First asymmetric synthesis of 6-methyl-3-nonanone, the female-produced sex pheromone of the caddisfly *Hesperophylax occidentalis*

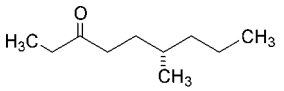
Dieter Enders* and Thomas Schüßeler

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor-Pirlet-Straße 1, 52074 Aachen, Germany. E-mail: Enders@RWTH-aachen.de; Fax +49 241 8888 127

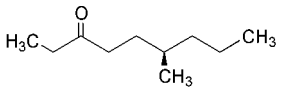
Received (in Montpellier, France) 16th August 2000, Accepted 27th September 2000
First published as an Advance Article on the web 20th November 2000

The asymmetric synthesis of the female-produced sex pheromone of the caddisfly *Hesperophylax occidentalis*, (*S*)- and (*R*)-6-methyl-3-nonanone, starting from the simple starting materials propanal, propyl iodide and 2-butanone, in good overall yields is described. The stereogenic centre at the C-6 position of the pheromone was generated *via* α-alkylation employing the SAMP/RAMP hydrazone method with high asymmetric induction (ee = 94 and 92%).

The female-produced sex pheromone of the caddisfly *Hesperophylax occidentalis* was isolated in 1996 by Bjostad *et al.*[1] and identified as 6-methyl-3-nonanone (**1**). By synthesizing this racemic ketone and closely related analogues they demonstrated by an electroantennogram experiment that *rac*-**1** shows the strongest response.[1] However, at this stage the absolute configuration of this natural product, an important question in the pheromone area,[2] could not be determined.



(*S*)-**1**



(*R*)-**1**

sex pheromone of the caddisfly *Hesperophylax occidentalis*

In 1997 Mori *et al.*[3] obtained both enantiomers of **1** by an *ex chiral pool* approach starting from (*S*)- or (*R*)-citronellal, respectively. The overall yield of the pheromone (ee = *ca.* 97%) was 12–18% over six steps. The biological evaluation of these samples by Bjostad *et al.*[4] showed that the *R* enantiomer of **1** is much more active than the *S*-configurated ketone.

Because metallated hydrazones are the reagents of choice for the regio- and stereoselective synthesis of substituted ketones, we decided to attempt the first asymmetric synthesis of both enantiomers of the title pheromone employing our SAMP/RAMP hydrazone methodology.[5]

Results and discussion

Scheme 1 summarizes the asymmetric synthesis of the enantiomers of **1**. The synthesis of iodide (*S*)-**8** was previously reported by our laboratory in a total synthesis of (+)-pectinatone.[6] Meanwhile we could optimize the synthesis of this important key building block of pheromone (*S*)-**1** with better yields and a better enantiomeric excess.

Hydrazone (*S*)-**3** was formed in virtually quantitative yield by treating propanal (**2**) with (*S*)-1-amino-2-(methoxymethyl) pyrrolidine (SAMP). Deprotonation of (*S*)-**3** was achieved with lithium tetramethylpiperidide (LiTMP) at 0 °C. Alkylation of the azaenolate with 1-iodopropane at −78 °C gave the α-alkylated SAMP-hydrazone (*S*,*S*)-**4** in excellent yield and a diastereomeric excess (de) of 95%.

Usually the oxidative cleavage of SAMP hydrazones with ozone is a clean and quantitative method, however, the susceptibility of the liberated aldehyde in this case to further oxidation led us to search for alternative conditions.[7] Therefore, we chose 3 M HCl for the cleavage of the hydrazone.[7]

Reduction of the aldehyde (*S*)-**5** without isolation was conveniently carried out using the borane dimethyl sulfide complex. Gas chromatography on a chiral stationary phase showed that the cleavage of the hydrazone and reduction of the aldehyde proceeded with no detectable racemization. The crude alcohol (*S*)-**6** was directly converted to nosylate (*S*)-**7**. Previously the nosylate (*S*)-**7** was obtained in 30% overall yield from (*S*)-**3** (75% per step) by using the salt method[5–7] for the cleavage of the SAMP hydrazone. By using 3 M HCl for the cleavage we obtained nosylate (*S*)-**7** in 69% yield over four steps.

