Synthesis of Menthol Glycinates and Their Potential as Cooling Agents

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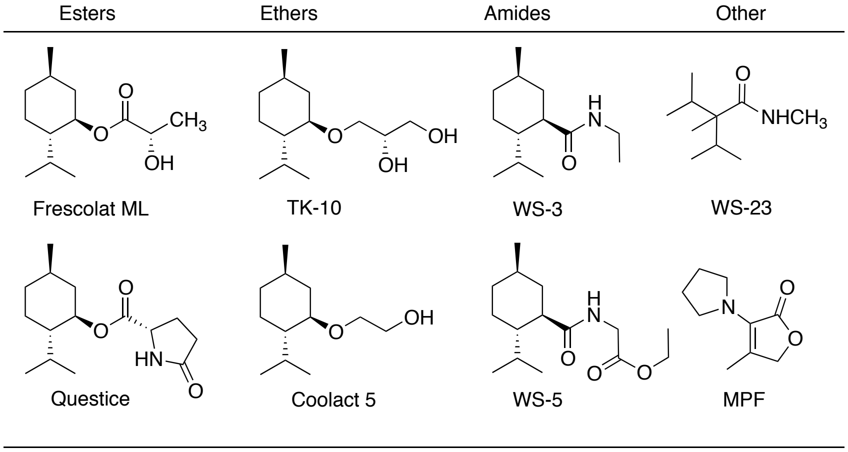
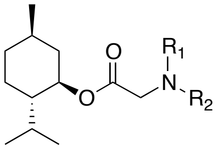
Abstract: A convenient method of synthesis has been developed for a new class of potential cooling agents, menthol glycinates. These compounds are prepared in two synthetic steps, starting from bromoacetyl bromide and (-)-menthol. The resulting brominated menthol ester readily undergoes substitution reactions with NH_3 and 1° or 2° amines to provide menthol glycinates. For most of the prepared compounds, the two-step synthetic procedure requires no aqueous phase extractions.

Menthol is major commodity chemical which is derived from both natural and semi-synthetic sources.[1] Worldwide usage of purified menthol is estimated to be over 20,000 metric tons annually.[2] Its usage includes numerous flavor applications as a cooling component and as a local anesthetic in medicinal formulations and skin products. Among the several known stereoisomers of (-)-menthol, these have been shown to less effective cooling agents than (-)-menthol. In taste dilution tests, (-)-isomenthol exhibits a cooling threshold at 30.0 ppm while (-)-menthol has a cooling threshold of just 0.8 ppm.[3] Nevertheless, there has been ongoing interest in the development of agents having even more potent cooling effects. This includes (-)-menthol derivatives such as esters of (-)-menthol, (-)-menthol ethers, menthol related amides, and other varied structures (Figure 1).[3] Depending on the assay used, WS-3 and WS-5 are both shown to have stronger cooling effects than (-)-menthol while 4-methyl-3-(1-pyrrolidinyl)-2[5H]-furanone (MPF) is estimated to have 35 times more cooling effects than (-)-menthol.[3]

Figure 1. Known cooling agents.

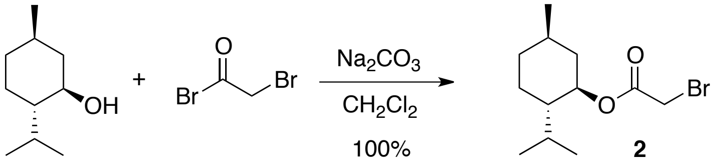


Among the derivatives of (-)-menthol that show cooling effects, no one has examined the use of menthol glycinates (**1**). Glycine itself has been used as flavor enhancing component,[4] so we reasoned that glycine esters with (-)-menthol could have potential as cooling agents. In the following Note, we describe an efficient synthetic route to a diverse set of menthol glycinates.



1, menthol glycinate

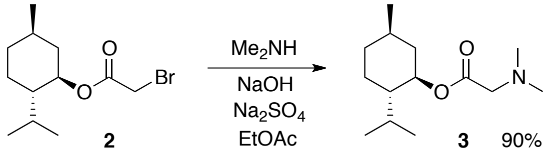
Initial efforts to prepare menthol glycinates sought to couple glycine and related derivatives with (-)-menthol. However, these reactions were less than satisfactory so an alternative route was devised. We hypothesized that the menthol glycinates could be built step-wise by a sequence involving acyl transfer chemistry followed by nucleophilic substitution. Thus, an optimized procedure coupled (-)-menthol with bromoacetyl bromide in DCM with excess anhydrous sodium carbonate (eq 1).[5] The conversion is quantitative and product **2** is sufficiently pure that no purification steps are generally required. The acyl transfer chemistry is complete within 3 hours, after which the product is isolated by simple filtration and removal of the DCM solvent. If NMR or GC analysis of **2** shows any remaining (-)-menthol, product **2** is readily purified by vacuum distillation. Similar coupling reactions are known for chloroacetyl



