# Simple Synthesis of Both Enantiomers of 3-Methyl-*N*-(3-methylbutyl)pyrrolidine

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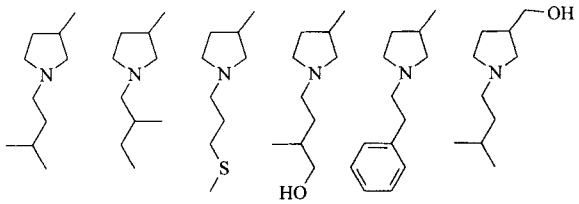
(*S*)-3-Methyl-*N*-(3-methylbutyl)pyrrolidine (**1**) and its antipode (*R*)-**1** have been prepared by reduction of (*S*)-4,5-dihydro-3-methyl-2(3*H*)furanone (**7**) and dimethyl (*R*)-2-methylsuccinate (**11**), bromination thereof, and ring closure of the intermediates (*S*)-**9** and *R*)-**9**, respectively, with 3-methylbutylamine (**10**). An alternative synthesis of (*R*)-**1** by mesylation of (*R*)-**8** is also described. Both enantiomers of **1** were obtained in excellent enantiomeric excesses (*ee* = 96%).

A number of substituted nitrogen heterocycles such as piperidines, pyrroles, pyrrolidines, pyrrolizidines, and indolizidines have been found as pheromones as well as chemical weapons of several species of ants[1]. There is enormous interest in syntheses[2] and biological evaluations[3] to get more insight into the biochemical effects of these compounds. We have previously described the isolation of the novel *N*-alkylated 3-methylpyrrolidines **1**–**6** (Scheme 1) from the poison glands of ants *Leptothoracini* (*Myrmicinae*) and their identification by GC-MS analysis[4]. The main component could be identified as 3-methyl-*N*-(3-methylbutyl)pyrrolidine (**1**), which was called Leptothoracine. This compound, however, is hitherto unreported in optically pure form[4,5]. As an extension of our ongoing program we aimed at the preparation of both enantiomers of **1** in order to determine the biologically active form.

Scheme 1. *N*-Alkylated pyrrolidines from the species of ant *Harpagoxenus sublaevis*




**1** **2** **3** **4** **5** **6**

In this paper we describe the first syntheses of both stereoisomers (*S*)-**1** and (*R*)-**1**, which have been accomplished in three steps, starting from commercially available γ-furanone (*S*)-**7** and dimethyl (*R*)-2-methylsuccinate (**11**), respectively.

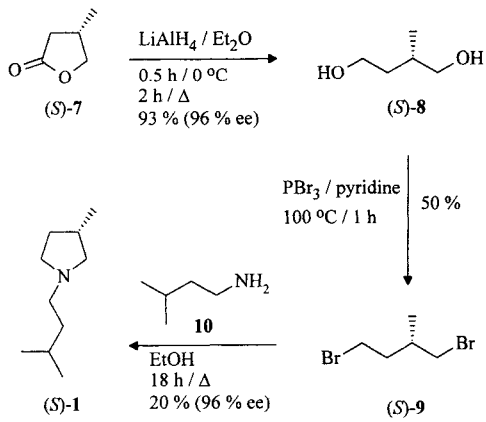
## Results

### Synthesis of (*S*)-3-Methyl-*N*-(3-methylbutyl)pyrrolidine (1)

The synthesis of (*S*)-3-methyl-*N*-(3-methylbutyl)pyrrolidine (**1**) was accomplished in three steps starting from the optically pure 4-methyl substituted γ-lactone (*S*)-**7** (Scheme 2). The reduction of (*S*)-**7** with 1.85 equivalents of lithium aluminium hydride (LAH) provided the 1,4-diol (*S*)-**8** in excellent yield (93%) and in high optically purity (96% *ee*). The enantiomeric excess (*ee*) of compound **8** was ascertained by comparing its $[\alpha]_D$ value with the reported one[6].

The subsequent substitution reaction of (*S*)-**8** with phosphorus tribromide was performed under well-known conditions (pyridine, 100 °C, 1 h)[6a] and led to the corresponding 1,4-dibromo substituted compound (*S*)-**9** (50% yield). Reaction of (*S*)-**9** with 3-methylbutylamine (**10**) afforded the expected 3-methyl substituted pyrrolidine (*S*)-**1**, albeit in moderate but not optimized yield (20%). The *S*-configured pyrrolidine **1** was obtained in high enantiomeric excess (96% *ee*).