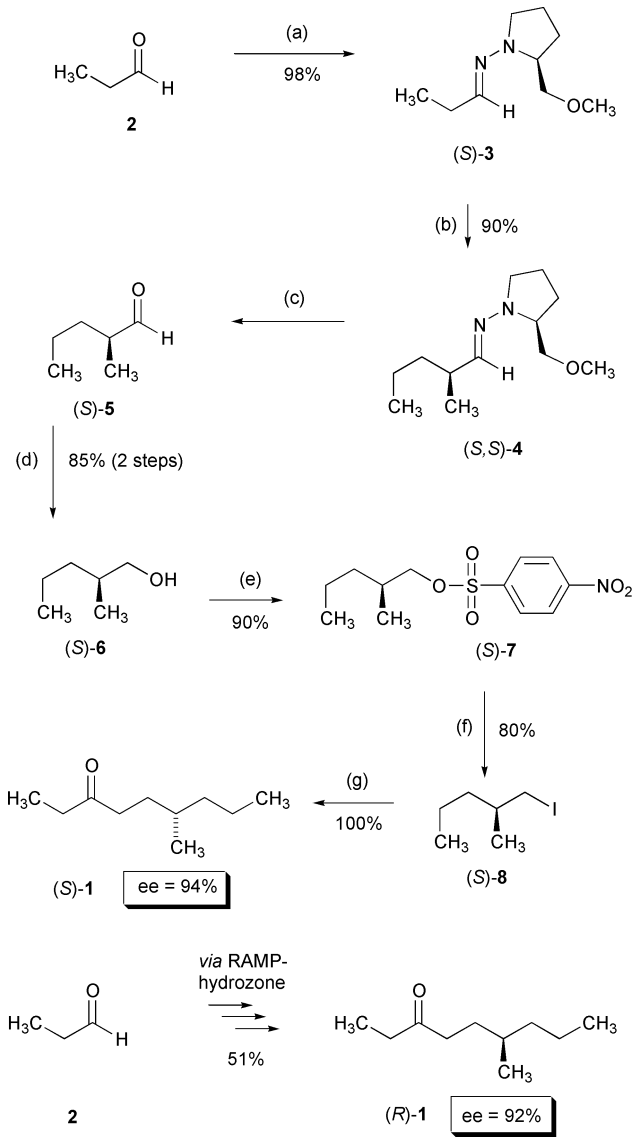
We envisaged the *in situ* conversion of the sulfonate (*S*)-**7** to the iodide (*S*)-**8** and subsequent α-alkylation of butanone dimethylhydrazone, however, all attempts to use the *in situ* iodide proceeded without success. Small amounts of free iodine seem to interfere with the alkylation. It was necessary, therefore, to isolate and purify iodide (*S*)-**8**. The regioselective alkylation of 2-butanone with (*S*)-**8** was carried out *via* the corresponding lithiated dimethylhydrazone and proceeded in nearly quantitative yield.[8,9] The hydrazone was cleaved with 2 M HCl on work up, and the pheromone (*S*)-**1** was obtained in high purity, enantiomeric excess (ee = 94%) and yield after chromatography.

Similarly, the enantiomer (*R*)-**1** was synthesized with an enantiomeric excess of 92%, starting from propanal (**2**) and using RAMP as the chiral auxiliary. In this case the diastereomeric excess of the alkylation was excellent, too. (*R*,*R*)-**4** was isolated in 93% yield and de ⩾ 94%.

In conclusion, the first asymmetric synthesis of both enantiomers of the sex pheromone of the caddisfly *H. occidentalis* was achieved employing the SAMP/RAMP-hydrazone method and starting from the simple substrates propanal, propyl iodide and 2-butanone. The yield from **2** of (*S*)-**1** (ee = 94%) over seven steps was 55% and that of (*R*)-**1** (ee = 92%) reached 51%.

Experimental

All reagents were of commercial quality used from freshly opened containers. Solvents were dried and purified by conventional methods prior to use. THF was freshly distilled from sodium–lead alloy under Ar. All aqueous solutions were saturated. All reactions were carried out under an argon



Scheme 1 Synthesis of (*R*)- and (*S*)-6-methyl-3-nonanone (**1**). *Reagents and conditions*: (a) SAMP, CH_2Cl_2, rt; (b) LiTMP, THF, 0 °C, then *n*-C_3H_7I, −78 °C to rt, 20 h; (c) 3 M HCl, pentane; (d) $BH_3 \cdot Me_2S$, Et_2O; (e) *p*-$NO_2C_6H_4SO_2Cl$, pyr, DMAP, CH_2Cl_2, rt; (f) LiI, CH_2Cl_2; (g) 1. $C_2H_5[C{=}N{-}N(CH_3)_2]CH_3$, *n*-BuLi, THF, 0 °C; 2. 2 M HCl.

