266. Synthesis and Absolute Configuration of Naturally Occurring Dactyloxene-B and -C

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Summary

Natural (+)-dactyloxene-B (**12**) and -C (**13**) have been synthesized starting from (+)-*trans*-2,5,6-trimethyl-1-cyclohexene-1-carbaldehyde (**1**) which is shown to have the (5*S*,6*R*)-configuration by chemical correlation with (+)-(2*R*,3*S*,6*S*)-2,3,6-trimethylcyclohexanone. The absolute configurations are therefore (2*R*,5*R*,9*S*,10*R*) for (+)-dactyloxene-B and (2*R*,5*S*,9*S*,10*R*) for (+)-dactyloxene-C.

We recently reported the first total synthesis of the racemic sesquiterpene ethers dactyloxene-B and -C and assigned their relative configuration [1]. However, the chirality of the dextrorotatory compounds isolated from the sea hare *Aplysia dactylomela* [2] [3] remained unknown.

We now report the synthesis of natural (+)-dactyloxene-B (**12**) and -C (**13**) using our previous method *(Scheme 1)* [1] but starting with optically pure (+)-*trans*-2,5,6-trimethyl-1-cyclohexene-1-carbaldehyde (**1**). The chirality of this aldehyde is shown to be (5*S*,6*R*) by its chemical transformation into the equilibrium mixture of diastereoisomeric (3*S*)-2,3,6-trimethylcyclohexanones ((+)-**15**). Therefore the absolute configurations of (+)-dactyloxene-B (**12**) and -C (**13**) are (2*R*,5*R*,9*S*,10*R*) and (2*R*,5*S*,9*S*,10*R*), respectively.

The starting aldehyde (+)-**1** was obtained by resolution of the racemate using (−)-menthyl *N*-aminocarbamate (='(−)-menthydrazide') [4]. The formation of the mixture of diastereoisomeric (menthyloxycarbonyl)hydrazones (='menthydrazones')[1]) proceeded well, but the separation of the mixture was difficult due to the slight differences in the solubilities of the components. The less soluble 'menthydrazone' of (+)-**1** was obtained in pure form after twelve recrystallizations from ethanol (yield 5.7%); the more soluble derivative of (−)-**1** was obtained in a pure state from the first mother liquor after fourteen recrystallizations from ethanol (yield 1.9%)[2]).

[1]) In this work we named (+)-**1**- resp. (−)-**1**-(−)-menthydrazones the diastereomeric hydrazones which are obtained when (+)-**1** resp. (−)-**1** react with '(−)-menthydrazide', without any indication of the optical activity of the hydrazones.

[2]) The diastereoisomeric 'menthydrazones' of (±)-**1** were also separated by chromatography on a silica gel column (see exper. part).

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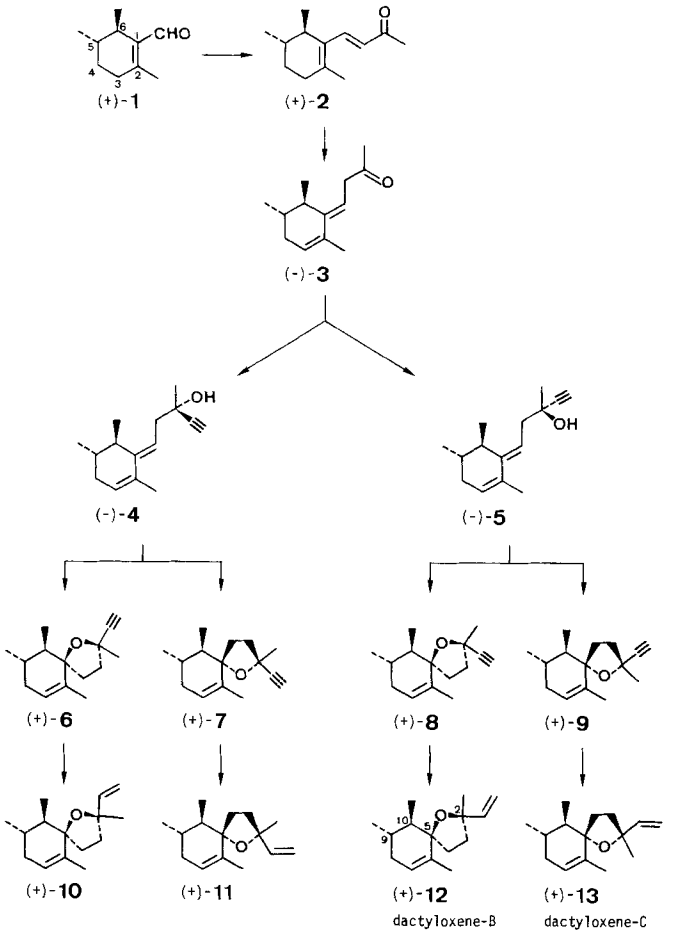
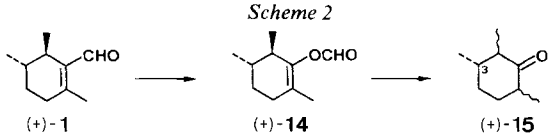
Scheme 1



