Synthesis of (1*S*,2*R*,5*R*)-2-Ethyl-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane, the Aggregation Pheromone of Male Beech Bark Beetles, *Taphrorychus bicolor* (Col., Scol.)

Wittko Francke*[a], Frank Schröder[a], Ulrich Kohnle[b], and Matthias Simon[c]

Institut für Organische Chemie der Universität Hamburg[a],
Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany
Telefax: (internat.) +49(0)40/4123 3834
E-mail: fschroed@chemie.uni-hamburg.de

Forstzoologisches Institut Freiburg[b],
Bertoldstraße 17, D-79098 Freiburg, Germany

Zoologisches Institut der Universität Marburg[c],
D-35032 Marburg, Germany

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The absolute configuration of the new bicyclic acetal 2-ethyl-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**1**), identified as an aggregation pheromone of males of the beech bark beetle, *Taphrorychus bicolor*, was determined by unambiguous synthesis and NMR experiments. The syntheses of the racemates of both diastereomers and of optically pure samples are described. The natural product proved to show (1*S*,2*R*,5*R*) configuration.

Males of the beech bark beetle, *Taphrorychus bicolor*, release a sex-specific aggregation pheromone[1] which attracts both males and females. The compound was identified as 2-ethyl-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**1**)[2]. In this paper we present a detailed description of the synthesis and the elucidation of the absolute configuration of this new bicyclic acetal, which we name "bicolorin". The identification of bicolorin was based on its mass spectrometric and gas chromatographic properties and on a ^{1}H-NMR spectrum obtained from a sample of less than 1 μg isolated from the frass produced by boring beetles. Since neither the relative nor the absolute configuration of the natural product could be determined from these data, we started with a synthesis of the racemates of the two diastereomers (1*S**,2*R**,5*R**)-**1** and (1*S**, 2*S**,5*R**)-**1** (Scheme 1).

A Grignard reagent prepared from the protected bromoketone **3** was treated with propanal (**2**). The resulting alcohol was converted to the bromide **4**, and the corresponding Grignard reagent was treated with acetaldehyde to yield alcohol **5**, the oxidation of which with pyridinium dichromate and Wittig reaction gave alkene **6**. Epoxidation of **6** with *m*-chloroperbenzoic acid furnished a mixture of the epoxides **7** which could be separated by column chromatography. Treatment with aqueous hydrochloric acid finally produced the bicyclic acetals (1*S**,2*R**,5*R**)-**1** and (1*S**, 2*S**,5*R**)-**1**. The relative configuration of the two diastereomers was established by NMR experiments. The long-range coupling (^4J = 1.3 Hz) between 7-H_{exo} and 2-H observed for one of the diastereomers indicates an axial position of 2-H, corresponding to an equatorial position of the ethyl group at C-2, i.e. (1*S**,2*R**,5*R**) configuration. This assignment was corroborated by the observation of a positive NOE between 7-H_{endo} and the CH_2 protons of the ethyl side chain of this diastereomer. The other diastereomer of **1** shows a positive NOE between 7-H_{endo} and 2-H, indicating an axial position of the ethyl group, corresponding to a (1*S**,2*S**,5*R**) configuration. Comparison of the ^{1}H-NMR spectra and gas-chromatographic retention times of natural bicolorin and the two synthetic diastereomers proved the natural product to be (1*S*,2*R*,5*R*)-**1** or its enantiomer.

For determination of the absolute configuration of natural bicolorin, pure (1*S*,2*R*,5*R*)-**1** was prepared according to the strategy employed by Hosokawa el al. for the synthesis of (−)-frontalin[3] (Scheme 2). Sharpless epoxidation[4] of (2*E*)-2-methyl-2-penten-1-ol (**8**) by using diisopropyl D-(−)-tartrate furnished epoxy alcohol (2*R*,3*R*)-**9** of 92.3% *ee*, as determined by chiral gas chromatography[5]. Recrystallization of the 3,5-dinitrobenzoate of (2*R*,3*R*)-**9** and subsequent hydrolysis yielded (2*R*,3*R*)-**9** of 98.8% *ee*. Epoxy alcohol (2*R*,3*R*)-**9** was then treated with 3-butenylmagnesium bromide in the presence of copper iodide to give the diol (2*S*,3*R*)-**10**.

Unexpectedly, the structure of the compound prepared by Wacker oxidation[6] of **10** strongly depends on the solvent employed. The use of a mixture of DMF and water furnished (1*R*,4*S*,5*R*)-1,5-diethyl-4-methyl-2,7-dioxabicyclo[2.2.1]heptane [(1*R*,4*S*,5*R*)-**11**] as the main product and only minor amounts of the desired acetal (1*S*,2*R*,5*R*)-**1**. In contrast, in ethanol (1*S*,2*R*,5*R*)-**1** of more than 98% purity (GC) was obtained. Apparently, double bond migration in

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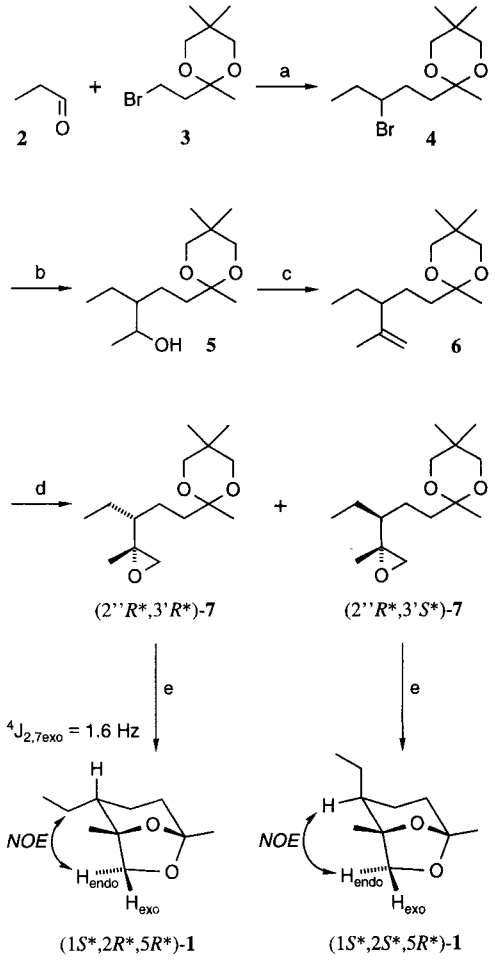
Scheme 1. a: 1. Mg/THF, 2. TsCl/pyridine, 3. LiBr/THF. – b: Mg, CH_3CHO/THF. – c: 1. PDC/CH_2Cl_2, 2. Ph_3PCH_3Br, *n*BuLi/THF. – d: 1. *m*-CPBA/CH_2Cl_2, 2. separation. – e: 8 N H_2SO_4



