Enantioselective Synthesis of (*S*)-1-Methyldodecyl Acetate, a Pheromone of *Drosophila mulleri*, via (−)-Sparteine-Assisted Deprotonation of 1-Dodecanol

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Dedicated to Professor Marc Julia on the occasion of his 70th birthday

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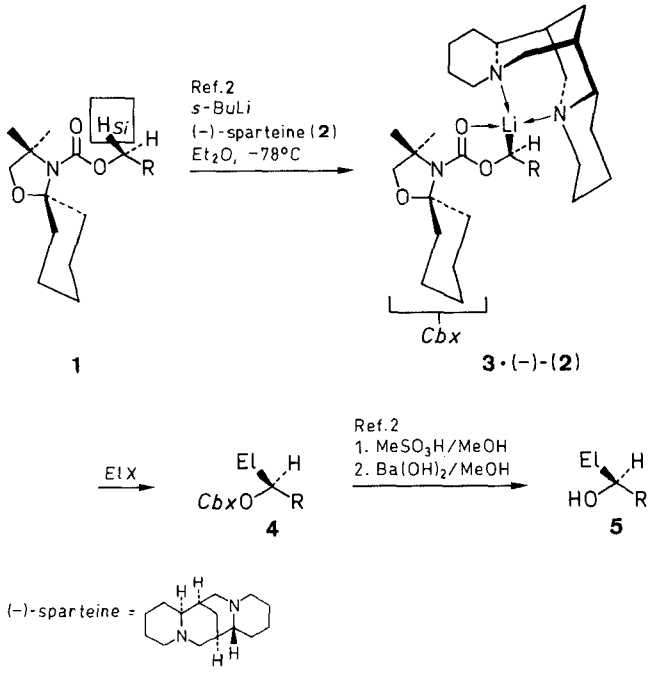
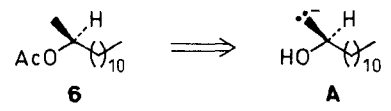
The title compound was synthesized with 98 % ee by enantioselective lithiation and methylation of 1-dodecanol, employing a new protection/activation method for primary alcohols, followed by asymmetric deprotonation of the carbamate.

As we recently reported,[2] 1-alkanols can be activated for α-deprotonation by conversion into sterically blocked *O*-carbamates **1**, derived from 1,3-oxazolidines, and further, the lithiation in presence of (−)-sparteine **2**[3] exchanges enantioselectively with > 97 % ee the *Si*-proton. The lithium carbanion **3** is configurationally stable below −30 °C and is substituted by electrophiles with strict stereoretention. Due to the amino acetal moiety in the carbamate residue deblocking of the hydroxy group proceeds under mild conditions[2] (Scheme 1).

In this paper, we introduce a more convenient activating/protecting group and apply the new strategy to the short synthesis of (*S*)-1-methyldodecyl acetate (**6**), an aggregation pheromone component of the fruit fly *Drosophila mulleri*,[4] which has been prepared by several methods.[4–6] Our synthesis consists in the stereospecific alkylation of the chiral synthon **A** (Scheme 2).