(1)

chloride,[6] however in our hands these conversions were not as clean as the synthesis of derivative **2**. Compound **2** is the ideal scaffold for building menthol glycinates as it is expected to be highly reactive towards nucleophilic substitution.[5a]

An optimized substitution reaction was developed by reacting compound **2** with amines in ethyl acetate (Table 1). For example, dimethylamine is added to a solution of bromide **2** with added NaOH and anhydrous Na_2SO_4 (eq 2). With vacuum distillation, the menthol glycinate **3** is



(2)

isolated in 90% yield. In order to achieve substitution with ammonia, the chemistry was done in by adding an ethyl acetate solution of bromide **2** directly into a flask containing liquid ammonia at -78 °C. This provides the glycine ester of menthol (**4**) in good yield. A variety of secondary amines provided the corresponding menthol glycinates. This includes the dialkylamines to give products **5-7**, **13**, and **15-16**. Heterocyclic systems, such as pyrrolidine and piperidine, were also found to give the substitution products (**8** and **9**, respectively) in good yields. Primary amines also give the expected substitution products **10**, **12**, **14**, and **17**. The synthetic method is amenable to incorporating structural components such as cycloalkyl groups, benzyl groups, ethers, and heterocycles. In the case the pyridyl derivative **18**, this compound is modelled after the known cooling agent, amide **19** (FEMA 4549), which is estimated to be about 100 times

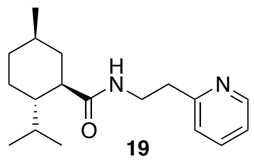


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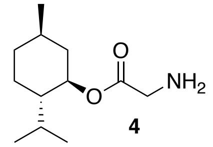
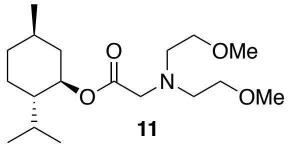
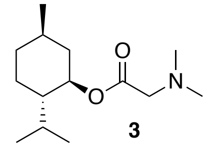
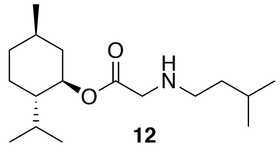
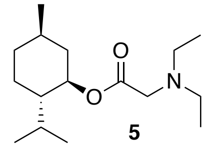
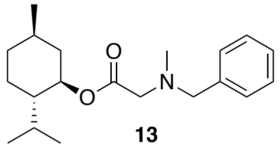
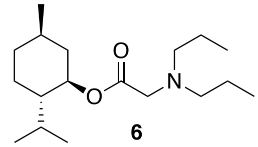
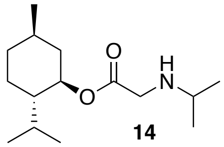
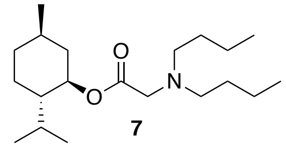
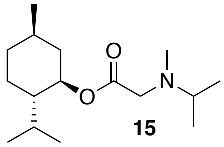
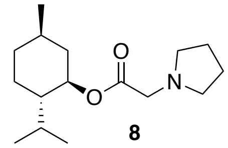
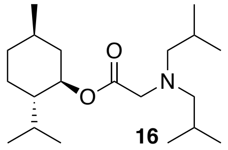
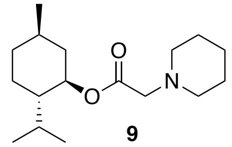
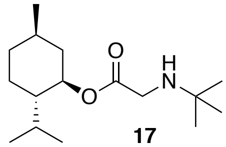
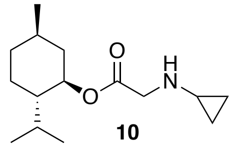
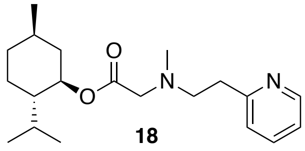
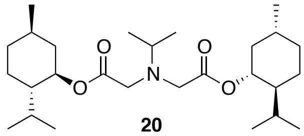
Table 1. Products and yields from substitution reactions of bromide **2** with amines or ammonia.