Scheme 2. Synthesis of (*S*)-**1**




### Synthesis of (*R*)-3-Methyl-*N*-(3-methylbutyl)pyrrolidine (1)

For the preparation of the *R*-configured stereoisomer of **1**, the commercially available dimethyl (*R*)-2-methylsuccinate (**11**) was used as starting material. We first employed LAH as the reducing agent under the same reduction con-

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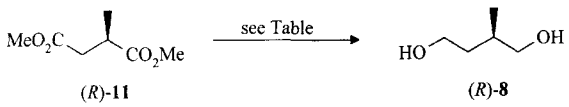



(*R*)-**11** (*R*)-**8**

Table. Reduction of (*R*)-**11**

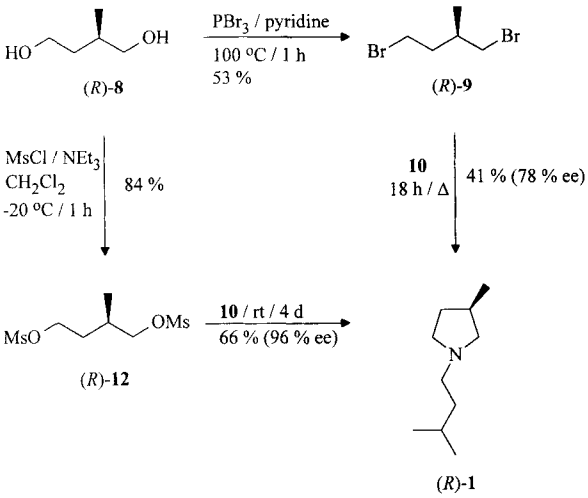
| Entry | Reducing agent | Reaction conditions | Yield | *ee* |
|---|---|---|---|---|
| 1 | LAH | a) $Et_2O$, 0.5 h / 0 °C, b) 4 h / reflux | 97% | 65% |
| 2 | LAH | $Et_2O$, 4 h / rt | 90% | 97% |
| 3 | Super Hydride® | $Et_2O$, 2.5 h / 0 °C | 63% | 76% |

ditions as above (see Table, entry 1), mainly in view of its successful use in the synthesis of the *S*-configured stereoisomer. In this case, however, we isolated the 1,4-diol (*R*)-**8** with markedly lower enantioselectivity (65% *ee*). Fortunately, we were able to optimize the stereoselectivity of the reduction using LAH at ambient temperature (97% *ee*, 90% yield). In contrast, when Super Hydride® was used instead of LAH (entries 2 and 3 in the Table), the resulting product (*R*)-**8** was formed with lower enantioselectivity (76% *ee*).

Following the protocol with (*R*)-**8** (76% *ee*, from Super Hydride® reduction) as described above, we prepared the *R*-configured 1,4-dibromo compound **9** (53% yield, Scheme 3) which was converted to the (*R*)-3-methyl substituted pyrrolidine **1** (78% *ee*, 41% yield).

The % *ee* of both enantiomers (*S*)-**1** and (*R*)-**1**, respectively, were determined by their optical rotations. The *ee*-values were verified by chiral gas chromatography analyses of the respective trifluoroacetyl derivative[7], and its diastereomeric carbamates[8].

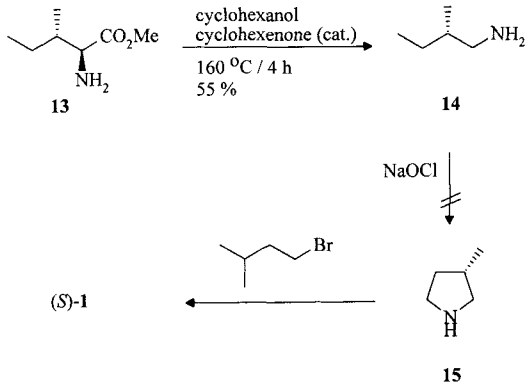
Scheme 3. Synthesis of (*R*)-**1**




(*R*)-**8** (*R*)-**9** (*R*)-**12** (*R*)-**1**

In connection with our efforts to prepare (*R*)-**1** starting from (*R*)-**11**, we also investigated an alternative synthetic route. Having mesylated both hydroxyl groups in (*R*)-**8** under standard conditions[9] the ring closure was achieved by reaction of (*R*)-**12** with amine **10** at room temperature to give the product (*R*)-**1** in 66% yield with 96% *ee*. The reaction sequence via mesylation of 1,4-diol **8** worked well and was easy to perform (Scheme 3). Thus, it may be that this

Scheme 4




**13** **14** (*S*)-**1** **15**

is the method of choice for synthesis of pyrrolidine derivatives like **1**.