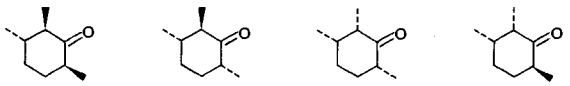
Hydrolysis of the 'menthydrazones' of **1** by the method of *Woodward et al.* [4] (short boiling in 10% H_2SO_4-solution in the presence of ethanol, isolation by steam distillation) or according to *Sobotka et al.* [5] (steam distillation in the presence of phthalic anhydride) gave only low yields (< 5%) of regenerated aldehyde. However, if the hydrolysis was carried out in 50% aqueous acetic acid in the presence of pyruvic acid (*cf.* [6]), aldehyde **1** was regenerated in *ca.* 90% yield.

Next the absolute configuration of the starting aldehyde (+)-**1** was determined *(Scheme 2). Baeyer-Villiger* oxidation of (+)-**1** with 1 mol-equiv. of peracetic acid in

Scheme 2



the presence of 1 mol-equiv. of boron trifluoride etherate[3]) took place easily to give the cyclohexenyl formate (+)-**14** in good yield (some ketone (+)-**15** arising from partial hydrolysis of **14** was also formed). Alkaline hydrolysis of the crude formate (+)-**14** gave the equilibrium mixture of diastereoisomeric (3*S*)-2,3,6-trimethylcyclohexanones ((+)-**15**) with a specific rotation $[\alpha]_D^{20} = +18°$ ($c = 2.3$, $CHCl_3$). This agrees with the value reported for the enantiomeric (3*R*)-ketone ($[\alpha]_D = -17°$ ($c = 2.4$) resp. $-16°$ ($c = 2.0$)) [7], which is presumably also an equilibrium mixture. The equilibrated mixture consists of the four diastereoisomers **15a** (73%), **15b** (9%), **15c** (13%), and **15d** (5%)[4]), easily separable by GLC. on capillary columns. The



15a **15b** **15c** **15d**

main isomer **15a** was isolated in pure form by preparative GLC. and its specific rotation ($[\alpha]_D^{20} = +16.8°$ ($c = 1.25$)) was about the same as for the equilibrium mixture (+)-**15**.

Since the chiral centre C(5) of (+)-**1** is not involved during the synthesis of the (+)-dactyloxenes and in the course of the oxidative degradation leading to (+)-**15**, the (+)-dactyloxenes must have the (9*S*) configuration.

Experimental Part

General remarks. See [1]. In ambiguous cases the assignments of 360-MHz-^{1}H-NMR. signals are based on extensive decoupling experiments (not described in detail). Specific rotations $[\alpha]_D$ were measured in $CHCl_3$. The melting points of the 'menthydrazones' were determined in open capillary tubes in an oil bath and are not corrected; sample heating was started just 2° below the m.p. because of decomposition.