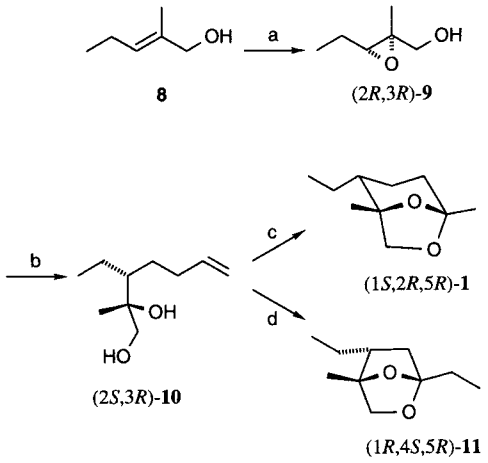
10 occurs more rapidly in DMF than in ethanol. The optical purity of (1*S*,2*R*,5*R*)-**1** was determined by chiral gas chromatography to be 98.6%. Coinjection of natural and synthetic samples showed natural bicolorin to be the (–)-isomer (1*S*,2*R*,5*R*)-**1** of at least 99.5% *ee*.

Field tests with optically pure samples proves (–)-bicolorin to be highly attractive to both sexes of *T. bicolor* (see Table 1), while pure acetophenone[2], another male specific compound, did not exhibit significant attractivity.

Experimental

NMR: Bruker DRX 500 (500 MHz for ^1H, 126 MHz for ^{13}C), Bruker AMX 400 (400 MHz for ^1H, 101 MHz for ^{13}C) and Bruker AC 250-P (250 MHz for ^1H, 62.9 MHz for ^{13}C), TMS as the internal standard. The multiplicity of the ^{13}C-NMR signals was determined by DEPT experiments. If multiplets in one-dimensional ^1H-NMR experiments were not completly resolved, $^1H,^1H$ coupling constants were derived from phase-sensitive ($^1H,^1H$)-COSY and *E*-COSY experiments. NOE data were taken from phase-sensitive 2D-NOESY spectra. In some cases, additional one-dimensional NOE experiments were performed. – IR: Perkin-Elmer FT-IR spectrometer 1720 X. – GC/MS: HP5890/VG70/250SE and Fisons GC8008/MD 800; helium served as carrier gas. – Gas chromatography: Fisons GC 8008 with flame ionization detector and split injector; hydrogen served as carrier gas; columns: 50-m FS-FFAP, 0.32 mm i.d. (Macherey & Nagel); 30 m DB5, 0.32 mm i.d. (J & W). – Chiral gas chromatography: 25-m fused silica column, 0.25 mm i.d., coated with a mixture of 50% OV1701 and 50% heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin[5]. – Column chromatography: flash chromatography on silica gel (Merck Kieselgel 60, 240–400 mesh). – Optical rotations: Perkin-Elmer 243.

Scheme 2. a: 1. diisopropyl D-(–)-tartrate, *t*BuOOH, $Ti(OiPr)_4$/CH_2Cl_2; 2. DNBCl, NEt_3; 3. aqueous KOH/MeOH/THF. – b: C_4H_7MgBr, CuI/THF. – c: $PdCl_2$, CuCl, O_2/EtOH. – d: $PdCl_2$, CuCl, O_2/DMF/H_2O



1-(2,5,5-Trimethyl-1,3-dioxan-2-yl)-3-pentanol: A solution of propanal (380 mg, 66.6 mmol) in THF (20 ml) was added to a stirred Grignard reagent prepared from **3** (1.5 g, 6.3 mmol) and Mg (250 mg, 10.4 mmol) in THF (25 ml) at –10 °C under argon. After the addition was complete, stirring was continued for 10 min at –10 °C. Subsequently, an ice-cold saturated NH_4Cl solution (50 ml) was added. The organic layer was separated and the aqueous layer extracted with three 50-ml portions of diethyl ether. The combined organic layers were washed with a saturated $NaHCO_3$ solution and brine, dried with Na_2SO_4 and concentrated in vacuo. Column chromatography of the residue (100 g of silica gel, 30–60% ethyl acetate in hexane v/v) gave 1.9 g (5.5 mmol, 87%) of 1-(2,5,5-trimethyl-1,3-dioxan-2-yl)-3-pentanol as a colorless oil. – ^1H NMR (C_6D_6, 400 MHz): δ = 0.60 (s, 3H), 0.94 (t, *J* = 7.4 Hz, 3H, 5-H), 0.95 (s, 3H), 1.31 (s, 3H), 1.38–1.48 (m, 2H, 4-H), 1.61–1.76 (m, 2H, 2-H), 1.82 (ddd, $J_{1a,1b}$ = 13.8, *J* = 9.9, 5.8 Hz, 1H, 1-H_a), 2.01 (ddd, $J_{1a,1b}$ = 13.8, *J* = 9.5, 6.0 Hz, 1H, 1-H_b), 2.15–2.20 (m, 1H, OH), 3.27–3.32 (m, 2H), 3.35–3.48 (m, 3H). – ^{13}C NMR (C_6D_6, 62.9 MHz): δ = 10.3 (q), 19.9 (q), 22.4 (q), 23.0 (q), 29.9 (s), 30.7 (t), 30.9 (t), 35.7 (t), 70.44 (t), 70.46 (t), 73.3 (d), 99.2 (s). – $C_{12}H_{24}O_3$: calcd. 216.1725; found 216.1743 (MS).

