], THF (100 mL), and a slurry of Raney-Ni (10.0 g) in THF. The flask was carefully evacuated and flushed three times with H_2. The mixture was shaken under a reservoir of H_2 (balloon) at r.t. for 3 d. The Raney-Ni was then carefully filtered off, washed with THF (250 mL), and the solvent was removed in vacuo [***Caution!*** The filter paper with the Raney-Ni is highly pyrophoric, controlled incineration is recommended]. *rac*-Menthylamine (±)-**4** (27.0 g, 98%) was obtained as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 (m, 1 H, 3-H), 2.10 (m, 1 H, 8-H), 1.81 (m, 1 H, 2-H), 1.67 (m, 1 H, 6-H), 1.58 (m, 1 H, 5-H), 1.39 (m, 1 H, 1-H), 0.96 (m, 2 H, 4-H, 5-H), 0.91 (d, *J* = 6.9 Hz, 3 H, 10-H), 0.87 (d, *J* = 6.5 Hz, 3 H, 7-H), 0.82 (m, 2 H, 2-H, 6-H), 0.76 (d, *J* = 7.0 Hz, 3 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.6 (C-3), 50.4 (C-4), 45.7 (C-2), 34.9 (C-6), 32.0 (C-1), 26.0 (C-8), 23.2 (C-5), 22.4 (C-7), 21.3 (C-10), 15.5 (C-9).

MS (EI, 70 eV): *m*/*z* (%) = 155.1 (6, $[M]^+$), 140.1 (5, $[M - CH_3]^+$), 138.1 (5, $[M - NH_3]^+$), 98.0 (8, $[140 - C_3H_6]^+$), 70.0 (100, $[C_5H_{10}]^+$).

(–)-Menthylamine [(–)-4]

L-(+)-Tartaric acid (0.94 g, 6.25 mmol) was dissolved in aq MeOH (5 mL, 5% H_2O) and *rac*-menthylamine [(±)-**4**; 0.97 g, 6.25 mmol] was added. With a seed crystal, the solution was stored at 10 °C for 3 d. The precipitate was filtered off and dried. The residue was suspended in a mixture of *tert*-butyl methyl ether (20 mL) and aq 10% NaOH (20 mL) and stirred until dissolution occurred. The aqueous layer was extracted with *tert*-butyl methyl ether (2 × 50 mL). The combined organic layers were dried with CaO powder and concentrated in vacuo to obtain the (–)-menthylamine [(–)-**4**] (0.13 g, 13%, >95% ee); $[\alpha]_D^{20}$ –36.1 (*c* 0.5, $CHCl_3$) {Lit.[26] $[\alpha]_D^{20}$ –35.7 (*c* 1.39, $CHCl_3$)}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 (m, 1 H, 3-H), 2.10 (m, 1 H, 8-H), 1.81 (m, 1 H, 2-H), 1.67 (m, 1 H, 6-H), 1.58 (m, 1 H, 5-H), 1.39 (m, 1 H, 1-H), 0.96 (m, 2 H, 4-H, 5-H), 0.91 (d, *J* = 6.9 Hz, 3 H, 10-H), 0.87 (d, *J* = 6.5 Hz, 3 H, 7-H), 0.82 (m, 2 H, 2-H, 6-H), 0.76 (d, *J* = 7.0 Hz, 3 H, 9-H).

(+)-Menthylamine [(+)-4]

D-(–)-Tartaric acid (4.10 g, 26.5 mmol) was dissolved in aq MeOH (21.2 mL, 5% H_2O) and the filtrate of the chiral resolution of *rac*-menthylamine, which is enriched with (+)-menthylamine (3.97 g, 26.5 mmol) was added. With a seed crystal, the solution was stored at 10 °C for 3 d. The precipitate was filtered off and dried. The workup is done as described above. After the first resolution with D-(–)-tartaric acid, (+)-menthylamine (1.80 g, 44%, 81% ee) was isolated; $[\alpha]_D^{20}$ +28.9 (*c* 0.5, $CHCl_3$).

(–)-Menthyl Isothiocyanate [(–)-15]

A solution of (–)-menthylamine [(–)-**4**; 0.40 g, 2.58 mmol] in CH_2Cl_2 (16 mL) was charged with a solution of sat. aq $NaHCO_3$ (16 mL). Thiophosgene (0.22 mL, 2.84 mmol) was added via syringe to the organic layer. The biphasic mixture was stirred vigorously for 30 min at r.t. After the separation of the two layers, the aqueous fraction was extracted with CH_2Cl_2 (2 × 25 mL). The combined organics were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was removed and the crude product was sub-

jected to column chromatography (cyclohexane) to afford the isothiocyanate as a colorless liquid (0.44 g, 86%); R_f = 0.67 (cyclohexane–EtOAc, 95:5); $[\alpha]_D^{20}$ –74.2 (*c* 0.52, $CHCl_3$).

IR (neat): 2956m, 2924m, 28970w, 2127s, 2066s, 1455m, 720m cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.42 (ddd, *J* = 4.0, 11.1 Hz, 1 H, 3-H), 2.12 (m, 2 H, 2-H, 8-H), 1.68 (m, 2 H, 5-H, 6-H), 1.38 (m, 2 H, 1-H, 4-H), 1.27 (m, 1 H, 2-H), 1.00 (m, 1 H, 5-H), 0.94 (d, *J* = 7.2 Hz, 3 H, 10-H), 0.92 (d, *J* = 6.6 Hz, 3 H, 7-H), 0.88 (m, 1 H, 6-H), 0.80 (d, *J* = 6.9 Hz, 3 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.8 (C-3), 48.5 (C-4), 42.9 (C-2), 33.9 (C-6), 31.6 (C-1), 27.5 (C-8), 23.3 (C-5), 21.7 (C-7), 20.7 (C-10), 15.7 (C-9).

MS (EI 70 eV): *m*/*z* (%) = 197.2 (100, $[M]^+$), 182.2 (40, $[M - CH_3]^+$), 139.2 (25, $[M - NCS]^+$), 97.1 (15), 83.1 (72), 69.1 (18), 55.1 (24, $[C_4H_7]^+$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{19}NS$: 197.1241; found: 197.1238.

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