Product	Yield	Product	Yield
 **4**	42%	 **11**	68%
 **3**	90%	 **12**	83%
 **5**	92%	 **13**	90%
 **6**	81%	 **14**	88%
 **7**	79%	 **15**	81%
 **8**	81%	 **16**	86%
 **9**	61%	 **17**	88%
 **10**	74%	 **18**	75%

cooler than menthol.[3] In addition to monosubstitution, products may be prepared from double substitution reactions. Isopropyl amine reacts twice when an excess of bromide **2** is used and compound **20** is isolated. Similarly, *N,N'*-dimethylethylene diamine reacts twice with bromide **2** to provide compound **21**. Both **20** and **21** are purified by removal of excess bromide **2** via distillation, followed by purification using silica gel chromatography.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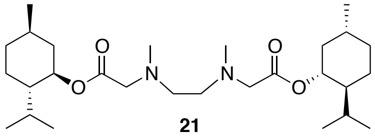
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For most of the substitution reactions described above, the optimized procedure involves using an excess of the amine nucleophile. The menthol glycinate products are isolated in pure form by removing the ethyl acetate solvent and excess amine by reduced pressure. Then the menthol glycinate is typically distilled at 150-220 °C @ 1 mm Hg. Optimization studies revealed that excess amine allows the substitution chemistry to go to completion within a relatively short amount of time. For example, dibutylamine was reacted with bromide **2** to provide compound **7**, and with 1.1 equivalents of the amine, the substitution reaction is only 79% complete after 3 hours. If the amount of dibutylamine is increased to 1.6 equivalents (0.13 M in ethyl acetate), then the substitution reaction is 100% complete in less than 3 hours.

In summary, we have developed a simple methodology to prepare a series of menthol glycinates. Starting from bromoacetyl bromide, the bromoester **2** is prepared quantitatively. This substrate undergoes substitution reactions with a series of N-nucleophiles to give menthol glycinates **3-21** is generally good yields. The procedure avoids the needs for extractions or aqueous work up. The product menthol glycinates are consider potential cooling agents, similar to other derivatives of menthol. As variants of (L)-menthol, it is expected that some of these derivatives should have strong affinities for the TRMP8 receptor site which provides the physiological sensation of cooling, as well as other biological or medicinal effects.[7]

Experimental

Preparation of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (2).[8] To 100 mL of CH_2Cl_2, (L)-menthol (7.2 g, 0.046 mmol) is dissolved and anhydrous Na_2CO_3 is added. The resulting solution is cooled to 0 °C and the flask is fitted with a $CaCl_2$ drying tube. Bromoacetyl bromide (4.0 mL, 0.046 mol) is then added, the cooling bath is removed, and the solution is stirred a minimum of four hours. Following the reaction period, the solution is filtered through glass wool and the solvent removed by vacuum. The product is isolated as a clear colorless oil (12.2 g, 0.044 mol, 96%). Analysis of the crude product by GC-FID and NMR shows an extremely high purity of product, however, the oil may be further refined by distillation (ca. 120 °C, 2 mm). With repeated runs, yields of the crude product varies from 95-100%.

General procedure for the synthesis of menthol glycinates (1° amines). The amine (0.02 mmol) is dissolved in 25 mL of EtOAc after which is added NaOH (0.6 g, 15 mmol) and anhydrous sodium sulfate (0.5 g, 3.5 mmol). To this solution, the (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (1.68 g, 6.06 mmol) is slowly added. The mixture is stirred 6 h or until GC-FID analysis shows no remaining bromoester (**2**). The solution is then filtered through a plug of glass wool and the solvent removed by reduced pressure. For low boiling amines, the excess amine is removed during this step. For less volatile amines, fractional distillation may be necessary. Final purification of the menthol glycinate is achieve by vacuum distillation.