2-(3-Bromopentyl)-2,5,5-trimethyl-1,3-dioxane (**4**): *p*-Toluenesulfonyl chloride (950 mg, 5.0 mmol) was added to a stirred solution of 1-(2,5,5-trimethyl-1,3-dioxan-2-yl)-3-pentanol (1.04 g, 4.8 mmol) in pyridine (15 ml) at 0 °C. After 28 h at +4 °C, the reaction mixture was poured into a saturated $NaHCO_3$ solution (50 ml). The mixture was extracted with three 50-ml portions of diethyl ether, the combined extracts were washed with five 10-ml portions of a 0.5 N $CuSO_4$ solution, then with brine, dried with Na_2SO_4 and concentrated in vacuo. The residue was dissolved in dry THF (50 ml), LiBr (860 mg, 10 mmol) was added to the solution, and the mixture was refluxed for 1 h under argon. Subsequently, hexane (50 ml) was added, and the turbid solution was washed with water (twice

Table 1. Number of trap catches of *T. bicolor* by date in 1995; data A-E from Lahnberge (Marburg, Germany), data F, G from Schorndorf (Freiburg i.Br., Germany); A, B, C, F = traps baited with (−)-bicolorin of 98.6% *ee*, D, G = traps baited with acetophenone, E = control

	25.04.-01.05.	02.05.-08.05.	23.05.-29.05.	20.06.-26.06.	27.06.-03.07.	25.07.-31.07.	01.08.-07.08.	05.08.-06.08.	06.08.-07.08.	07.08.-11.08.	11.08.-12.08.	12.08.-13.08.	13.08.-18.08.
A	1682	9373	4863	4446	4264	2335	2230						
B	2126	8435	spoilt	1500	1097	982	196						
C	1228	6090	4995	1865	1422	1214	2283						
D	15	142	74	76	74	16	32						
E	0	0	2	0	0	0	0						
F								3546	1692	5151	3800	2582	6400
G								112	214	81	78	103	179

50 ml). The combined aqueous washings were extracted with diethyl ether (50 ml), and the combined organic solutions were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. Column chromatography of the residue (100 g of silica gel, 10% ethyl acetate in hexane) gave 1.21 g (4.33 mmol, 90%) of **4** as a colorless oil. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (s, 3H), 1.02 (s, 3H), 1.05 (t, *J* = 7.3 Hz, 3H, 5′-H), 1.38 (s, 3H), 1.72–2.06 (m, 6H), 3.42–3.47 (m, 2H), 3.53–3.58 (m, 2H), 3.98–4.05 (m, 1H, 3′-H). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 12.1 (q), 20.5 (q), 22.5 (q), 22.8 (q), 29.9 (s), 32.4 (t), 32.6 (t), 36.3 (t), 60.9 (d), 70.38 (t), 70.40 (t), 98.6 (s). – $C_{12}H_{23}{}^{79}BrO_2$: calcd. 278.0881; found 278.0887 (HRMS).

3-Ethyl-5-(2,5,5-trimethyl-1,3-dioxan-2-yl)-2-pentanol (**5**): The reaction was performed ad described above for the preparation of 1-(2,5,5-trimethyl-1,3-dioxan-2-yl)-3-pentanol, in this case starting from **4** (1.12 g, 4.01 mmol), Mg (200 mg, 8.3 mmol), and acetaldehyde (181 mg, 4.10 mmol). Column chromatography gave 0.86 g (3.52 mmol, 88%) of **5** as a colorless oil. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (s, 3/2H), 0.89 (s, 3/2H), 0.92 (t, *J* = 7.3 Hz, 3H), 1.03 (s, 3/2H), 1.04 (s, 3/2H), 1.155 (d, *J* = 5.5 Hz, 3/2H), 1.171 (d, *J* = 5.5 Hz, 3/2H), 1.19–1.78 (m, 7H, 1.37 (s, 3H), 3.41–3.45 (m, 2H), 3.53–3.59 (m, 2H), 3.74–3.88 (m, 1H). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 11.8 (q), 19.7 (q), 19.9 (q), 20.1 (q), 20.2 (q), 21.9 (t), 22.2 (t), 22.4 (t), 22.46 (q), 22.48 (q), 22.81 (q), 22.85 (q), 29.9 (s), 34.3 (t), 35.9 (t), 46.4 (d), 46.7 (d), 69.2 (d), 69.3 (d), 70.32 (t), 70.34 (t), 99.19 (s), 99.25 (s). – MS (EI, 70 eV), *m/z* (%): 244 (1) [M^+], 230 (4), 229 [$M^+ - CH_3$], 159 (3), 144 (4), 143 (4), 141 (8), 140 (8), 130 (6), 129 (67), 125 (12), 123 (9), 111 (10), 99 (4), 97 (10), 86 (9), 83 (14), 82 (6), 81 (4), 73 (6), 71 (26), 70 (8), 69 (39), 68 (5), 67 (8), 59 (7), 58 (15), 57 (10), 56 (18), 55 (45), 45 (20), 43 (100), 41 (34). – $C_{14}H_{28}O_3$: calcd. 244.2038; found 244.2043 (MS):