1. Resolution of (±)-*trans*-2,5,6-trimethyl-1-cyclohexene-1-carbaldehyde (1). – Racemic *trans*-aldehyde (±)-**1** (96.4 g, 0.634 mol) [1] was added to a hot solution of '(−)-menthydrazide' (135.7 g, 0.634 mol) [4] in 2 l of 94% ethanol, containing 40 g of sodium acetate and 20 ml of acetic acid. The clear solution was heated under reflux for 2 h and cooled to 20°. Fine needles (132 g, fraction A) of a mixture of diastereoisomeric 'menthydrazones' crystallized. The mother liquor was chilled (0°), and a further crop of crystals (17 g, fraction B) was collected. After evaporation of the mother liquor to dryness (90°/10 Torr), the residue was taken up in boiling CH_2Cl_2 (500 ml) and filtered from the insoluble sodium acetate. The filtrate was evaporated, and the residue (69 g), after recrystallization from 700 ml of ethanol at 0°, gave 21.5 g (fraction C) of crystals. TLC.[5]) showed fraction A to be slightly enriched with '(+)-**1**-(−)-menthydrazone' (higher Rf-value), whereas fractions B and C both contained an excess of '(−)-**1**-(−)-menthydrazone' and were therefore combined. Fraction A, after 12 recrystallizations at 0° from ethanol (*ca.* 20fold amount of the solute), gave 12.5 g (5.7%) of pure '(+)-**1**-(−)-*menthydrazone*' as fine needles, m.p. 201.5–202°, $[\alpha]_D^{20} = -20.6°$ ($c = 1.2$). – Characteristic ^{1}H-NMR. signals (360 MHz): 0.81 (*d*, $J = 7$, 3 H, $H_3C(7)$ of menthyl); 0.90 (*d*, $J \approx 7$, 9 H, $(CH_3)_2CH$ and $H_3C-C(5)$); 1.14 (*d*, $J = 7$, 3 H, $H_3C-C(6)$); 1.80 (br. *s*, 3 H, $H_3C-C(2)$); 4.65 ($t \times d$, $J_1 = 11$, $J_2 = 4.5$, 1 H, H–C(3) of menthyl).

$C_{21}H_{36}N_2O_2$ (348.51) Calc. C 72.37 H 10.41 N 8.04% Found C 71.90 H 10.44 N 8.00%

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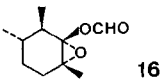
[3]) In the absence of BF_3-etherate both peracetic and *m*-chloroperbenzoic acid reacted sluggishly and less selectively. At *ca.* 50% conversion of **1**, a substantial amount of epoxycyclohexyl formate **16** was formed.



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[4]) The relative configurations of **15a–d** were assigned by 360-MHz-^{1}H-NMR. spectroscopy (see exper. part).

[5]) Precoated silica gel plates *Merck* F 254, thickness 0.25 mm; solvent toluene/ether 8:2.

The combined fractions B and C, after 14 recrystallizations from ethanol (0°, *ca.* 20fold amount of the solute), gave 4.3 g (1.9%) of pure '(−)-**1**-(−)-*menthydrazone*' as fine needles, m.p. 190–190.5°, $[\alpha]_D^{20} = -78.7°$ ($c = 0.9$). – Characteristic ^{1}H-NMR. signals (360 MHz): 0.79 (*d*, $J = 7$, 3 H, $H_3C(7)$ of menthyl); 0.89 (*d*, $J \approx 7$, 3 H, $H_3C-C(5)$); 0.91 (*d*, $J = 7$, 6 H, $(CH_3)_2CH$); 1.12 (*d*, $J = 7$, 3 H, $H_3C-C(6)$); 1.80 (br. *s*, 3 H, $H_3C-C(2)$); 4.67 ($t \times d$, $J_1 = 10.5$, $J_2 = 4$, 1 H, H–C(3) of menthyl).

$C_{21}H_{36}N_2O_2$ (348.51) Calc. C 72.37 H 10.41 N 8.04% Found C 72.10 H 10.49 N 8.04%

Chromatographic separation of '(+)-**1**-' and '(−)-**1**-(−)-*menthydrazone*'. A solution of 0.35 g of the diastereoisomeric mixture (ratio *ca.* 1:1) in 10 ml of toluene was chromatographed on a column of 100 g silica gel *Merck* (particle size <0.063 mm) using dry toluene as eluent. The chromatogram was monitored by TLC.[5]). After *ca.* 1.5 l of eluent, the following fractions were obtained: A) 300 ml (17 mg, impurities; discarded), B) 300 ml (140 mg of pure '(+)-**1**-(−)-menthydrazone'), C) 250 ml (*ca.* 100 mg of a mixture of the diastereoisomeric hydrazones), and D) 600 ml (90 mg of pure '(−)-**1**-(−)-menthydrazone').