It should be noted that in connection with our efforts to prepare (*S*)-**1**, we also studied a further alternative route starting from isoleucine **13** (Scheme 4)[10]. However, although the first step (**13** → **14**)[11] worked well, the subsequent Hofmann-Löffler-Freytag reaction[12] of **14** using sodium hypochlorite under various reaction conditions was not successful[10].

In conclusion, we have performed the first synthesis of (*S*)-**1** and (*R*)-**1**, respectively, in high optical yields (both 96% *ee*). Studies to investigate the application of this reaction sequence for the preparation of further interesting optically active *N*-alkylated pyrrolidine derivatives are currently in progress.

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## Experimental Section

$^1$H-NMR spectra were recorded with a Bruker WM 300. The $^1$H chemical shifts are given in ppm relative to TMS from the solvent ($CDCl_3$) signal ($\delta = 7.27$). Optical rotations were measured at 20 °C with a Perkin-Elmer polarimeter 141 (concentration in g/100 ml). Boiling points of compounds obtained in small-scale experiments refer to the temperature in a Büchi kugelrohr oven. All reactions were performed in flame-dried reaction vessels under a slight pressure of nitrogen.

Solvents were dried by standard methods. All other commercially available reagents were used without further purification. EI- and FI-mass spectra were recorded with a Finnigan MAT 311A instrument; GC-MS spectra: Varian 3700 gas chromatograph coupled directly to a Finnigan MAT 212 mass spectrometer. For data acquisition a Teknivent Data System was used. For identification the samples were introduced onto a fused-silica DB5 or a Carbowax-20-M-AM column. Operating conditions were as follows: column oven temperature: 1 min at 50 °C, programmed to 300 °C and 210 °C at 15 °C/min, respectively. Retention indices have been published[4].

*(S)-2-Methyl-1,4-butanediol* (**8**): To an ice-cooled suspension of LAH (0.760 g, 20.0 mmol) in diethyl ether (100 ml) was added a solution of (*S*)-4,5-dihydro-3-methyl-2(3*H*)furanone (**7**) (1.08 g, 10.8 mmol) in diethyl ether (15 ml) under a nitrogen atmosphere.

The resulting mixture was stirred for 0.5 h at 0 °C and then heated at reflux for 2 h. After the reaction was complete, the mixture was cooled to 0 °C and the excess of LAH was destroyed by careful addition of water. The mixture was filtered, extracted with diethyl ether (3 d in a Soxhlet apparatus), dried ($Na_2SO_4$) and the organic solution was concentrated in vacuo. The residue was purified by kugelrohr distillation (b.p. 55 °C/0.03 Torr). Yield of (*S*)-**8**: 1.05 g (93%) as a colourless oil; $[\alpha]_D^{20} = -13.8$ (*c* = 1.24, MeOH), 96% *ee*. Ref.[6b]: b.p. 131–132 °C/18 Torr, $[\alpha]_D^{20} = -14.4$ (*c* = 0.6, MeOH). – $^1$H NMR ($CDCl_3$, 300 MHz): δ = 4.15 (br s, 2H, OH), 3.78–3.70, 3.65–3.58 (2 m, 2H, 4-H), 3.53 (dd, *J* = 4.5, 10.5 Hz, 1H, 1-H), 3.38 (dd, *J* = 7.5, 10.5 Hz, 1H, 1-H), 1.84–1.73 (m, 1H, 2-H), 1.68–1.47 (m, 2H, 3-H), 0.91 (d, *J* = 7 Hz, 3H, 2-Me). – MS (FI): *m/z* (%): 104 (100, $M^{+\bullet}$); MS (EI, 70 eV): *m/z* (%): 86 (2, $[M - 18]^{+\bullet}$), 56 (100), 55 (42), 41 (63).