3-Ethyl-5-(2,5,5-trimethyl-1,3-dioxan-2-yl)-2-pentanone: Powdered molecular sieves (2.0 g, Merck, 4 Å) was added to a stirred solution of **5** (1.01 g, 4.13 mmol) in CH_2Cl_2 (15 ml) at 0 °C under argon. After stirring for 15 min, pyridinium dichromate (3.2 g, 8.5 mmol) was added. Stirring was continued for 2 h at 20 °C. Subsequently, the mixture was diluted with hexane (30 ml) and filtered through a short column (60 g silica gel, elution with 30% diethyl ether in hexane). Concentration gave 0.94 g (3.88 mmol, 94%) of 3-ethyl-5-(2,5,5-trimethyl-1,3-dioxan-2-yl)-2-pentanone as a colorless oil. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.855 (s, 3H), 0.855 (t, 7.4 Hz, 3H), 1.00 (s, 3H), 1.13 (s, 3H), 1.42–1.77 (m, 6H), 2.11 (s, 3H), 2.33–2.40 (m, 1H), 3.35–3.41 (m, 2H), 3.50–3.55 (m, 2H). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 11.7 (q), 20.1 (q), 22.5 (q), 22.8 (q), 24.60 (t), 24.68 (t), 28.7 (q), 29.9 (s), 35.9 (t), 54.6 (d), 70.3 (t, 2 C), 98.6 (s), 212.8 (s). – MS (EI, 70 eV), *m/z* (%): 242 (1) [M^+], 228 (4), 227 (20) [$M^+ - CH_3$], 157 (5), 141 (17), 139 (8), 130 (4), 129 (52), 113 (11), 99 (6), 87 (4), 86 (3), 72 (2), 71 (10), 70 (3), 69 (34), 58 (6), 57 (5), 56 (8), 55 (12), 43 (100), 41 (20). – $C_{14}H_{26}O_3$: calcd. 242.1882; found 242.1876 (HRMS).

2-(3-Ethyl-4-methyl-4-pentenyl)-2,5,5-trimethyl-1,3-dioxane (**6**): Methyltriphenylphosphonium iodide (1.62 g, 4.00 mmol) in THF (20 ml) was treated with *n*BuLi (4.0 mmol, 2.5 ml of a 1.6 N solution in hexane) at 0 °C under argon. After stirring for 30 min, the mixture was cooled to −30 °C, and a solution of 3-ethyl-5-(2,5,5-trimethyl-1,3-dioxan-2-yl)-2-pentanone (0.89 g, 3.67 mmol) in diethyl ether (10 ml) was added. The mixture was allowed to warm to 0 °C, was washed with water (50 ml) and brine (50 ml), dried with Na_2SO_4 and concentrated in vacuo. Column chromatography (60 g of silica gel, 5% ethyl acetate in hexane) of the residue gave 715 mg (2.98 mmol, 81%) of **6** as a colorless oil. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.81 (t, *J* = 7.4 Hz, 3H), 0.90 (s, 3H), 0.99 (s, 3H), 1.28–1.69 (m, 9H), 1.34 (s, 3H), 1.84–1.92 (m, 1H), 3.41–3.45 (m, 2H), 3.50–3.54 (m, 2H), 4.67–4.69 (m, 1H), 4.75–4.77 (m, 1H). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 12.9 (q), 17.9 (q), 20.7 (q), 22.6 (q), 22.7 (q), 26.3 (t), 26.7 (t), 30.0 (s), 35.6 (t), 49.5 (d), 70.35 (t), 70.36 (t), 99.1 (s), 111.8 (t), 147.2 (s). – MS (EI, 70 eV), *m/z* (%): 226 (1), 225 (6) [$M^+ - CH_3$], 211 (1), 157 (4), 141 (10), 139 (7), 137 (5), 136 (7), 130 (7), 129 (74), 121 (4), 107 (6), 97 (5), 96 (4), 95 (3), 83 (3), 81 (7), 71 (12), 69 (51), 68 (4), 67 (5), 58 (5), 57 (4), 56 (9), 55 (26), 43 (100), 41 (33). – $C_{15}H_{28}O_2$: calcd. 240.2089; found 240.2083 (HRMS).

(2″R,3′R*)-2,5,5-Trimethyl-2-[3′-(2″-methyloxiran-2″-yl)-pentyl]-1,3-dioxane* [(2″*R**,3′*R**)-**7**] *and (2″R*,3′S*)-2,5,5-Trimethyl-2-[3′-(2″-methyloxiran-2″-yl)pentyl]-1,3-dioxane* [(2″*R**,3′*S**)-**7**]: A solution of **6** (650 mg, 2.70 mmol) and *m*-chloroperbenzoic acid (3.5 mmol, 710 mg of a mixture containing 15% *m*-chlorobenzoic acid) in CH_2Cl_2 (20 ml) was stirred for 2 h at 0 °C. The solvent was removed in vacuo, and the residue was subjected to column chromatography (50 g of silica, 15% ethyl acetate in hexane) yielding 630 mg (2.46 mmol, 91%) of a mixture of (2″*R**,3′*R**)-**7** and (2″*R**,3′*S**)-**7** (approx. 1:1). This material was rechromatographed (200 g of silica gel, 20% diethyl ether in hexane) to give 40 mg of pure (2″*R**,3′*R*)-**7**, *de* > 98% (^{1}H NMR), and 25 mg of (2″*R**,3′*S**)-**7**, *de* = 80% (^{1}H NMR).