atmosphere using dry solvents unless otherwise stated. *n*-BuLi (1.6 M in hexane) was purchased from Merck, Darmstadt. Preparative column chromatography used Merck silica gel 60, particle size 0.040–0.063 mm (230–400 mesh, flash). Analytical TLC used silica gel 60 F_{254} plates from Merck, Darmstadt. Optical rotation values were measured on a Perkin–Elmer P241 polarimeter; solvents used were of Merck UVASOL-quality. Microanalyses were obtained with a Heraeus CHN-O-RAPID element analyzer. Mass spectra were acquired on a Finnigan MAT 212 (CI 100 eV; EI 70 eV) spectrometer. IR spectra were taken on a Perkin–Elmer FT/IR 1750. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded on Gemini 300 or Varian Inova 400 ($CDCl_3$ as solvent, TMS as internal standard) spectrometers.

Synthesis and characterization

(*S*)-(−)-2-Methoxymethyl-1-(1′-propylidenamino)-pyrrolidine, [(*S*)-3]. To a cooled solution (0 °C) of SAMP (3.06 g, 23.6 mmol) in CH_2Cl_2 (10 ml), molecular sieves (4 Å, 2 g) and propanal **2** (1.64 g, 28.3 mmol) were added sequentially. The mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with CH_2Cl_2 (50 ml) and filtered. The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil. The crude product was distilled under reduced pressure (bp 67 °C at 3 mbar) to yield hydrazone (*S*)-**3** as a colourless oil (3.91 g, 98%). The analytical data were consistent with the data given in the literature.[5]

(*R*)-(−)-2-Methoxymethyl-1-(1′-propylidenamino)-pyrrolidine, [(*R*)-3]. In the same manner as described above **2** (2.60 g, 45.7 mmol) was converted to (*R*)-**3** (6.68 g, 95%) using RAMP (5.40 g, 41.5 mmol) as the chiral auxiliary.

(2*S*,2′*S*)-2-Methoxymethyl-1-(2′-methyl-1′-pentyliden-amino)pyrrolidine, [(*S*,*S*)-4]. To a cooled solution (0 °C) of 2,2,6,6-tetramethylpiperidine (3.24 g, 23 mmol) in dry THF (20 ml) under Ar was slowly added *n*-BuLi (1.6 M in hexane, 14.4 ml, 23 mmol); the mixture was stirred for 1 h. A solution of (*S*)-**3** (3.55 g, 21 mmol) in dry THF (5 ml) was added slowly and stirring maintained at 0 °C for 1 h. The resulting orange solution was cooled to −78 °C and 1-iodopropane (3.91 g, 23 mmol) added dropwise. The mixture was allowed to warm to room temperature over 20 h before being quenched with pH 7 buffer (20 ml). The aqueous phase was extracted with Et_2O (2 × 25 ml), the combined organic extracts washed with aqueous NH_4Cl (50 ml) and brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica gel; pentane–Et_2O, 4 : 1, containing 1% Et_3N, R_f 0.67) gave (*S*,*S*)-**4** (3.99 g, 90%, de ⩾ 95% by ^{13}C NMR) as an oil. The analytical data were consistent with the data given in the literature.[5]

(2*R*,2′*R*)-2-Methoxymethyl-1-(2′methyl-1′-pentyliden-amino)pyrrolidine, [(*R*,*R*)-4]. In the same manner as described above, (*R*)-**3** (4.47 g, 26.3 mmol) was converted to (*R*,*R*)-**4** (4.59 g, 93%, de ⩾ 94% by ^{13}C NMR), which was obtained as a pale oil.

(*S*)-(−)-2-Methylpentanal [(*S*)-5]. A solution of the hydrazone (*S*,*S*)-**4** (705 mg, 3.33 mmol) in pentane (30 ml) was stirred with aqueous 3 M HCl (20 ml) at room temperature for 15 min. The two phases were separated, and the aqueous phase was extracted with Et_2O (3 × 15 ml). The combined organic extracts were washed with aqueous $NaHCO_3$ (20 ml) and brine (20 ml), dried ($MgSO_4$) and used in the next step (reduction) without isolation. The analytical data (after isolation of a small aliquot) were consistent with the data given in the literature.[5,10]

(*R*)-(+)-2-Methylpentanal, [(*R*)-5]. In the same manner as described above (*R*,*R*)-**4** (703 mg, 3.32 mmol) was converted to (*R*)-**5**.