*(S)-1,4-Dibromo-2-methylbutane* (**9**): To a solution of (*S*)-**8** (0.940 g, 9.04 mmol) in dry pyridine (1.06 g, 13.4 mmol), $PBr_3$ (5.04 g, 18.6 mmol) was added dropwise and the mixture was heated to 100 °C for 1 h. After cooling to room temp., the suspension was poured into iced-water. The mixture was extracted with hexane and the combined organic extracts were dried with $Na_2SO_4$. The solvent was removed under reduced pressure. Purification of the crude product by kugelrohr distillation (b.p. 30 °C/0.2 Torr) gave 1.04 g (50%) of (*S*)-**9** as a colourless liquid; $[\alpha]_D^{20} = -5.50$ (*c* = 1.0, EtOH). Ref.[6a]: b.p. 79 °C/10 Torr. – $^1$H NMR ($CDCl_3$, 300 MHz): δ = 3.52–3.39 (m, 4H, 1-H, 4-H), 2.16–1.98 (m, 2H, 3-H), 1.87–1.74 (m, 1H, 2-H), 1.05 (d, *J* = 6.5 Hz, 3H, 2-Me). – MS (EI, 70 eV): *m/z* (%): 232 (1, $M^{+\bullet}$, $^{81}Br_2$), 230 (2, $M^{+\bullet}$, $^{79}Br^{81}Br$), 228 (1, $M^{+\bullet}$, $^{79}Br_2$), 151 (22), 150 (15), 148 (22), 69 (90), 41 (100).

*(S)-3-Methyl-N-(3-methylbutyl)pyrrolidine* (**1**): To a stirred solution of (*S*)-**9** (0.870 g, 3.78 mmol) in dry ethanol (10 ml), 3-methylbutylamine (**10**) (0.660 g, 7.57 mmol) was added dropwise at 0 °C. The solution was refluxed for 18 h and then the solvent was removed under reduced pressure. 2 N HCl solution (5 ml) was added to the residue and the mixture was extracted with diethyl ether (2 × 15 ml). The aqueous layer was brought to pH 11 by addition of 2 N NaOH solution and extracted with diethyl ether (3 × 15 ml). The combined extracts were dried with solid KOH. Evaporation of the diethyl ether and purification of the residue by kugelrohr distillation (b.p. 80 °C/38 Torr) provided 0.120 g (20%) of (*S*)-**1** as a colourless liquid; $[\alpha]_D^{20} = +1.81$ (*c* = 3.03, EtOH), 96% *ee*. – $^1$H NMR ($CDCl_3$, 300 MHz): δ = 2.83, 1.96 (2 dd, each *J* = 7.5, 9 Hz, 2H, 2-H), 2.73–2.65 (m, 1H, 5-H), 2.49–2.34 (m, 3H, 1′-H, 5-H), 2.32–2.18 (m, 1H, 3-H), 2.07–1.97 (m, 1H, 4-H), 1.58 ($m_c$, 1H, 3′-H), 1.43–1.35 (m, 2H, 2′-H), 1.34–1.27 (m, 1H, 4-H), 1.02 (d, *J* = 6.5 Hz, 3H, 3-Me), 0.89 (d, *J* = 7 Hz, 6H, 4′-H, 3′-Me); MS (EI, 70 eV): *m/z* (%): 155 (10, $M^{+\bullet}$), 98 (100), 42 (41), 41 (40).

*Reduction of Dimethyl (R)-Methylsuccinate* (**11**) *to (R)-2-Methyl-1,4-butanediol* (**8**)

*Method A:* According to the preparation of (*S*)-**8** as described above, a mixture of LAH (2.60 g, 68.5 mmol) and dimethyl (*R*)-methylsuccinate (**11**) (5.31 g, 32.2 mmol) in diethyl ether (60 ml) was refluxed for 4 h and then worked up. Purification of the crude product by kugelrohr distillation (b.p. 55 °C/0.3 Torr) yielded 3.35 g (97%) of (*R*)-**8**; $[\alpha]_D^{20} = +9.42$ (*c* = 1.04, MeOH), 65% *ee*. Ref.[6a]: b.p. 100 °C/1 Torr, $[\alpha]_D^{22} = +14.4$ (*c* = 2.0, MeOH).

*Method B:* A solution of (*R*)-**11** (0.425 g, 2.65 mmol) in dry diethyl ether (5 ml) was added dropwise to a stirred suspension of LAH (0.162 g, 4.25 mmol) in dry diethyl ether (7 ml) at 0 °C. After 4 h at room temp., the excess LAH was decomposed by the successive addition of water (0.2 ml), 15% aqueous NaOH solution (0.2 ml) and water (0.4 ml) to the stirred and ice-cooled mixture. The mixture was then stirred for a further 2 h at room temp. After filtration and washing of the solid with diethyl ether, the combined filtrate and washings were dried ($K_2CO_3$) and concentrated in vacuo. The resulting residue was distilled (b.p. 55 °C/0.3 Torr) to give 0.247 g (90%) of (*R*)-**8**; $[\alpha]_D^{20} = +13.9$ (*c* = 1.35, MeOH), 97% *ee*.