(2″*R**,3′*R**)-**7**: ^{1}H NMR (C_6D_6, 400 MHz): δ = 0.63 (s, 3H, 5-CH_3), 0.77 (t, *J* = 7.4 Hz, 3H, 5′-H), 0.88–0.95 (m, 1H, 3′-H), 0.94 (s, 3H, 5-CH_3), 1.06 (s, 3H, 2″-CH_3), 1.10–1.34 (m, 2H, 4′-H), 1.34 (s, 3H, 2-CH_3), 1.62–1.71 (m, 1H, 2′-H_a), 1.78–1.94 (m, 2H, 1′-H_a and 2′-H_b), 2.04–2.15 (m, 1H, 1′-H_b), 2.22 (d, *J* = 5.2 Hz, 1H, 3″-H_a), 2.26 (dd, *J* = 5.2, 0.7 Hz, 1H, 3″-H_b), 3.31–3.41 (m, 4H, 4,6-H). – ^{13}C NMR (C_6D_6, 101 MHz): δ = 12.4 (q), 16.5 (q), 20.3 (q), 22.4 (q), 22.9 (q), 25.6 (t), 25.7 (t), 29.8 (s), 37.0 (t), 47.4 (d), 53.4 (t), 58.2 (s), 70.3 (t, 2 C), 99.1 (s). – $C_{15}H_{28}O_3$: calcd. 256.2038; found 256.2027 (MS).

[(2″*R**,3′*S**)-7]: ^{1}H NMR (C_6D_6, 400 MHz): δ = 0.58 (s, 3H, 5-CH_3), 0.88–0.98 (m, 1H, 3′-H), 0.98 (s, 3H, 5-CH_3), 1.00 (t, *J* = 7.4 Hz, 3H, 5′-H), 1.07 (s, 3H, 2″-CH_3), 1.25–1.36 (m, 1H, 4′-H_a), 1.30 (s, 3H, 2-CH_3), 1.44–1.84 (m, 5H), 2.22 (d, *J* = 5.2 Hz, 1H, 3″-H), 2.28–2.30 (m, 1H, 3″-H), 3.25–3.29 (m, 2H, 4,6-H), 3.37–3.41 (m, 2H, 4,6-H). – ^{13}C NMR (C_6D_6, 101 MHz): δ = 12.4 (q), 16.7 (q), 19.5 (q), 22.3 (q), 23.0 (q), 25.2 (t), 25.8 (t), 29.9 (s), 38.0 (t), 47.4 (d), 53.5 (t), 58.3 (s), 70.4 (t, 2 C), 99.0 (s). – $C_{15}H_{28}O_3$: calcd. 256.2038; found 256.2032 (HRMS).

(1S,2S*,5R*)-2-Ethyl-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]-octane* [(1*S**,2*S**,5*R**)-**1**] *and (1S*,2R*,5R*)-2-Ethyl-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane* [(1*S**,2*R**,5*R**)-**1**, *rac*-Bicolorin]. A mixture of (2″*R**,3′*S**)-**7** (20 mg, 0.078 mmol, 80% *de*) in diethyl ether (5 ml) and 8 N H_2SO_4 (0.4 ml) was vigorously stirred for 3 h at 20°C. After the addition of a saturated $NaHCO_3$ solution (5 ml), the organic layer was separated, and the aqueous phase was extracted with two 10-ml portions of diethyl ether. The combined organic solutions were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. Column chromatography (5 g of silica, diethyl ether/pentane, 1:8) of the residue yielded 9.8 mg (0.062 mmol, 79%) of (1*S**,2*S**,5*R**)-**1** as a colorless oil, *de* = 76% (^{1}H NMR). – ^{1}H NMR (C_6D_6, 500 MHz): δ = 0.805 (t, 3H, 2-CH_2CH_3), 0.81–0.85 (m, 1H, 2-H), 1.09 (s, 3H, 1-CH_3), 1.37–1.46 (m, 1H, 2-$CH_aH_bCH_3$), 1.38–1.43 (m, 1H, 3-H_{eq} and 4-H_{eq}), 1.47–1.53 (m, 1H, 4-H_{ax}), 1.48–1.57 (m, 1H, 2″-$CH_aH_bCH_3$), 1.53 (s, 3H, 5-CH_3), 1.80–1.89 (m, 1H, 3-H_{ax}), 3.44 (d, 1H, 7-H_{exo}), 3.74 (d, 1H, 7-H_{endo}); $J_{2\text{-}CH_2CH_3,2\text{-}CH_2CH_3}$ = 7.4, $J_{2\text{-}CHaHbCH_3,2\text{-}CHaHbCH_3}$ = 13.8, $J_{2,2\text{-}CHaHbCH_3}$ = 10.2, $J_{2,2\text{-}CHaHbCH_3}$ = 3.6, $J_{2,3ax}$ = 5.6, $J_{3ax,3eq}$ = 13.7, $J_{3ax,4ax}$ = 12, $J_{2,7exo}$ < 0.5, $J_{7exo,7endo}$ = 6.8 Hz. – ^{13}C NMR (C_6D_6, 126 MHz): δ = 12.9 (q, 2-CH_2CH_3), 20.4 (t, 2-CH_2CH_3), 20.79 (t, C-3), 20.83 (t, q, 1-CH_3), 24.9 (q, 5-CH_3), 31.7 (t, C-4), 41.9 (d, C-2), 76.5 (t, C-7), 82.0 (s, C-1), 108.5 (s, C-5). – MS (EI, 70 eV), *m/z* (%): 171 (1), 170 (8) [M^+], 155 (1) [$M^+ - CH_3$], 142 (2), 141 (4), 140 (5), 129 (3), 128 (22), [$M^+ - C_2H_2O$], 125 (7), 115 (2), 114 (16) [$M^+ - C_4H_8$], 113 (3), 112 (2), 111 (7), 110 (4), 109 (2), 107 (1), 101 (2), 100 (20), 99 (19), 97 (3), 95 (5), 93 (1), 85 (8), 84 (9), 83 (7), 82 (79); 81 (8), 79 (3), 77 (1), 72 (9), 71 (19), 69 (11), 67 (33), 61 (2), 58 (3), 57 (5), 55 (16), 53 (6), 43 (100) [$C_2H_3O^+$], 41 (18). – $C_{10}H_{18}O_2$: calcd. 170.1307; found 170.1315 (HRMS).