(*S*)-(−)-2-Methyl-1-pentanol, [(*S*)-6]. To a cooled solution (0 °C) of the crude aldehyde (*S*)-**5** in Et_2O–pentane (3 : 2, 75 ml) under Ar was slowly added $BH_3 \cdot Me_2S$ (1.27 g,16.7 mmol) and the mixture stirred for 45 min. The mixture was quenched with aqueous 3 M HCl (20 ml) and stirred at room temperature for another 90 min. The aqueous phase was extracted with Et_2O (3 × 20 ml). The combined organic extracts were washed with aqueous Na_2SO_3 (30 ml) and dried ($MgSO_4$). Concentration *in vacuo* gave alcohol (*S*)-**6** [288 mg, 85%, ee ⩾ 94% by GC-CSP (column: Lipodex A)] as a colourless oil. No further purification was necessary. The analytical data were consistent with the data given in the literature.[11]

(*R*)-(+)-2-Methyl-1-pentanol, [(*R*)-6]. In the same manner as described above, (*R*)-**5** was converted to (*R*)-**6** [276 mg, 82%, ee ⩾ 93% by GC-CSP (column: Lipodex A)] which was obtained as a colourless oil.

(*S*)-(+)-2-Methylpentyl *p*-nitrophenylsulfonate, [(*S*)-7]. To a cooled solution (0 °C) of (*S*)-**6** (238 mg, 2.3 mmol) in dry CH_2Cl_2 (50 ml) under Ar was added pyridine (360 mg, 4.6 mmol) and DMAP (20 mg, cat.). A solution of *p*-nitrophenylsulfonyl chloride (559 mg, 2.5 mmol) in CH_2Cl_2 (10 ml) was added slowly. The resulting yellow reaction mixture was stirred for 30 h and quenched with 1 M HCl (20 ml). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 ml); the combined organic extracts were washed with aqueous $NaHCO_3$ (20 ml) and brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give nosylate (*S*)-**7** (594 mg, 90%) as a yellow solid. $[\alpha]_D^{25}$: +2.8 (c = 1.05, $CHCl_3$), mp 39 °C. IR (KBr) ν: 3113, 2961, 2933, 2874, 1610, 1541, 1469, 1405, 1366, 1353, 1314, 1186, 1110, 1096, 1013, 962, 933, 897, 857, 843, 823, 739, 683, 619, 596, 568, 467 cm^{-1}. EI-MS (70 eV) m/z: 204 (5), 187 (9), 186 (17), 157 (4), 123 (7), 122 (17), 92 (6), 85 (11), 84 ($C_6H_{12}^+$, 100), 77 (4), 76 (12), 75 (13), 71 (56), 70 (14), 69 (33), 57 (5), 56 (54), 55 (26), 50 (8%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (2H, d, J = 9.06, H_9), 8.11 (2H, d, J = 9.06, H_8), 4.00 (1H, dd, J = 5.71, J = 9.40, H_1), 3.92 (1H, dd, J = 6.71, J = 9.40, H_1), 1.83 (1H, oct, J = 5.71, H_2), 1.05–1.35 (4H, m, H_4, H_3), 0.91 (3H, d, J = 6.72, H_6), 0.86 (3H, t, J = 7.05 Hz, H_2, H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.74 (C_{10}), 142.07 (C_7), 129.21 (C_9), 124.45 (C_8), 76.42 (C_1), 34.79 (C_3), 32.66 (C_2), 19.72 (C_4), 16.35 (C_6), 14.06 (C_5). Anal. calc. for $C_{12}H_{17}NO_5S$: C 50.16, H 5.96, N 4.87; found: C 50.32, H 5.96, N 4.62%.

(*R*)-(−)-2-Methylpentyl *p*-nitrophenylsulfonate, [(*R*)-7]. In the same manner as described above, (*R*)-**6** (251 mg, 2.46 mmol) was converted to (*R*)-**7** (607 mg, 86%), which was obtained as a yellow solid. $[\alpha]_D^{25}$: −2.7 (c = 1.25, $CHCl_3$).