Hydrolysis of 'menthydrazones'. A mixture of '(+)-**1**-(−)-menthydrazone' (21.4 g, 61.4 mmol), acetic acid (112 ml), water (112 ml) and pyruvic acid (27.0 g) was heated under reflux for 2 h under argon (*cf.* [6]). The clear solution was cooled and slowly added (with cooling) to 10% aq. NaOH solution (1 liter). The alkaline mixture (2 phases) was extracted with hexane/ether 1:1 (5 times 200 ml). The organic extract was washed with aq. saturated $NaHCO_3$ solution (2 times 100 ml), dried (Na_2SO_4) and the solvents were distilled (60°/10 Torr). The residue (10.7 g) was distilled in a bulb-tube (150° (oven)/10 Torr) to give 8.4 g (90%) of optically pure (+)-**1** as an oil (containing *ca.* 2% of (−)-menthol). A sample was purified by GLC. (silicone 160°) and immediately stabilized by the addition of 0.5% of 2,6-di-*t*-butyl-4-methylphenol[6]). $[\alpha]_D^{20} = +93.3°$ ($c = 1.2$). By the same procedure (−)-**1** of $[\alpha]_D^{20} = -92.6°$ ($c = 0.9$) was regenerated in 89% yield from '(−)-**1**-(−)-menthydrazone'. – Spectral data of **1**, see [1].

2. Synthesis of (+)-dactyloxene-B (12) and -C (13) starting from optically pure (+)-(5*S*,6*R*)-2,5,6-trimethyl-1-cyclohexene-1-carbaldehyde (1; *Scheme 1*). Experimental details and spectral data for the optically active compounds **2**–**13** are the same as described for the racemates [1].

The specific rotations ($[\alpha]_D^{20}$) for the compounds (+)-**2** to (+)-**13** are listed below.

(+)-**2**: +84.2° ($c = 1.2$) (−)-**5**: −116.8° ($c = 1.0$) (+)-**8**: +132.8° ($c = 1.2$) (+)-**11**: +53.1° ($c = 1.1$)
(−)-**3**: −179.9° ($c = 0.9$) (+)-**6**: +83.0° ($c = 0.9$) (+)-**9**: +52.4° ($c = 1.3$) (+)-**12**: +111.6° ($c = 1.3$)
(−)-**4**: −109.2° ($c = 0.9$) (+)-**7**: +56.3° ($c = 1.4$) (+)-**10**: +79.8° ($c = 1.2$) (+)-**13**: +48.8° ($c = 1.3$)

The specific rotations of synthetic (+)-dactyloxene-B (**12**) and -C (**13**) are in agreement with those reported for the natural compounds (+110.2° ($c = 0.74$) for **12** and +45.8° ($c = 0.9$) for **13**) [3].

3. Oxidative degradation of (+)-1 *(Scheme 2). – Synthesis of (+)-(5S,6R)-2,5,6-Trimethyl-1-cyclohexenyl formate* (**14**). BF_3-etherate (0.405 ml, 3.29 mmol) was added at RT. to a stirred solution of optically pure (+)-**1** (500 mg, 3.29 mmol) in dichloromethane (5 ml). After 5 min a solution of commercial 40% peracetic acid (0.50 ml, 3.29 mmol) in dichloromethane (3 ml) was added within 5 min. The exothermic reaction was kept below *ca.* 30° by cooling with a water bath. After 30 min of stirring at RT., the solution was diluted with ether (30 ml), washed neutral with aq. $NaHCO_3$ and NaCl-solution, dried (Na_2SO_4) and concentrated. Distillation of the crude product in a bulb-tube (100° (oven)/0.01 Torr) gave 470 mg of an oil, which consisted of **15** (*ca.* 20%), **14** (*ca.* 70%), **1** (*ca.* 6%), and **16**[7])

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[6]) In the absence of an antioxidant, pure samples of aldehyde **1** in air underwent rapid autoxidation to give a mixture of the corresponding carboxylic acid and the formate **16**. These products probably arise from the *Baeyer-Villiger* oxidation of **1** by initially formed peracid.