General procedure for the synthesis of menthol glycinates (2° amines). The (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (1.68 g, 6.06 mmol) is dissolved in 25 mL of EtOAc. To this solution, the amine (9 mmol) is added, followed by NaOH (0.6 g, 15 mmol) and anhydrous sodium sulfate (0.5 g, 3.5 mmol). The mixture is stirred 6 h or until GC-FID analysis shows no remaining bromoester (**2**). The solution is then filtered through a plug of glass wool and the solvent removed by reduced pressure. For low boiling amines, the excess amine is removed during this step. For less volatile amines, fractional distillation may be necessary. Final purification of the menthol glycinate is achieve by vacuum distillation.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(dimethylamino)acetate (3).[9] Using the general procedure for 2° amines, the (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with dimethylamine (2.0 M solution in THF) to provide the methylglycinate **3** in 86% yield as clear oil (bp, ca. 140 °C at 1 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.36-0.42 (m, 2H), 0.42-0.48 (m, 2H), 0.78 (d, 3H, *J* = 7.0 Hz), 0.85-0.90 (m, 6H), 0.96-1.13 (m, 2H), 1.34-1.44 (m, 1H), 1.46-1.57 (m, 1H), 1.67-1.73 (m, 2H), 1.82-1.90 (m, 1H), 1.97-2.04 (m, 1H), 2.20-2.26 (m, 1H), 2.40 (bs, 1H), 3.34-3.42 (m, 2H), 4.71-4.76 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 16.2, 20.7, 22.0, 23.3, 26.3, 31.4, 34.2, 40.9, 45.1, 46.9, 60.5, 74.6, 169.9. Low resolution MS (electron impact ionization): 241 (M+), 226, 138, 123, 102.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-aminoacetate (4).[10] Into a cooled (-78°C) round bottom flask, ammonia (ca. 2 mL, 80 mmol) is condensed and NaOH (0.5 g, 12.5 mmol) is added to the flask. To this flask, an addition funnel is connected. Menthol bromoacetate (**1**, 1.4 g, 5.0 mmol) is dissolved in 10 mL of ethyl acetate and this solution is placed in the addition funnel. The solution of **1** is then added slowly to the liquid ammonia. The resulting mixture is stirred at -30°C and monitored by periodically taking samples and subjecting these samples to GCMS analysis. Typically, the conversion is complete within 6 hrs. If it is only partially complete, additional ammonia is condensed into the cooled flask. Following completion of the reaction, the mixture is allowed to warm to room temperature and the excess ammonia boils off. To the reaction mixture, anhydrous sodium sulfate is added and the mixture is filtered through a plug of silica gel. The reaction flask is rinsed with 10 mL of ethyl acetate and the solution is passed through the silica gel. The solvent is removed by vacuum to provide a clear oil. Further purification is accomplished by vacuum distillation 150 °C (1 mm), 0.467 g (2.2 mmol, 42%).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(diethylamino)acetate (5).[11] Using the general procedure for 2° amines, the (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with diethylamine to provide the methylglycinate **5** in 92% yield as clear oil (bp, ca. 160 °C at 1 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.73 (d, 3H, *J* = 7.0 Hz), 0.82-0.91 (m, 7H), 0.92-1.2 (m, 1H), 1.05 (t, 6H, *J* = 7.2 Hz), 1.31-1.40 (m, 1H), 1.40-1.54 (m, 1H), 1.60-1.73 (m, 2H), 1.79-1.89 (m, 1H), 1.94-2.04 (m, 1H), 2.66 (q, 4H, *J* = 7.2 Hz), 3.30 (s, 2H), 4.67-4.76 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 9.1, 11.2, 16.0, 20.7, 21.8, 23.1, 26.1, 31.4, 33.8, 40.4, 42.6, 46.5, 56.9, 58.4, 77.8, 164.4. Low resolution MS (electron impact ionization): 269 (M+), 132, 130, 116, 102.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(dipropylamino)acetate (6). Using the general procedure for 2° amines, the (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with dipropylamine to provide the methylglycinate **6** in 81% yield as clear oil (bp, ca. 170 °C at 1 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.73 (d, 3H, *J* = 7.0 Hz), 0.80-0.89 (m, 13H), 0.90-1.08 (m, 1H), 1.30-1.51 (m, 6H), 1.60-1.67 (m, 2H), 1.79-1.88 (m, 1H), 1.92-2.03 (m, 1H), 2.48-2.55 (m, 4H), 3.29 (s, 2H), 4.65-4.74 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 11.7, 16.2, 20.6, 20.7, 22.0, 23.3, 26.2, 31.3, 34.2, 40.9, 46.9, 55.2, 56.3, 74.1, 171.1. Low resolution MS (electron impact ionization): 297 (M+), 268, 158, 130, 114, 102. High resolution MS (ESI), calcd for $C_{18}H_{36}NO_2$: 298.2746. Found: 298.2731.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(dibutylamino)acetate (7). Using the general procedure for 2° amines (on larger scale), the (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**, 12.97 g, 0.047 mol) is reacted with dibutylamine (16 mL, 0.095 mol) to provide the methylglycinate **7** (12.08 g, 0.036 mmol, 79% yield) as clear oil (bp, ca. 200 °C at 1 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.72 (d, 3H, *J* = 7.0), 0.83-0.90 (m, 13H), 0.90-1.10 (m, 3H), 1.19-1.53 (m, 9H), 1.61-1.69 (m, 2H), 1.76-1.90 (m, 1H), 1.91-2.01 (m, 1H), 2.54 (t, 4H, *J* = 7.2), 3.27 (s, 2H), 4.65-4.74 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 14.0, 16.2, 20.7, 22.0, 23.3, 26.2, 29.6, 31.3, 34.2, 40.9, 47.0, 54.2, 55.2, 74.1, 171.2. Low resolution MS (electron impact ionization): 325 (M+), 282, 144, 143, 142, 102, 100. High resolution MS (ESI), calcd for $C_{20}H_{40}NO_2$: 326.3059. Found: 326.3038.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(pyrrolidin-1-yl)acetate (8). Using the general procedure for 2° amines, the (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with pyrollidine to provide the methylglycinate **8** in 81% yield as clear oil (bp, ca. 160 °C at 1 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.75 (d, 3H, *J* = 7.0), 0.82-0.93 (m, 7H), 0.95-1.11 (m, 2H), 1.33-1.40 (m, 1H), 1.41-1.56 (m, 1H), 1.64-1.72 (m, 2H), 1.76-1.92 (m, 5H), 1.95-2.07 (m, 1H), 2.60-2.70 (m, 4H), 3.25-3.38 (m, 2H), 4.71-4.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 16.3, 20.7, 22.0, 23.4, 23.8, 26.3, 31.4, 34.2, 40.9, 46.9, 53.9, 57.1, 74.3, 170.4. Low resolution MS (electron impact ionization): 267 (M+), 224, 130, 128, 100. High resolution MS (ESI), calcd for $C_{16}H_{33}NO_2$: 268.2277. Found: 268.2238.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-(piperidin-1-yl)acetate (9). Using the general procedure for 2° amines, the (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with piperidine to provide the methylglycinate **9** in 61% yield as clear oil (bp, ca. 180 °C at 1 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.70 (d, 3H, *J* = 4.2 Hz), 0.72-0.80 (m, 1H), 0.84 (d, 3H, *J* = 3.6 Hz), 0.86 (d, 3H, *J* = 3.0 Hz), 0.87-1.0 (m, 3H), 1.34-1.42 (m, 3H), 1.54-1.65 (m, 6H), 1.72-1.86 (m, 1H), 1.90-1.96 (m, 1H), 2.37-2.57 (m, 4H), 3.07 and 3.14 (ABq, 2H, *J* = 16.5 Hz), 4.61-4.75 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 16.3, 20.7, 22.0, 23.4, 26.3, 31.4, 34.2, 41.0, 42.2, 46.9, 53.9, 58.2, 74.6, 170.0. Low resolution MS (electron impact ionization): 281 (M+), 266, 144, 142. High resolution MS (ESI), calcd for $C_{17}H_{32}NO_2$: 282.2433. Found: 282.2404.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-(cyclopropylamino)acetate (10). Using the general procedure for 1° amines, the (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-

