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Asymmetric synthesis of all stereoisomers of 7,11-dimethylheptadecane and 7-methylheptadecane, the female pheromone components of the spring hemlock looper and the pitch pine looper

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Abstract—The asymmetric synthesis of the stereoisomers of 7,11-dimethylheptadecane (**1**) and 7-methylheptadecane (**2**) via α-alkylation employing the SAMP/RAMP hydrazone method with high asymmetric induction and good overall yields is described. A mixture of (7*S*,11*R*)-**1** and (*S*)-**2** is the female-produced sex pheromone of the spring hemlock looper moth (*Lambdina athasaria*) and the pitch pine looper moth (*Lambdina pellucidaria*). They are both forest pests in northeastern North America.

Compounds with stereochemically defined alkyl-branched hydrocarbon chains are widespread in nature and especially in the field of pheromones, for instance as components of the pheromone of different *Lambdina* species.[1] In 1994 Gries et al. isolated the two methyl-substituted hydrocarbons, 7,11-dimethylheptadecane (**1**) and 7-methylheptadecane (**2**) as components of the female sex pheromone of the spring hemlock looper (SHL), *Lambdina athasaria*.[2] The spring hemlock looper feeds primarily on hemlock (*Tsuga canadensis*) and is a forest pest in northeastern North America (Fig. 1).

In 1998, the same two methyl-branched alkanes **1** and **2** were identified as the sex pheromone components of the female pitch pine looper (PPL), *Lambdina pellucidaria*, whose larvae damage pitch pines, *Pinus rigida*, in northeastern North America during sporadic outbreaks.[3] Synthetic samples of the racemates of (±)-**1**, *meso*-**1** and (±)-**2** were found to be bioactive.[2]

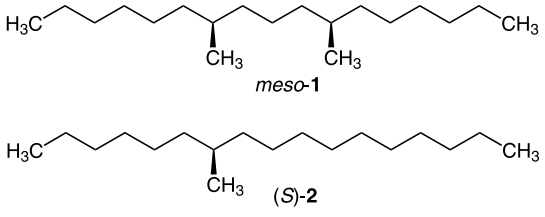

Figure 1. Pheromones of the spring hemlock looper and the pitch pine looper.

The absolute configuration could be determined by an *ex chiral pool* approach starting from the enantiomers of citronellol and methyl 3-hydroxy-2-methylpropanoate by Mori et al. in 1999.[4] The overall yield of the pheromones (ee = 97%) was 57–74% over five steps for (*R*)- and (*S*)-**2**; for (*R*,*R*)-, (*S*,*S*)- and *meso*-**1** the yield (de >99.9%) was ca. 15–16% over 11 steps. In coupled gas chromatographic-electroantennographic detection analyses, Gries et al. have recently established that the bioactive pheromone compounds are (7*R*,11*S*)-**1** (*meso*-**1**) and the (*S*)-configured alkane **2**.[5]

A further synthesis of the stereoisomers of **1** and **2** starting from both enantiomers of 2,3-epoxy-1-hydroxy-undecane delivered the alkanes *meso*-**1** in 14% yield over 24 steps [(*S*,*S*)- and (*R*,*R*)-**1** 9% over 27 steps] and (*S*)- and (*R*)-**2** in 32% yield over 13 steps.[6]

Because metallated hydrazones are the reagents of choice for the regio- and stereoselective synthesis of α-substituted aldehydes and ketones, we decided to attempt the asymmetric synthesis of all the stereoisomers of the title pheromones employing the SAMP/RAMP hydrazone methodology.[7,8]

Keywords: asymmetric synthesis; pheromones; hydrazones; α-alkylation; hydrocarbon; dithians.

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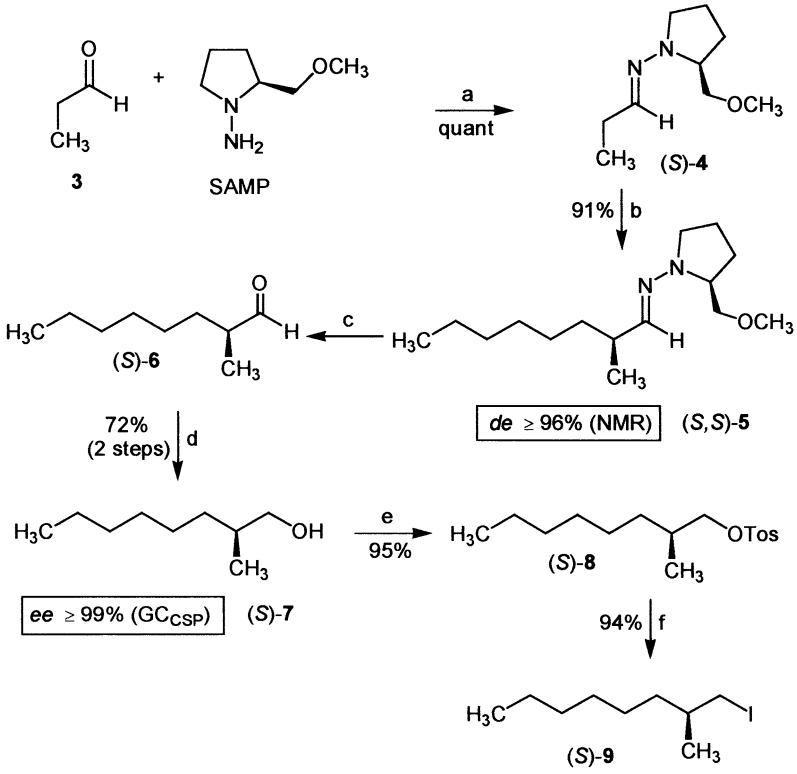
As depicted in Scheme 1 the hydrazone (*S*)-**4** was formed in virtually quantitative yield by treating *n*-propanal (**3**) with (*S*)-1-amino-2-(methoxymethyl)-pyrrolidine (SAMP). Deprotonation of (*S*)-**4** was achieved with lithium tetramethylpiperidide (LiTMP) at 0°C. Alkylation of the azaenolate with 1-iodohexane at −100°C gave the α-alkylated SAMP-hydrazone (*S*,*S*)-**5** in excellent yield and a diastereomeric excess de ≥96% (^{13}C NMR). Under the usual alkylation conditions at −78°C the de was only 90%.