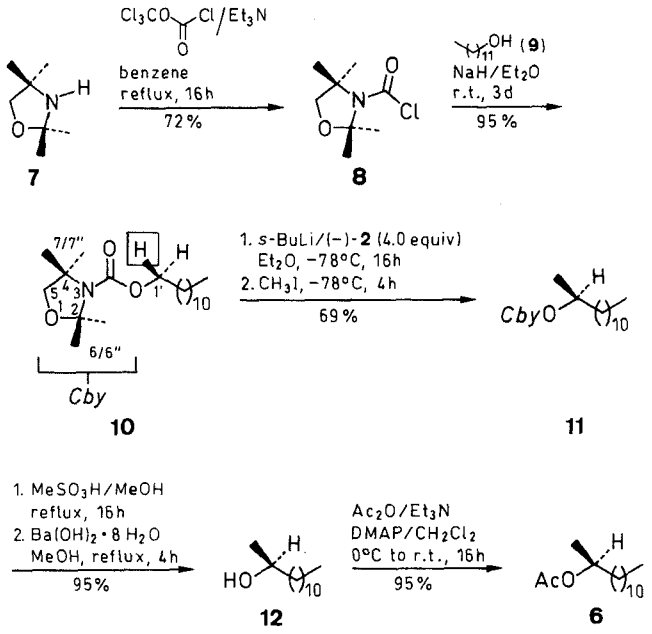


Scheme 1



Scheme 2

The tetramethyl-1,3-oxazolidine **7**, easily available from acetone and 2-amino-2-methylpropanol by condensation according to a method of Michon and Rassat,[7] was converted via the acid chloride **8** to the dodecyl carbamate **10** (Scheme 3). Treatment of **10** with excess *sec*-butyllithium/(−)-sparteine, followed by methyl iodide, afforded the branched carbamate **11**. Sequential treatment of **11** with acid and base in methanol[2] cleaved the carbamate to yield the (*S*)-alcohol **12**, which was found to have a purity of at least 98% ee by careful ^{1}H NMR analysis in the presence of Pr(hfc)$_3$.[8] Finally, acetylation led to the acetate **13** (98.4% ee, determined by GC).



Scheme 3

The carbamates **10** and **11** exist as an *E*/*Z*-mixture of amide isomers which do not interconvert at room temperature in the time scale of the NMR spectrometer. Thus, all signals of the oxazolidine ring are doubled. However, the alkyl residue in the tetramethyl derivatives is less affected than that in the spiro compounds of type **1**, which greatly facilitates the evaluation of the spectra.

The strategy outlined here should be generally applicable to the synthesis of (*S*)-2-alkanols.

Experiments involving metal-organic intermediates were carried out under Ar atmosphere with oven dried glassware. Et_2O was dried ($LiAlH_4$) eluents for chromatography were distilled prior to use. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 200 P and Bruker AM 300 spectrometer with TMS as internal standard. IR spectra were recorded on Perkin-Elmer 283b spectrophotometer. Optical rotation values were measured on Perkin-Elmer 241 polarimeter.

2,2,4,4-Tetramethyl-1,3-oxazolidine (7):
A solution of 2-amino-2-methylpropanol (45.0 g, 0.5 mol), acetone (40.0 g, 0.7 mol) and $MeSO_3H$ (15 drops, ca. 0.5 mL) in CH_2Cl_2 (250 mL) was refluxed with water trap for 48 h.[7] After cooling, the mixture was washed with sat. K_2CO_3 (50 mL) and dried (Na_2SO_4). Distillation of the carefully evaporated residue afforded two fractions: One boiling from 60 to 132 °C (mixture of acetone, CH_2Cl_2 and **7**; 16.3 g containing 12.1 g **7** (NMR); the mixture can directly be used to prepare **8**) and one boiling at 132–134 °C (**7**, 31.8 g). The total amount of **7** obtained was 43.9 g (68%).

$C_7H_{15}NO$ (129.2) calc. C 65.08 H 11.70
found 64.91 11.74

IR (film): ν = 3660–3060 cm^{-1} (NH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.61 (s, 5-H$_2$), 1.81 (br s, NH), 1.40 (s, 6/6″-H$_3$), 1.26 (s, 7/7″-H$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 95.03 (C-2), 76.91 (C-5), 59.31 (C-4), 28.65 (C-6/6″), 28.13 (C-7/7″).

2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carbonyl Chloride (8):
The reaction must be carried out in a well-vented hood! A mixture of **7** (8.48 g, 65.6 mmol) and Et_3N (5.78 g, 57.1 mmol) was added dropwise with stirring to a solution of trichloromethyl chloroformate (diphosgene; 7.49 g, 37.9 mmol) in benzene (80 mL). The mixture was heated under reflux for 16 h. The yellow slurry, after cooling, was poured into 2 N aq HCl (60 mL), and the aqueous phase extracted with Et_2O (2 × 50 mL). Washing the combined solution with sat. $NaHCO_3$ (10 mL), drying (Na_2SO_4), evaporation and distillation afforded **8** as a pale yellow solid, yield 9.10 g (72%, based on **7**), bp 73–74 °C/4 mbar, mp 43 °C (from the melt).

$C_8H_{14}ClNO_2$ (191.7) calc. C 50.14 H 7.36 N 7.34
found 49.6 7.34 7.49

IR (KBr): ν = 1730 cm^{-1} (NCO).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.83 (3.77)[9] (s, 5-H$_2$), (1.72) 1.59 (s, 6/6″-H$_3$), 1.54 (1.46) (s, 7/7″-H$_3$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 143.56 (142.37) (NCO), 99.06 (97.27) (C-2), 76.80 (75.23) (C-5), (64.79) 62.21 (C-4), (26.67) 25.36 (C-6/6″), 24.39 (23.38) (C-7/7″).