bromoacetate (**2**) is reacted with cyclopropylamine to provide the methylglycinate **10** in 74% yield as clear oil (bp, ca. 140 °C at 1 mm). ^{1}H NMR (300 MHz, CDCl$_3$) δ, 0.36-0.42 (m, 2H), 0.42-0.48 (m, 2H), 0.78 (d, 3H, *J* = 7.0 Hz), 0.85-0.90 (m, 6H), 0.96-1.13 (m, 2H), 1.34-1.44 (m, 1H), 1.46-1.57 (m, 1H), 1.67-1.73 (m, 2H), 1.82-1.90 (m, 1H), 1.97-2.04 (m, 1H), 2.20-2.26 (m, 1H), 2.40 (bs, 1H), 3.34-3.42 (m, 2H), 4.71-4.76 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ, 6.2, 6.3, 16.4, 20.7, 22.0, 23.5, 26.3, 29.9, 31.4, 34.2, 40.9, 47.0, 50.8, 74.7, 172.2. Low resolution MS (electron impact ionization): 253 (M+), 224, 138, 116, 102. High resolution MS (ESI), calcd for $C_{15}H_{28}NO_2$: 254.2120. Found: 254.2083.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(bis(2-methoxyethyl)amino)acetate (11). Using the general procedure for 2° amines, the (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with bis(2-methoxyethyl)amine to provide the methylglycinate **11** in 68% yield as clear oil (bp, ca. 200 °C at 1 mm). ^{1}H NMR (300 MHz, CDCl$_3$) δ, 0.69 (d, 3H, *J* = 7.0), 0.75-0.86 (m, 7H), 0.88-1.07 (m, 2H), 1.25-1.35 (m, 1H), 1.35-1.48 (m, 1H), 1.54-1.66 (m, 2H), 1.73-1.85 (m, 1H), 1.87-1.96 (m, 1H), 2.83-2.90 (m, 4H), 3.24-3.28 (m, 6H), 3.37-3.45 (m, 6H), 4.59-4.71 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ, 16.2, 20.7, 22.0, 23.3, 26.2, 31.3, 34.2, 41.0, 46.9, 53.9, 55.9, 58.7, 71.4, 74.1, 171.1. Low resolution MS (electron impact ionization): 297 (M+), 284, 190, 160, 146. High resolution MS (ESI), calcd for $C_{18}H_{36}NO_4$: 330.2644. Found: 330.2615.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(isopentylamino)acetate (12). Using the general procedure for 1° amines, the (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with isopentylamine to provide the methylglycinate **12** in 90% yield as clear oil (bp, ca. 180 °C at 1 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.75 (d, 3H, *J* = 7.0 Hz), 0.87-0.92 (m, 13H), 0.95-1.01 (m, 1H), 1.03-1.13 (m, 1H), 1.35-1.43 (m, 3H), 1.43-1.59 (m, 1H), 1.61-1.74 (m, 3H), 1.77-1.89 (m, 1H), 1.95-2.03 (m, 1H), 2.10 (s, 1H), 2.59-2.64 (m, 2H), 3.38 (s, 2H), 4.70-4.79 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 16.3, 20.7, 21.9, 22.6, 23.4, 26.0, 26.3, 31.4, 34.2, 38.9, 40.9, 47.0, 47.7, 51.1, 74.7, 171.9. Low resolution MS (electron impact ionization): 283 (M+), 226, 145, 138, 123, 100. High resolution MS (ESI), calcd for $C_{17}H_{34}NO_2$: 284.2590. Found: 284.2554.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(benzyl(methyl)amino)acetate (13). Using the general procedure for 2° amines, the (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with *N*-methylbenzylamine to provide the methylglycinate **13** in 90% yield as clear oil (bp, ca. 210 °C at 1 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.78 (d, 3H, *J* = 7.0 Hz), 0.89 (d, 3H, *J* = 7.0 Hz), 0.91 (d, 3H, *J* = 7.0 Hz), 0.96-1.14 (m, 2H), 1.34-1.43 (m, 1H), 1.44-1.57 (m, 1H), 1.64-1.72 (m, 2H), 1.82-1.92 (m, 1H), 1.99-2.05 (m, 1H), 2.39 (s, 3H), 3.24 (s, 2H), 3.69 (s, 2H), 4.73-4.82 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 16.3, 20.7, 22.0, 23.4, 26.3, 31.4, 34.2, 41.0, 47.0, 57.7, 74.2, 127.1, 128.2, 129.1, 138.4, 170.5. Low resolution MS (electron impact ionization): 317 (M+), 180, 178, 135, 134, 120. High resolution MS (ESI), calcd for $C_{20}H_{32}NO_2$: 318.2433. Found: 318.2372.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(isopropylamino)acetate (14). Using the general procedure for 1° amines, the (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with isopropylamine to provide the methylglycinate **14** in 88% yield as clear oil (bp, ca.