In the same manner, a sample of (1*S**,2*R**,5*R**)-**1** was prepared by starting from (2″*R**,3′*R**)-**7** (40 mg, 0.16 mmol, 98% *de*). Yield: 21 mg (0.12 mmol, 79%) of (1*S**,2*R**,5*R**)-**1** as a colorless oil, *de* = 96% (^{1}H NMR). – ^{1}H NMR (C_6D_6, 500 MHz): δ = 0.55–0.65 (m, 1H, 2-$CH_aH_bCH_3$), 0.71 (t, *J* = 7.3 Hz, 3H, 2-$CH_aH_bCH_3$), 1.12 (s, 3H, 1-CH_3), 1.14–1.22 (m, 1H, 2-$CH_aH_bCH_3$), 1.21–1.30 (m, 1H, 3-H_{ax}), 1.51 (s, 3H, 5-CH_3), 1.51–1.65 (m, 3H, 3-H_{eq}, 4-H_{ax} and 4-H_{eq}), 3.26 (dd, 1H, 7-H_{exo}), 3.78 (d, 1H, 7-H_{endo}); $J_{7endo,7exo}$ = 7.1, $^4J_{7exo,2}$ = 1.3, $J_{2,CHaHb,2\text{-}CHaHb}$ = 13.5, $J_{2\text{-}CHaHb,2}$ = 10.3, $J_{2\text{-}CHaHb,2}$ = 4.0, $J_{2,3ax}$ = 12.2, $J_{2,3eq}$ = 4.5 Hz. – ^{13}C NMR (C_6H_6, 101 MHz): δ = 11.6 (q, 2-CH_2CH_3), 21.7 (q, 1-CH_3), 24.0 (t, 2-CH_2CH_3), 24.1 (t, C-3), 24.8 (q, 5-CH_3), 36.3 (t, C-4), 44.3 (d, C-2), 71.1 (t, C-7), 83.0 (s, C-1), 107.4 (s, C-5). – MS (EI, 70 eV), *m/z* (%): 171 (1), 170 (8) [M^+], 155 (1) [$M^+ - CH_3$], 142 (2), 141 (4), 140 (6), 129 (3), 128 (22) [$M^+ - C_2H_2O$], 125 (7), 115 (2), 114 (16) [$M^+ - C_4H_8$], 113 (3), 112 (2), 111 (7), 110 (4), 109 (2), 107 (1), 101 (2), 100 (19), 99 (20), 97 (3), 95 (5), 93 (1), 85 (8), 84 (9), 83 (7), 82 (81); 81 (9), 79 (3), 77 (2), 72 (9), 71 (19), 69 (11), 67 (34), 61 (2), 58 (3), 57 (5), 55 (16), 53 (6), 43 (100) [$C_2H_3O^+$], 41 (18). – $C_{10}H_{18}O_2$ (170.3): calcd. C 70.55, H 10.66; found C 70.69, H 10.58.

(2R,3R)-(3-Ethyl-2-methyloxiran-2-yl)methanol [(2*R*,3*R*)-**9**][4]: Diisopropyl D-(–)-tartrate (7.03 g, 30 mmol) was added to a stirred suspension of molecular sieves (8 g, 4 Å) in dry CH_2Cl_2 (400 ml) under argon. After stirring for 15 min at room temp., the mixture was cooled to –20°C, and 7.12 g (25 mmol) of Ti(O*i*Pr)$_4$ was added. Stirring was continued for 30 min at –20°C. Subsequently, 0.4 mol of *tert*-butyl hydroperoxide (62.5 ml of a 6.4 N solution in CH_2Cl_2) was added. After additional 10 min at –20°C, the mixture was cooled to –33°C, and a solution of freshly distilled (2*E*)-2-methyl-2-penten-1-ol (**8**) (25 g, 0.25 mol) in CH_2Cl_2 (100 ml) was added dropwise over a period of 30 min. The reaction mixture was stirred for 3 h at –33°C and subsequently poured into an ice-cold solution of tartaric acid (15 g, 0.1 mol) in water (200 ml). The resulting two-phase mixture was vigorously stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with four 50-ml portions of CH_2Cl_2. The combined organic organic phases were washed brine, dried with Na_2SO_4 and carefully concentrated in vacuo. The residue was chromatographed on silica gel (1000 g, hexane/diethyl ether, 1:1) yielding 21.3 g of crude **9**. Distillation gave 18.1 g (156 mmol, 62.4%) of pure **9** as a colorless oil; b.p. 72–74°C/13 hPa; $[\alpha]_D^{21}$ = +18.2 (*c* = 2.6 in $CHCl_3$). Determination of the optical purity of (+)-**9** by chiral gas chromatography. Conditions: 3 min at 60°C, then programmed at a rate of 3°C/min to 170°C; R_t = 7.14 min for (+)-**9** and R_t = 7.56 min for (–)-**9**. The *ee* of (+)-**9** was estimated to be 92.3%. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.04 (t, *J* = 7.4 Hz, 3H), 1.29 (s, 3H), 1.50–1.70 (m, 2H), 1.79 (dd, *J* = 8.4, 4.6 Hz, 1H, OH), 3.00 (t, *J* = 6.5 Hz, 1H, 3-H), 3.58 (dd, *J* = 12.2, 8.4 Hz, 1H, 1-H_a), 3.68 (dd, *J* = 12.2, 4.6 Hz, 1H, 1-H_b). – ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 10.5 (q), 14.1 (q), 21.54 (t, C-4), 61.0 (s, C-2), 61.3 (d, C-3), 65.5 (t, C-1). – MS (EI, 70 eV), *m/z* (%): 39 (14), 40 (11), 41 (24), 43 (68), 55 (11), 57 (58), 58 (100), 59 (49), 69 (5), 71 (6), 74 (8), 98 (2), 116 (0.3) [M^+]. – IR (neat): $\tilde{\nu}$ = 3445, 2971, 2878, 1461, 1385, 1041, 878 cm^{-1}. – $C_6H_{12}O_2$ (116.2): calcd. C 62.04, H 10.41; found C 61.62, H 10.58.