Dodecyl 2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylate (10):
To a suspension of NaH (80% in paraffin oil; 444 mg, 15.4 mmol) in Et_2O (16 mL) was added 1-dodecanol (**9**; 2.40 g, 12.9 mmol) and the mixture was stirred at r.t. for 30 min. Then **8** (1.92 g, 10.0 mmol), dissolved in Et_2O (8 mL), was added. After stirring the reaction at r.t. for 3 d, the mixture was poured to 2 N aq HCl (25 mL), the aqueous phase extracted with Et_2O (3 × 20 mL), the combined etheral solution neutralized and dried ($NaHCO_3$/Na_2SO_4, 1:2). Evaporation and purification by LC on silica gel (Et_2O/pentane, 1:5) afforded **10** as a colorless oil, yield 3.25 g (95%), R_f = 0.47 (Et_2O/pentane, 1:4).

$C_{20}H_{39}NO_3$ (341.5) calc. C 70.34 H 11.51
found 70.53 11.48

IR (film): ν = 1700 cm^{-1} (NCO).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08 (4.07) (t, J = 6.6 Hz, 1′-H$_2$), 3.73 (s, 5-H$_2$), 1.70–1.57 (m, 2H; 2′-H$_2$), 1.57 (1.52) (s, 6/6″-H$_3$), (1.43) 1.37 (7/7″-H$_3$), 1.36–1.25 (m, 18H; 3′- to 10′-H$_2$), 0.88 (t, J = 6.5 Hz, 12′-H$_3$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 152.98 (152.34) (NCO), 95.82 (94.82) (C-2), 76.49 (76.23) (C-5), 64.65 (C-1′), (60.53) 59.64 (C-4), 31.97 (C-11′), 29.68, 29.59, 29.38, 29.30, 29.04, 26.23, 22.72 (C-2′ to C-10′), (26.58) 25.37 (C-6/6″), 25.37 (24.22), (C-7/7″), 14.11 (C-12′).

(*S*)-(+)-1-Methyldodecyl 2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylate (11):
A solution of (−)-sparteine (**2**) (938 mg, 4.0 mmol), and **10** (341 mg, 1.0 mmol) in Et_2O (8 mL) was cooled to −78 °C, *s*-BuLi (1.6 M in cyclohexane/isopentane; 4.0 mmol) was added dropwise via syringe and the mixture was stirred at −78 °C for 16 h. CH_3I (710 mg, 5.0 mmol), dissolved in Et_2O (2 mL), was added dropwise and reaction completed by stirring for further 4 h at −78 °C. The mixture was warmed to r.t., poured into 2 N aq HCL (10 mL) and Et_2O (10 mL), the aqueous layer extracted with Et_2O (2 × 20 mL), and the combined etheral solution neutralized and dried ($NaHCO_3$/Na_2SO_4, 1:2). After evaporation of the solvent and purification of the crude product by flash chromatography on silica

gel (70 g, 32–63 μm) with Et_2O/pentane (1:10) **11** was obtained as a colorless oil, yield: 244 mg (69%), $R_f = 0.55$ (Et_2O/pentane 1:4), $[\alpha]_D^{19} = +14.2$ ($c = 1.22$, acetone). When the experiment was performed with 2.8 mmol each of **2** and *s*-BuLi, the yield was 60%.

$C_{21}H_{41}NO_3$	calc.	C 70.94	H 11.62
(355.4)	found	70.91	11.50

IR (film): $\nu = 1690\ cm^{-1}$ (NCO).

^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.86$ (tq, $J_{1',13'} = J_{1',2'} = 6.2$ Hz, 1′-H_1), 3.72 (s, 5-H_2), 1.56 (1.52) (s, 6/6″-H_3), (1.42) 1.36 (7/7″-H_3), 1.31–1.24 (m, 20H; 2′- to 11′-H_2), 1.23 (d, 13′-H_3), 0.88 (t, $J = 6.5$ Hz, 12′-H_3).