140 °C at 1 mm). ^{1}H NMR (500 MHz, $CDCl_3$) δ, 0.75 (d, 3H, *J* = 7.0 Hz), 0.84-0.91 (m, 7H), 0.92-1.0 (m, 1H), 1.05 (d, 6H, *J* = 6.3 Hz), 1.34-1.40 (m, 1H), 1.45-1.53 (m, 1H), 1.64-1.69 (m, 2H), 1.80-1.86 (m, 1H), 1.96- 2.00 (m, 1H), 2.79 (sep, 1H, *J* = 6.2 Hz), 2.85 (bs, 1H), 3.35-3.39 (m, 2H), 4.70-4.76 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ, 16.3, 20.7, 22.0, 22.6, 23.4, 26.3, 31.3, 34.2, 40.9, 47.0, 48.3, 48.8, 48.8, 74.7, 172.2. Low resolution MS (electron impact ionization): 255 (M+), 240, 138, 116, 102. High resolution MS (ESI), calcd for $C_{15}H_{30}NO_2$: 256.2277. Found: 256.2262.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(isopropyl(methyl)amino)acetate (15). Using the general procedure for 2° amines, the (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with methyl-*iso*-propylamine to provide the methylglycinate **15** in 88% yield as clear oil (bp, ca. 160 °C at 1 mm). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 16.2, 18.4, 18.4, 20.7, 22.0, 23.4, 26.3, 31.3, 34.2, 38.3, 40.9, 46.9, 53.4, 55.1, 74.3, 171.0. Low resolution MS (electron impact ionization): 269 (M+), 254, 138, 132, 130, 116. High resolution MS (ESI), calcd for $C_{16}H_{32}NO_2$: 270.2433. Found: 270.2405.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(diisobutylamino)acetate (16). Using the general procedure for 2° amines, the (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with diisobutylamine to provide the methylglycinate **16** in 86% yield as clear oil (bp, ca. 180 °C at 1 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.74 (d, 3H, *J* = 7.0), 0.82-0.91 (m, 19H), 0.92-1.11 (m, 2H), 1.30-1.38 (m, 1H), 1.40-1.54 (m, 1H), 1.60-1.71 (m, 4H), 1.81-1.91 (m, 1H), 1.94-2.01 (m, 1H), 2.31 (d, 4H, *J* = 7.3), 3.26 (s, 2H), 4.65-4.74 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 16.2, 20.6, 20.7, 22.0, 23.3, 26.2, 26.7, 31.4, 34.2, 41.0, 47.0, 56.0, 63.4, 73.9, 171.6. Low resolution