(*S*)-(+)-1-Iodo-2-methylpentane, [(*S*)-8]. Lithium iodide (300 mg, 2.23 mmol) was heated *in vacuo* before use. Nosylate (*S*)-**7** (535 mg, 1.86 mmol) was added in one portion, and the mixture was dissolved in dry THF (10 ml) and stirred at room temperature for 5 h. The precipitated lithium sulfonate salt was dissolved after adding pentane (5 ml) by quenching of aqueous 1 M HCl (20 ml). The aqueous phase was extracted with CH_2Cl_2 (20 ml), the combined organic extracts washed with aqueous $Na_2S_2O_3$ (20 ml) and brine (20 ml) and dried ($MgSO_4$). Concentration *in vacuo* gave iodide (*S*)-**8** [315 mg, 80%, ee ⩾ 94% by GC-CSP (column: Lipodex G)] as a colourless oil. No further purification was necessary. The analytical data were consistent with the data given in the literature.[11]

(*R*)-(−)-1-Iodo-2-methylpentane, [(*R*)-8]. In the same manner as described above (*R*)-**7** (571 mg, 1.99 mmol) was converted to (*R*)-**8** [354 mg, 84%, ee ⩾ 92% by GC-CSP (column: Lipodex G)] obtained as a colourless oil.

(*S*)-(+)-6-Methyl-3-nonanone, [(*S*)-1]. To a cooled solution (0 °C) of 2-butanone dimethylhydrazone (210 mg, 1.76 mmol) in dry THF (30 ml) under Ar was slowly added *n*-BuLi (1.6 M in hexane, 1.17 ml, 1.88 mmol); the mixture was stirred for 1 h. The resulting yellow solution of the aza-enolate was warmed up to room temperature and iodide (*S*)-**8** (265 mg, 1.25 mmol) was added dropwise. The colour changed immediately from yellow to a greenish brown–black. The solution was stirred at room temperature for 20 h and quenched with 2 M HCl over a period of 30 min. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 ml), the combined organic extracts washed with brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica gel, pentane–Et_2O, 4 : 1, containing 1% Et_3N, R_f 0.8) gave the title ketone (*S*)-**1** (195 mg, 100%) as a colourless oil. $[\alpha]_D^{22}$: +2.85 (c = 2.00, $CHCl_3$). Lit. $[\alpha]_D^{25}$: +3.07 (c = 12.1, $CHCl_3$).[3] The analytical data were consistent with the data given in the literature.[3]

(*R*)-(−)-6-Methyl-3-nonanone, [(*R*)-1]. In the same manner as described above, (*R*)-**8** (124 mg, 0.80 mmol) was converted to (*R*)-**1** (122 mg, 98%), which was obtained as a colourless oil. $[\alpha]_D^{22}$: −2.70 (c = 2.05, $CHCl_3$). Lit. $[\alpha]_D^{25}$: −3.12 (c = 12.1, $CHCl_3$).[3]

Acknowledgements

We thank Dr L. B. Bjostad for helpful discussions. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG and Bayer AG for the donation of chemicals.

References

1 L. B. Bjostad, D. K. Jewett and D. L. Brigham, *J. Chem. Ecol.*, 1996, **22**, 103.
2 K. Mori, *Chem. Commun.*, 1997, 1153.
3 H. Takikawa, H. Tamagawa and K. Mori, *J. Indian Chem. Soc.*, 1997, **74**, 855.
4 L. B. Bjostad, unpublished results (Colorado State University, Fort Collins, Colorado, USA, 1999).
5 D. Enders and H. Eichenauer, *Chem. Ber.*, 1979, **112**, 2933.
6 A. A. Birkbeck and D. Enders, *Tetrahedron Lett.*, 1998, **39**, 7823.
7 D. Enders, L. Wortmann and R. Peters, *Acc. Chem. Res.*, 2000, **33**, 157.
8 E. J. Corey and D. Enders, *Tetrahedron Lett.*, 1976, 3.
9 M. Yamashita, K. Matsumiya, M. Tanabe and R. Suemitsu, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 407.
10 W. Fenzl, R. Köster and H.-J. Zimmermann, *Liebigs Ann. Chem.*, 1975, 2201.
11 K. Mori and N. Murata, *Liebigs Ann. Chem.*, 1994, 1153.