[7]) *1,2-Epoxy*-c-*2*,t-*5*,c-*6-trimethylcyclohex*-r-*1-yl formate* (**16**) was obtained as the main product (>90%), when the above oxidation was carried out with an excess of peracetic acid (3 mol-equiv.) under identical conditions. A sample of the racemic compound was purified by prep. GLC. (silicone, 160°), m.p. 48.5–49.5°. – IR. ($CHCl_3$): 1725*s*, 1460*m*, 1385*m*, 1205*m*, 1180*m*, 1155*m*, 1120*m*. – ^{1}H-NMR. (360 MHz): 1.02*8* and 1.03*3* (2*d*, $J \approx 6$, 6 H, $H_3C-C(5)$ and $H_3C-C(6)$); 1.42 ($qa \times t \times d$, $J_1 \approx 6$, $J_2 \approx 11$, $J_3 \approx 4$, 1 H, $H_{ax}-C(5)$); 1.47 (*s*, 3 H, $H_3C-C(2)$); 1.52–1.78 (*m*, 3 H, $H_{ax'}-C(3)$ and $H_2C(4)$); 2.31 (*m*, 1 H, $H_{eq'}-C(3)$); 2.37 ($qa \times d$, $J_1 \approx 6$, $J_2 \approx 11$, 1 H, $H_{ax'}-C(6)$); 8.02 (*s*, 1 H, OCHO). – MS.: 184 (M^+, 23), 71 (100), 43 (65), 83 (60), 126 (52), 98 (37), 55 (36), 41 (33), 58 (26), 70 (22), 69 (20), 95 (16), 29 (15).

(*ca.* 4%) by GLC. (in order of elution on polar and apolar columns). A pure sample of the main product **14** was obtained by prep. GLC. *(Carbowax)* as an oil, $[\alpha]_D^{20} = +37.9°$ ($c = 0.58$). – IR. (neat): 1760 sh, 1735*s*, 1700*m*, 1465*m*, 1390*m*, 1135–1180*s* (several bands). – ^{1}H-NMR. (360 MHz): 1.017 and 1.019 (2*d*, $J \approx 6$, 6 H, $H_3C-C(5)$ and $H_3C-C(6)$); 1.36 (*m*, 1 H, $H_{ax}-C(4)$); 1.49 (*qa* × *d* × *d* × *d*, $J_1 = 6$, $J_2 = 9$, $J_3 = 7$, $J_4 = 3$, 1 H, $H_{ax}-C(5)$); 1.54 (*d*, $J \approx 1$, 3 H, $H_3C-C(2)$); 1.68 (*d* × *d* × *d* × *d*, $J_1 = 13$, $J_2 \approx J_3 \approx 5$, $J_4 = 3$, 1 H, $H_{eq}-C(4)$); 2.00 (*m*, 1 H, $H_{ax}-C(6)$); 2.03–2.15 (br., 2 H, $H_2C(3)$); 8.08 (*s*, 1 H, OCHO). – MS.: 168 (M^+, 56), 125 (100), 43 (82), 98 (74), 41 (66), 107 (58), 83 (56), 55 (56), 122 (44), 84 (44), 69 (44), 140 (43), 29 (30).

Equilibrium mixture of diastereoisomeric (3S)-2,3,6-trimethylcyclohexanones ((+)-**15**). The crude (+)-**14** (250 mg) was dissolved in a mixture of ethanol (2 ml) and 10% aq. NaOH-solution (1 ml), and stirred for 10 min at 80°. Ether (20 ml) was added and the organic phase was washed neutral with NaCl-solution, dried (Na_2SO_4) and the solvent distilled. The crude product, after distillation in a bulb tube (120° (oven)/10 Torr), gave 190 mg (77% based on **1**) of an oil which contained *ca.* 90% of the stereoisomeric mixture **15**. This mixture, after purification by prep. GLC. *(Carbowax)*, had $[\alpha]_D^{20} = +18°$ ($c = 2.3$) and was shown to contain **15a** (73%), **15b** (9%), **15c** (13%), and **15d** (5%) (order of increasing t_R) by analysis on a capillary glass column (50 m, *UCON*). The same, but racemic mixture was obtained by catalytic hydrogenation of 2,5,6-trimethyl-2-cyclohexen-1-one followed by base-catalyzed equilibration[8]).