MS (electron impact ionization): 325 (M+), 283, 282, 144, 142, 100. High resolution MS (ESI), calcd for $C_{20}H_{40}NO_2$: 326.3059. Found: 326.2999.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(*tert*-butylamino)acetate (17). Using the general procedure for 1° amines, the (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**) is reacted with *tert*-butylamine to provide the methylglycinate **17** in 78% yield as clear oil (bp, ca. 180 °C at 1 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.73 (d, 3H, *J* = 7.0 Hz), 0.86-0.90 (m, 7H), 0.90-1.04 (m, 1H), 1.09 (s, 9H), 1.29-1.37 (m, 1H), 1.38-1.54 (m, 1H), 1.57-1.72 (m, 3H), 1.79-1.92 (m, 1H), 1.94-2.07 (m, 1H), 3.35 (s, 2H), 4.68-4.77 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 16.3, 20.7, 21.9, 23.4, 26.2, 28.7, 31.3, 34.2, 40.8, 44.9, 47.0, 50.2, 74.6, 172.7. Low resolution MS (electron impact ionization): 269 (M+), 254, 130, 116. High resolution MS (ESI), calcd for $C_{16}H_{32}NO_2$: 270.2433. Found: 270.2416.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(methyl(2-(pyridin-2-yl)ethyl)amino)acetate (18). (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**, 1.3 g, 4.69 mmol) is dissolved in 25 mL EtOAc and to this solution is added NaOH (1.2 g, 0.03 mol) and anhydrous Na_2SO_4 (0.5 g). 2-(2-Methylaminoethyl)pyridine (1.0 mL, 7.22 mmol) is added to the solution and the mixture is stirred at room temperature for 4 h or until GC-FID analysis shows no remaining bromoester **2**. The solution is then filtered through glass wool and the solvent removed under reduced pressure. The resulting oil is subjected to vacuum distillation (120 °C at 1 mm for 2 h) to remove excess 2-(2-methylaminoethyl)pyridine. The residue oil is taken up in 20 mL of EtOAc and passed through a plug of SiO_2. Following removal of the solvent, an oil is obtained which is primarily methylglycinate **18** (1.54 g, 4.63 mmol, 99%). The product is further refined by distillation bp, ca. 230 °C at 1 mm) to provide pure methylglycinate **18** in 75% yield as clear oil (^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.73 (d, 3H, *J* = 7.0 Hz), 0.80-0.92 (m, 7H), 0.89-1.10 (m, 2H), 1.31-1.43 (m, 1H), 1.43-1.54 (m, 1H), 1.61-1.70 (m, 2H), 1.77-1.89 (m, 1H), 1.94-2.05 (m, 1H), 2.44 (s, 3H), 2.89-3.01 (m, 4H), 3.29 (s, 2H), 4.69-4.78 (m, 1H), 7.06-7.11 (m, 1H), 7.18 (d, 1H, *J* = 7.8 Hz), 7.54-7.60 (m, 1H), 8.49-8.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 16.2, 20.7, 22.0, 23.4, 26.3, 31.4, 34.2, 36.3, 41.0, 46.9, 56.8, 58.7, 74.4, 121.1, 123.1, 136.3, 149.2, 160.2, 170.5. High resolution MS (ESI), calcd for $C_{20}H_{33}N_2O_2$: 333.2542. Found: 333.2513.