(2R,3R)-(3-Ethyl-2-methyloxiran-2-yl)methyl 3,5-Dinitrobenzoate: A solution of 3,5-dinitrobenzoyl chloride (15.8 g, 130 mmol) in CH_2Cl_2 (100 ml) was added dropwise over a period of 30 min to a stirred solution of **9** (15 g, 0.129 mol) and triethylamine (25 ml, 0.19 mol) in CH_2Cl_2 at –20°C under argon. After stirring for 30 min at –20°C, the mixture was slowly poured into an ice-cold saturated $NaHCO_3$ solution (300 ml). The organic layer was separated, and the aqueous layer was extracted with two 50-ml portions of CH_2Cl_2. The combined organic extracts were washed with a saturated $NaHCO_3$ solution and brine, dried with Na_2SO_4 and concentrated in vacuo. After filtration through a short column of silica (300 g, hexane/ethyl acetate, 1:1) the residue was recrystallized three times from diethyl ether/hexane. The *ee* of the material obtained was monitored by hydrolysis of small samples and subsequent determination of the *ee* of the alcohol **9** by chiral gas chromatography (see above). Yield: 16.0 g (51.6 mmol, 40%) of pale yellow crystals of 98.8% *ee*; $[\alpha]_D^{20}$ = +5.65 (*c* = 3.5 in $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.08 (t, *J* = 7.6 Hz, 3H), 1.44 (s, 3H), 1.55–1.74 (m, 2H), 2.95 (t, *J* = 6.4 Hz, 1H, 3-H), 4.29 (d, *J* = 11.7 Hz, 1H, 1-H_a), 4.59 (d, *J* = 11.7 Hz, 1H, 1-H_b), 9.17 (d, *J* = 2.2 Hz, 2H), 9.25 (t, *J* = 2.2 Hz, 1H). – ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 10.4 (q), 14.3 (q), 21.4 (t), 58.1 (s, C-2), 62.6 (d, C-3), 70.8 (t), 122.6 (d), 129.5 (d, 2 C), 133.5 (s), 148.8 (s, 2 C), 162.2 (s). – IR (KBr): $\tilde{\nu}$ = 3114, 2976, 2936, 1726, 1631, 1551, 1462, 1347, 1291, 1178, 1075, 977, 732, 721, 698 cm^{-1}. – $C_{13}H_{14}N_2O_7$ (310.3): calcd. C 50.16, H 4.86, N 9.00; found C 49.86, H 4.69, N 9.07.

(2R,3R)-(3-Ethyl-2-methyloxiran-2-yl)methanol [(2*R*,3*R*)-**9**]: A solution of (2*R*,3*R*)-(3-ethyl-2-methyloxiran-2-yl)methyl 3,5-dinitrobenzoate (15.6 g, 50 mmol) in THF (100 ml) was added dropwise within 30 min to a stirred mixture of methanol (100 ml) and 1 M aqueous KOH solution (55 ml) at 0°C. After stirring for 30

min at room temp., the mixture was extracted with four 100-ml portions of CH_2Cl_2. The combined extracts were washed with a saturated $NaHCO_3$ solution and brine, dried with Na_2SO_4 and concentrated in vacuo. Distillation of the residue gave 4.87 g (42.0 mmol, 84%) of **9** as a colorless oil; *ee* = 98.8% (GC); b.p. 74°C/14 hPa; $[\alpha]_D^{21} = +19.9$ (c = 2.5 in $CHCl_3$).

(2S,3R)-3-Ethyl-2-methyl-6-heptene-1,2-diol [(2*S*,3*R*)-**10**]: A Grignard reagent prepared from 4-bromo-1-butene (29.7 g, 220 mmol) in diethyl ether (200 ml) was added to a stirred suspension of CuI (1.9 g, 10 mmol) in dry THF (300 ml) at −20°C under argon. After 10 min of stirring, a solution of **9** (8.0 g, 69 mmol) in diethyl ether (50 ml) was added dropwise within 10 min. Stirring was continued for 5 h at −5°C to 0°C. The reaction mixture was then poured into a beaker containing an ice-cold mixture of a saturated NH_4Cl solution (200 ml) and concentrated aqueous ammonia (10 ml). The resulting mixture was stirred for 30 min. Subsequently, the organic layer was separated, and the aqueous layer was extracted with four 50-ml portions of ethyl acetate. The combined organic phases were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. Column chromatography of the residue (600 g silica gel; hexane/ethyl acetate, 4:3) yielded 10.4 g (60.4 mmol, 88%) of **10** as a colorless oil; $[\alpha]_D^{21} = -1.3$ (c = 3.7 in $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.98 (t, J = 7.5 Hz, 3H, 3-CH_2CH_3), 1.10 (s, 3H, 2-CH_3), 1.16–1.29 (m, 2H, 7-$CH_aH_bCH_3$ and 4-H_a), 1.36 (tt, $J_{3,3\text{-}CHaHbCH_3} = J_{3,4a}$ = 7.5, $J_{3,3\text{-}CHaHbCH_3} = J_{3,4b}$ = 3.7 Hz, 1H, 3-H), 1.46 (dddd, $J_{4a,4b}$ = 13.5, $J_{4b,5a}$ = 9.9, $J_{4b,5b}$ = 6.4, $J_{4b,3}$ = 3.7 Hz, 1H, H-4$_b$), 1.68 (ddq, $J_{3\text{-}CHaHbCH_3}$ = 13.7, $J_{3\text{-}CHaHbCH_3}$ = 7.5, $J_{3,3\text{-}CHaHbCH_3}$ = 3.7 Hz, 1H, 3-$CH_aH_bCH_3$), 2.00–2.21 (m, 3H, 5-H and OH), 2.42 (br. s, 1H, OH), 3.41 (d, $J_{1a,1b}$ = 10.9 Hz, 1H, 1-H_a), 3.56 (d, $J_{1b,1a}$ = 10.9 Hz, 1H, 1-H_b), 4.955 (ddt, $J_{7c,6}$ = 10.3, $J_{7c,7t}$ = 2.0, $J_{7c,5}$ = 1.1 Hz, 1H, 7-H_c), 5.015 (dq, $J_{7t,6}$ = 17.0, $J_{7t,7c} = J_{7t,5}$ = 2.0 Hz, 1H, 7-H_t), 5.80 (ddt, $J_{6,7t}$ = 17.0, $J_{6,7c}$ = 10.3, $J_{6,5}$ = 6.6 Hz, 1H, 6-H). – ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 13.9 (q), 20.4 (q), 22.6 (t), 22.9 (t), 33.3 (t), 46.1 (d, C-3), 68.5 (t, C-1), 75.9 (s, C-2), 114.7 (t, C-7), 139.0 (d, C-6). – IR (neat): $\tilde{\nu}$ = 3436, 2937, 1641, 1462, 1380, 1103, 1039, 999, 910 cm^{-1}. – MS (EI, 70 eV), *m/z* (%): 39 (11), 41 (21), 43 (100), 45 (7), 55 (24), 56 (7), 57 (41), 58 (4), 67 (4), 69 (5), 71 (9), 74 (7), 75 (67), 81 (4), 97 (2), 99 (2), 123 (3), 141 (11) [M^+ − CH_2OH], 174 (0.1) [M^+]. – $C_{10}H_{20}O_2$ (172.3): calcd. C 69.72, H 11.70; found C 69.28, H 11.89.