Usually the oxidative cleavage of SAMP hydrazones with ozone is a clean and quantitative method.[9] Nevertheless we chose 4 M HCl for the cleavage of the hydrazone **5**, because the sensibility of the liberated aldehyde **6** to further oxidation required the use of alternative conditions.[8]

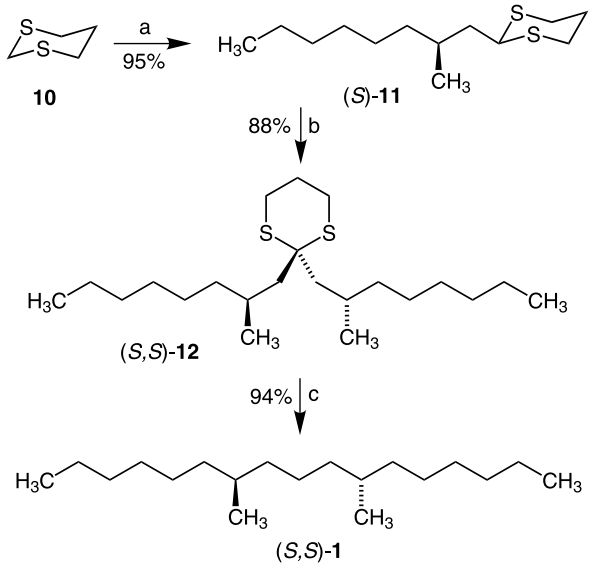
Reduction of the aldehyde (*S*)-**6** without isolation was conveniently carried out using borane dimethyl sulfide complex. Gas chromatography on a chiral stationary phase showed that the cleavage of the hydrazone and the reduction of the aldehyde proceeded with no detectable racemization, [(*S*)-**7**, ee ≥99% (GC_{CSP})]. The crude alcohol (*S*)-**7** was directly converted to the tosylate (*S*)-**8**. Former attempts to generate the more reactive nosylate gave only low yields (40%). The tosylate (*S*)-**8** gave the corresponding iodide (*S*)-**9** upon Finkelstein displacement in excellent yield.

Alkylation of the lithiated 1,3-dithiane (**10**) with (*S*)-**9** yielded (*S*)-**11**, which was again alkylated with (*S*)-**9** using *t*-butyllithium for the deprotonation to furnish the double alkylated dithiane (*S*,*S*)-**12**. Subsequent reductive desulfurization using Raney nickel gave the target molecule (*S*,*S*)-**1**, $[\alpha]_D^{25}=+1.74$ (hexane).[10] The yield from *n*-propanal (**3**) of (*S*,*S*)-**1** over nine steps was 46% (Scheme 2). Since there was no step to cause racemization at the stereogenic centers, (*S*,*S*)-**1** was assumed to be of high diastereo- and enantiomeric purity (de, ee ≥98%). Similarly, the enantiomer (*R*,*R*)-**1** was synthesized via double alkylation with the iodide (*R*)-**9** with diastereo- and enantiomeric excess of ≥98%, starting from propanal (**3**) and using RAMP as the chiral auxiliary via (*R*)-**4**, $[\alpha]_D^{26}=-1.48$ ($CHCl_3$).[10] The *meso*-alkane (*R*,*S*)-**1** was prepared from (*S*)-**11** by alkylation with the iodide (*R*)-**9** and subsequent reductive desulfurization.