Bis((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2,2'-(isopropylazanediyl)diacetate (20). 1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**, 2.33 g, 8.4 mmol) is dissolved in 25 mL EtOAc and to this solution is added NaOH (1.2 g, 0.03 mol) and anhydrous Na_2SO_4 (0.5 g). isopropylamine (0.25 mL, 2.9 mmol) is added to the solution and the mixture is stirred at room temperature for 5 h or until GC-FID analysis shows no remaining bromoester **2**. The solution is then filtered through glass wool and the solvent removed under reduced pressure. The resulting oil is subjected to vacuum distillation (160 °C at 1 mm for 20 min) to remove excess bromoester **2**. The distillate is a clear oil (ca. 0.5 g) which is identified as a mixture of bromoester **2** and the desired product **20**. The residue oil is taken up in 20 mL of EtOAc and passed through a plug of SiO_2. Following removal of the solvent, a clear oil is obtained which is methylglycinate **20** (0.425 g, 0.94 mmol, 32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 0.76 (d, 6H, *J* = 6.9 Hz), 0.85-0.95 (m, 14H), 0.94-1.04 (m, 2H), 1.04-1.10 (m, 4H), 1.33-1.42 (m, 2H), 1.42-1.55 (m, 2h), 1.64-1.73 (m, 4H), 1.80-1.93 (m, 2H), 1.96-2.04 (m, 2H), 3.04-3.13 (sep, 1H, *J* = 6.5 Hz), 3.54

(s, 4H), 4.68-4.77 (m, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ, 16.3, 20.3, 20.7, 22.0, 23.4, 26.3, 31.4, 34.3, 40.9, 47.0, 52.7, 74.2, 171.8. High resolution MS (ESI), calcd for $C_{27}H_{50}NO_4$: 452.3740. Found: 452.3701.

Bis((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2,2'-(ethane-1,2-diylbis(methylazanediyl))diacetate (21). 1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (**2**, 2.13 g, 7.7 mmol) is dissolved in 50 mL EtOAc and to this solution is added NaOH (1.2 g, 0.03 mol) and anhydrous Na_2SO_4 (0.5 g). *N,N*-dimethylethylenediamine (0.3 mL, 2.79 mmol) is added to the solution and the mixture is stirred at room temperature for 5 h or until GC-FID analysis shows no remaining bromoester **2**. The solution is then filtered through glass wool and the solvent removed under reduced pressure. The resulting oil is subjected to vacuum distillation (170-190 °C at 1 mm for 30 min) to remove excess bromoester **2**. The residue yellow oil is taken up in 20 mL of EtOAc and passed through a plug of SiO_2. Following removal of the solvent, a clear oil is obtained which is methylglycinate **21** (0.84 g, 1.75 mmol, 43%). ^{1}H NMR (500 MHz, CDCl$_3$) δ, 0.78 (d, 6H, *J* = 6.7 Hz), 0.82-0.95 (m, 14H), 0.96-1.13 (m, 4H), 1.37-1.42 (m, 2H), 1.43-1.55 (bs, 2H), 1.70 (d, 4H, *J* = 2.4 Hz), 1.80-1.90 (m, 2H), 2.00 (d, 2H, *J* = 6.9 Hz), 2.48 (s, 6H), 2.82 (s, 4H), 3.42 (s, 4H), 4.74-4.78 (m, 2H). ^{13}C NMR (125 MHz, CDCl$_3$) δ, 16.3, 20.7, 22.0, 23.4, 26.3, 31.4, 34.2, 41.0, 42.2, 46.9, 53.9, 58.2, 74.6, 170.0. High resolution MS (ESI), calcd for $C_{28}H_{53}N_2O_4$: 481.4005. Found: 481.3941.

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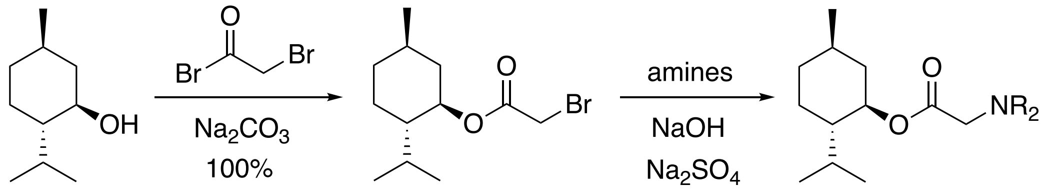
Graphical Abstract:



- 19 examples, 32-93% yields
- no aqueous workup
- 10+ g scale