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 152.63$ (151.89) (NCO), 95.81 (94.80) (C-2), 76.44 (76.20) (C-5), 71.16 (C-1′), (60.50) 59.60 (C-4), 36.38 (C-2′), 31.97 (C-11′), 29.68, 29.60, 29.38, 25.56, 22.72 (C-3′ to C-10′), (26.71) 25.40 (C-6/6″), 25.40 (24.29) (C-7/7″), 20.16 (C-13′), 14.11 (C-12′).

(*S*)-(+)-2-Tridecanol (12):

To a solution of **11** (198 mg, 0.56 mmol) in MeOH (5 mL) were added three drops (ca. 0.1 mL) $MeSO_3H$. The mixture was refluxed for 16 h. After addition of $Ba(OH)_2 \cdot 8H_2O$ (400 mg, 1.3 mmol) and refluxing the mixture for further 4 h, the mixture was cooled, filtered through silica gel, the residue washed with Et_2O (2 × 20 mL). Evaporation and purification by flash chromatography on silica gel (14 g, 32–63 μm) with Et_2O/pentane (1:3) afforded **12** as a colorless solid, yield: 108 mg (95%), mp: 26°C (from the melt), $R_f = 0.39$ (Et_2O/pentane 1:1), $[\alpha]_D^{20} = +7.1$ ($c = 2.10$, EtOH),[10] ≥ 98% ee ($Pr(hfc)_3$, NMR).[8]

IR (KBr): $\nu = 3560–3100\ cm^{-1}$ (OH).

^1H NMR (200 MHz, $CDCl_3$): $\delta = 3.79$ (tq, $J_{1,2} = J_{1',13'} = 6.2$ Hz, 1′-H_1), 1.61 (br s, OH), 1.51–1.21 (m, 20H; 2′- to 11′-H_2), 1.18 (d, 13′-H_3), 0.88 (t, $J = 6.5$ Hz, 12′-H_2).

^{13}C NMR (50 MHz, $CDCl_3$, Ref.: $CDCl_3$): $\delta = 68.15$ (C-1′), 39.41 (C-2′), 31.93 (C-11′), 29.67, 29.64, 29.35, 25.78, 22.68 (C-3′ to C-10′), 23.46 (C-13′), 14.07 (C-12′).

(*S*)-(+)-1-Methyldodecyl Acetate (6):

A stirred mixture of **12** (151 mg, 0.75 mmol), Et_3N (0.21 mL, 1.5 mmol), DMAP (5 mg, 0.04 mmol) in dry CH_2Cl_2 (3 mL) at 0°C was treated with Ac_2O (distilled prior to use; 0.11 mL, 1.2 mmol). The reaction was stirred 16 h, while warming to r. t. The solution was poured into 2 N aq HCl (5 mL) and Et_2O (5 mL), the aqueous layer extracted with Et_2O (2 × 15 mL), the combined etheral solution washed with sat. $NaHCO_3$ (10 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by flash chromatography on silica gel (20 g, 32–63 μm) with Et_2O/pentane (1:4) afforded pure **6** as a colorless oil, yield: 173 mg (95%), $R_f = 0.68$ (Et_2O/pentane 1:1), $[\alpha]_D^{18} = +4.5$ ($c = 0.98$, hexane), 98% ee (GC, heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin column),[11] spectroscopic data were identical with data given in the literature.[6]

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(8) Determined by 300 MHz ^1H NMR measurement of **12** (15.5 mg) and $Pr(hfc)_3$ (2.4 mg) in $CDCl_3$ (0.6 mL), compared to a racemic sample under same conditions. Doublet of the 13′-H_3-group separated for *rac*-**12**: $\delta = 0.59$ (d, $J = 6.2$ Hz), 0.58 (d, $J = 6.2$ Hz; peak separation: 1.7 Hz). For corresponding sample of **12** only one doublett appeared, the *R*-isomer was not detectable.
(9) The signals are doubled by presence of *E*/*Z* amide isomers. The less intensive signal is put in brackets.
(10) *R*-(−)-Isomer: $[\alpha]_D^{25} = -6.01$ ($c = 2.02$, EtOH).
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S-(+)-Isomer: $\alpha_D^{20} = +7.22$ (neat).
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(11) Determined on a CP-cyclodextrin-β-2,3,6-M-19 column (50 m × 0.25 mm fused silica gel; carrier gas H_2, 1.1 kg/cm²; 160°C isotherm), intensities 7933:62 (98.4% ee).