Next we turned our attention to the other component of the female sex pheromone 7-methylheptadecane (**2**) (Scheme 3). Hydrazone (*S*)-**14** was formed in virtually quantitative yield by the treatment of *n*-octanal (**13**) with SAMP. Metallation of (*S*)-**14** with LiTMP at 0°C and alkylation of the resulting azaenolate with 1-iododecane at −100°C gave the α-alkylated SAMP-hydrazone (*S*,*S*)-**15**. After warming to room temperature over 2 h it was necessary to reflux the mixture for 30 min to increase the yield. Nevertheless, the hydrazone (*S*,*S*)-**15** was formed in good yield (68%) and a de of



Scheme 1. *Reagents and conditions*: (a) rt, 16 h; (b) (i) LiTMP (1.1 equiv.), THF, 0°C, 1 h; (ii) *n*-HexI (1.1 equiv.), −100°C, 16 h; (c) 4 M HCl, pentane, rt, 15 min; (d) $BH_3{\cdot}SMe_2$ (5.0 equiv.), Et_2O, rt, 45 min; (e) TsCl (1.5 equiv.), pyridine, 0°C, 20 h; (f) NaI (1.4 equiv.), acetone, reflux, 16 h.



Scheme 2. *Reagents and conditions*: (a) (i) *t*-BuLi (1.1 equiv.), THF/HMPA (10:1), −78°C, 5 min; (ii) (*S*)-**9** (1.1 equiv.), −78°C, 20 min; (iii) rt, 20 min; (b) *t*-BuLi (1.5 equiv.), THF/HMPA (10:1), −78°C, 20 min; (ii) (*S*)-**9** (1.6 equiv.), −78°C, 60 min; (iii) reflux, 30 min; (c) Raney-Ni, H_2, *i*-PrOH, reflux, 16 h.

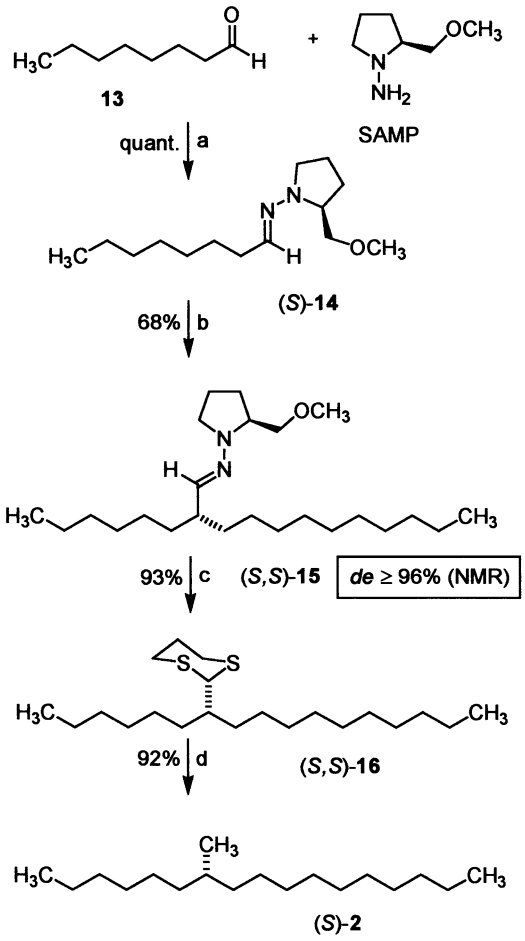
≥96% (^{13}C NMR). The cleavage of the hydrazone promoted by $BF_3{\cdot}OEt_2$ and direct dithioketalization with 1,3-propanedithiol gave the dithiane (*S*)-**16** in excellent yield and without racemization.[11] Desulfurization was carried out by using Raney nickel and hydrogen at room temperature.[12] In this way, the pheromone (*S*)-**2** was obtained in high purity, enantiomeric excess and in 58% overall yield (four steps) after chromatography, $[\alpha]_D^{24}=+0.27$ (hexane).[10] Similarly, the enantiomer (*R*)-**2** was synthesized starting from *n*-octanal (**13**) and RAMP as the chiral auxiliary via (*R*)-**14**, $[\alpha]_D^{25}=-0.26$ ($CHCl_3$).[10]

Because it was impossible to obtain separation of the enantiomers of **2** either by GC or HPLC on chiral stationary phases, the ee could only be determined by comparison of the optical rotation with the literature, which was consistent with the data given.[10]

Desulfurization in refluxing *i*-propanol with Raney nickel caused no epimerization at the stereocenter in the β-position of **12** even though it is well known that α-stereogenic centers such as in **16** can suffer from partial racemization via an elimination–addition process. Therefore, the desulfurization of **16** was performed at room temperature under an atmosphere of hydrogen for 48 h without detectable racemization.[12]

Conclusion

In summary, an efficient asymmetric synthesis of all possible stereoisomers of 7,11-dimethylheptadecane (**1**) and 7-methylheptadecane (**2**) was achieved employing the SAMP/RAMP-hydrazone method. The yield of



Scheme 3. *Reagents and conditions*: (a) rt, 16 h; (b) (i) LiTMP (1.2 equiv.), THF, 0°C, 2 h; (ii) *n*-DecI (1.1 equiv.), −100°C, 2 h; (iii) reflux, 30 min; (c) $BF_3{\cdot}OEt_2$ (6.0 equiv.), $HS(CH_2)_3SH$ (1.3 equiv.), CH_2Cl_2, reflux, 72 h; (d) Raney-Ni, H_2, *i*-PrOH, rt, 48 h.

meso-**1** over nine steps was 46% and that of (*S*)-**2** reached 58% over four steps.

Acknowledgements

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