(1S,2R,5R)-2-Ethyl-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane [(−)-Bicolorin, (1*S*,2*R*,5*R*)-**1**] *and (1R,4S,5R)-1,5-Diethyl-4-methyl-2,7-dioxabicyclo[2.2.1]heptane* [(1*R*,4*S*,5*R*)-**11**][6]: A suspension of $PdCl_2$ (833 mg, 4.7 mmol) and CuCl (4.75 g, 48 mmol) in ethanol (96%, 80 ml) was vigorously stirred for 3 h at 50°C under oxygen. The greenish solution was cooled to 18°C, and a solution of **10** (4.00 g, 23.3 mmol) in ethanol (96%, 30 ml) was added dropwise within 20 min. After the addition was complete, stirring was continued for 10 min. The reaction mixture was poured into brine (200 ml), and the resulting mixture was extracted with two 100-ml portions of pentane. The combined extracts were dried with Na_2SO_4, concentrated in vacuo and filtered through a short column of silica gel (100 g, diethyl ether/pentane, 1:8). Distillation gave 3.2 g (18.8 mmol, 81%) of **1** as a colorless oil; b.p. 75°C/15 hPa; $[\alpha]_D^{20} = -71.1$ (c = 1.0 in $CHCl_3$). Determination of the optical purity of (−)-**1** by chiral gas chromatography; conditions: 5 min at 60°C, then programmed at a rate of 5°C/min to 170°C; R_t = 13.82 min for (−)-**1** and R_t = 14.07 min for (+)-**1**. The *ee* of (−)-**1** was estimated to be 98.6%.

Using DMF (5 ml) and water (0.8 ml) instead of ethanol, oxidation of **10** (100 mg, 0.58 mmol) with 21 mg (0.12 mmol) of $PdCl_2$ and 119 mg (1.2 mmol) of CuCl yielded 72 mg (0.42 mmol) of a 2:1 mixture (GC) of (1*R*,4*S*,5*R*)-**11** and (1*S*,2*R*,5*R*)-**1**. – (1*R*,4*S*,5*R*)-**11**: ^{1}H NMR (C_6D_6, 400 MHz): δ = 0.77 (t, 3H, 5-CH_2CH_3), 1.03–1.21 (m, 2H, 5-CH_2CH_3), 1.12 (t, 3H, 1-CH_2CH_3), 1.19 (s, 3H, 4-CH_3), 1.36 (dd, 1H, 6-H_{endo}), 1.53–1.65 (m, 1H, 5-H), 1.85 (t, 1H, 6-H_{exo}), 1.90–2.00 (m, 2H, 1-CH_2CH_3), 3.22 (dd, 1H, 3-H_{exo}), 3.75 (d, 1H, 3-H_{endo}); $J_{1\text{-}CH_2CH_3}$ = 7.6, $J_{5\text{-}CH_2CH_3}$ = 7.4, $J_{3exo,3endo}$ = 6.6, $^4J_{3exo,5}$ = 2.0, $J_{6endo,6exo}$ = 11.7, $J_{6exo,5}$ = 11.2, $J_{6endo,5}$ = 5.3 Hz. – ^{13}C NMR (C_6H_6, 101 MHz): δ = 8.9 (q), 13.7 (q), 16.7 (q), 24.0 (t), 26.6 (t), 42.2 (t), 48.3 (d, C-5), 70.5 (t, C-3), 86.1 (s, C-4), 110.7 (s, C-1). – MS (EI, 70 eV), *m/z* (%): 170 (2) [M^+], 155 (2) [M^+ − CH_3], 152 (11) [M^+ − H_2O], 142 (2), 141 (14), 140 (3), 139 (2), 137 (1), 125 (2), 123 (4), 115 (1), 114 (5), 113 (15), 112 (3), 111 (16), 109 (2), 99 (2), 97 (4), 96 (17), 95 (4), 85 (3), 83 (6), 81 (26), 75 (6), 67 (9), 58 (5), 57 (100), 55 (23), 43 (25), 41 (12). – $C_{10}H_{18}O_2$: calcd. 170.1307; found 170.1328 (MS).

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