Careful preparative GLC. *(Carbowax)* allowed the optically active main isomer *(+)-(2R,3S,6S)-2,3,6-trimethylcyclohexanone* (**15a**) to be separated in pure form, $[\alpha]_D^{20} = +16.8°$ ($c = 1.25$). – IR. (neat): 1715*s*. – ^{1}H-NMR. (360 MHz): 1.01 (*d*, $J = 6$, 3 H, $H_3C-C(6)$); 1.02 (*d*, $J = 6$, 3 H, $H_3C-C(2)$); 1.05 (*d*, $J = 6$, 3 H, $H_3C-C(3)$); 1.35 (*qa* × *d*, $J_1 = 12.5$, $J_2 = 3.5$, 1 H, $H_{ax}-C(5)$); 1.45 (*m*, 1 H, $H_{ax}-C(3)$); 1.53 (*m*, 1 H, $H_{ax}-C(4)$); 1.81 (*qa* × *d*, $J_1 \approx 3.5$, $J_2 \approx 12$, 1 H, $H_{eq}-C(4)$); 2.04 (*m*, 2 H, $H_{ax}-C(2)$ and $H_{eq}-C(5)$); 2.38 (*qa* × *d* × *d*, $J_1 = 6$, $J_2 = 12.5$, $J_3 \approx 1.5$, 1 H, $H_{ax}-C(6)$). – MS.: 140 (M^+, 60), 55 (100), 83 (99), 82 (96), 70 (76), 41 (76), 56 (62), 112 (46), 69 (37), 27 (37), 39 (35), 42 (32), 29 (32).

The other isomers **15b–d** were not isolated in pure form; however, the signals of the methyl groups and of the adjacent protons in the 360-MHz-^{1}H-NMR. of a mixture **15b/15c** (ratio *ca.* 3:8, isolated by prep. GLC. on *Carbowax*) allowed the relative configuration of these isomers to be assigned. **15b** (*r*-2,*t*-3,*t*-6-trimethylcyclohexanone): ^{1}H-NMR. signals at 1.02 (*d*, $J = 6$, $H_3C-C(3)$); 1.09 (*d*, $J \approx 6.5$, $H_3C-C(2)$); 1.12 (*d*, $J \approx 7$, $H_3C-C(6)$); 2.24 (*qa* × *d*, $J_1 = 6.5$, $J_2 = 8$, $H_{ax}-C(2)$); 2.57 (*qa* × *d* × *d*, $J_1 \approx 7$, $J_2 \approx 6$, $J_3 \approx 5$, $H_{eq}-C(6)$); the signal for $H_{ax}-C(3)$ is hidden. **15c** (*r*-2,*c*-3,*c*-6-trimethylcyclohexanone): ^{1}H-NMR. signals at 0.76 (*d*, $J \approx 7$, $H_3C-C(3)$); 0.97 (*d*, $J = 6.5$, $H_3C-C(2)$); 1.00 (*d*, $J = 6$, $H_3C-C(6)$); 2.31 (*m*, no coupling constants > 6 with adjacent ring protons, $H_{eq}-C(3)$); 2.35 (*qa* × *d* × *d*, $J_1 = 6$, $J_2 = 12$, $J_3 = 5.5$, $H_{ax}-C(6)$); 2.66 (*qa* × *d* × *d*, $J_1 = 6.5$, $J_2 = 4.5$, $J_3 \approx 1$, $H_{ax}-C(2)$).

When the above oxidative degradation was carried out with the enantiomeric aldehyde (−)-**1**, the specific rotations of the compounds **14** ($[\alpha]_D^{20} = -36.5°$ ($c = 1.0$)) and **15** ($[\alpha]_D^{20} = -17.2°$ ($c = 1.3$), equilibrium mixture of stereoisomers) had about the same absolute values as their enantiomers.

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[8]) We are indebted to Mr. *P. Fankhauser* for communicating this result and providing a reference sample of the racemic equilibrated mixture **15**.