*Method C:* To a solution of (*R*)-**11** (0.640 g, 4.00 mmol) in THF (50 ml) a 1 M Super-Hydride® solution in THF (10.0 ml, 10.0 mmol) was slowly added over a period of 30 min at 0 °C. After stirring for 2 h at the same temperature, $H_2O$ (7 ml), 2 N NaOH solution (5 ml) and 30% $H_2O_2$ solution (3.5 ml) were successively added. The mixture was concentrated in vacuo, the residue was diluted with brine (20 ml) and the aqueous phase was extracted with diethyl ether (3 × 15 ml). The combined organic phases were washed with brine (20 ml), dried with $Na_2SO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by kugelrohr distillation (b.p. 60 °C/0.5 Torr) provided 0.263 g (63%) of (*R*)-**8**; $[\alpha]_D^{20} = +11.0$ (*c* = 0.91, MeOH), 76% *ee*.

*(R)-1,4-Dibromo-2-methylbutane* (**9**): According to the preparation of (*S*)-**9**, the reaction of (*R*)-**8** (0.130 g, 1.25 mmol; 76% *ee*, method C) with $PBr_3$ (0.681 g, 2.52 mmol) in dry pyridine (0.102 g, 1.29 mmol) provided after workup and kugelrohr distillation (b.p. 40 °C/0.5 Torr) 0.152 g (53%) of (*R*)-**9** as a colourless liquid; $[\alpha]_D^{20} = +4.05$ (*c* = 1.6, EtOH). Ref.[6a]: b.p. 79 °C/10 Torr.

*(R)-3-Methyl-N-(3-methylbutyl)pyrrolidine* (**1**): According to the preparation of (*S*)-**1**, treatment of (*R*)-**9** (0.075 g, 0.327 mmol) with 3-methylbutylamine (**10**) (0.057 g, 0.655 mmol) in dry ethanol (2 ml) gave after purification by kugelrohr distillation (b.p. 75 °C/40 Torr) 0.021 g (41%) of (*R*)-**1** as a colourless liquid; $[\alpha]_D^{20} = -1.47$ (*c* = 0.3, EtOH), 78% *ee*.

*(R)-2-Methyl-1,4-bis(methylsulfonyl)butane* (**12**): To a solution of (*R*)-**8** (0.224 g, 2.15 mmol; 97% *ee*, method B) in dichloromethane (6 ml) was added triethylamine (0.76 ml, 5.41 mmol). The solution was cooled to −20 °C, and methanesulfonyl chloride (0.37 ml, 4.80 mmol) was added dropwise with vigorous stirring over 1 h while the temp. was maintained between −20 and −15 °C. After the addition was complete, the mixture was allowed to warm to 0 °C and then poured into cold 1 N HCl solution (2.8 ml). The organic layer was separated, and the aqueous phase was extracted with dichloromethane (2 × 1.5 ml). The combined organic extracts were washed with sat. $NaHCO_3$ solution (2.8 ml), dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The resulting product (*R*)-**12** (0.469 g, 84%) was used directly for the next step. $^1$H NMR ($CDCl_3$, 200 MHz): δ = 4.33–4.21 (m, 2H, 4-H), 4.11 (dd, *J* = 5.5, 10 Hz, 1H, 1-H), 4.06 (dd, *J* = 6, 10 Hz, 1H, 1-H), 3.00 (s, 6H, $SO_2Me$), 2.12–2.01, 1.95–1.82, 1.69–1.62 (3 m, 3H, 2-H, 3-H), 1.03 (d, *J* = 7 Hz, 3H, 2-Me).

*Reaction of (R)-12 with Amine* **10**: The bis(methanesulfonate) (*R*)-**12** (0.455 g, 1.75 mmol) was dissolved in amine **10** (1.5 ml) and allowed to stand at room temp. for 4 d. The mixture was then diluted with diethyl ether (10 ml). Filtration, evaporation of the solvent and purification by kugelrohr distillation (b.p. 75 °C/40 Torr) provided 0.179 g (66%) of (*R*)-**1**; $[\alpha]_D^{20} = -1.80$ (*c* = 0.96, EtOH), 96% *ee* (GC determined).

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