

CHIRAL BUILDING UNITS FROM CARBOHYDRATES - XIII.

IDENTIFICATION OF THE ABSOLUTE CONFIGURATION OF endo-BREVICOMIN FROM
Dendroctonus frontalis
AND SYNTHESIS OF BOTH ENANTIOMERS FROM D-RIBOSE

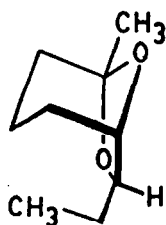
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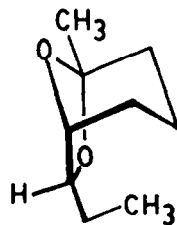
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Summary - The synthesis of both enantiomers of endo-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (endo-brevicomín, 12 and 12a) starting from D-ribose is described. Key intermediate is the open chain derivative 7, a chiral building unit easily available from carbohydrates. Complexation gas chromatography showed the natural pheromone of males of the southern pine beetle, Dendroctonus frontalis Zimm., to be (1R,5S,7S)- endo-brevicomín.

The exo- and endo-isomers of brevicomín, 7-ethyl-5-methyl-6,8-dioxabicyclo-[3.2.1]octane, were first identified from the frass of females of the western pine beetle, Dendroctonus brevicomís¹. The compounds were later found as components of the pheromone systems also of other bark beetle species. Natural exo-brevicomín, the female released aggregation pheromone of D. brevicomís was shown to have (1R,5S,7R)-configuration². Complexation gas chromatography³ of abdominal volatiles of males of the mountain pine beetle, D. ponderosae revealed the presence of (1R,5S,7R)-(+)-exo-brevicomín of high enantiomeric purity, while enantiomeric proportions of the additionally produced (1R,5S,7S)-(+)-endo-isomer range between 65-75%ee only, showing some variation in different populations⁴. Similarly, males of Dryocoetes confusus contain (+)-exo-brevicomín of 98%ee and (+)-endo-brevicomín of low optical purity⁴.



(1S,5R,7R)-(-)-12



(1R,5S,7S)-(+)-12a

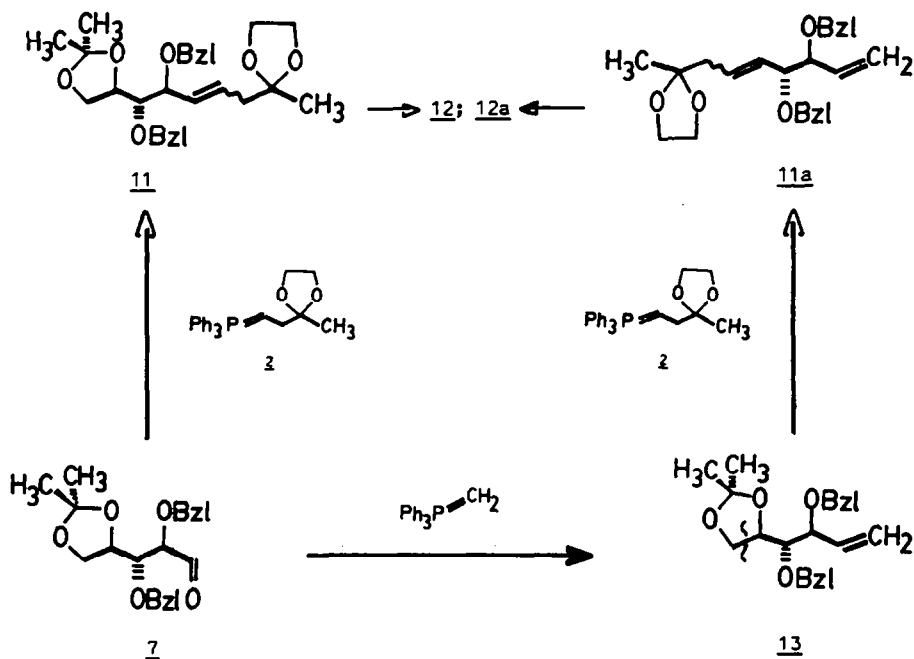
Already 15 years ago Vité and Renwick⁵ identified endo-brevicomín from males of the southern pine beetle, Dendroctonus frontalis, however, the absolute configuration of the compound remained undetermined. We now wish to present our results on the analysis of the enantiomeric composition of the natural pheromone and the synthesis of both of its enantiomers.

Analysis: Head space analyses of living beetles and of dissected hindguts as well as extracts of hindguts showed that D. frontalis males release endo- and exo-brevicomín in a ratio of 97:3; (1R,5S,7S)-(+)-endo-brevicomín is the naturally occurring enantiomer, present in an enantiomeric purity of about 97%.

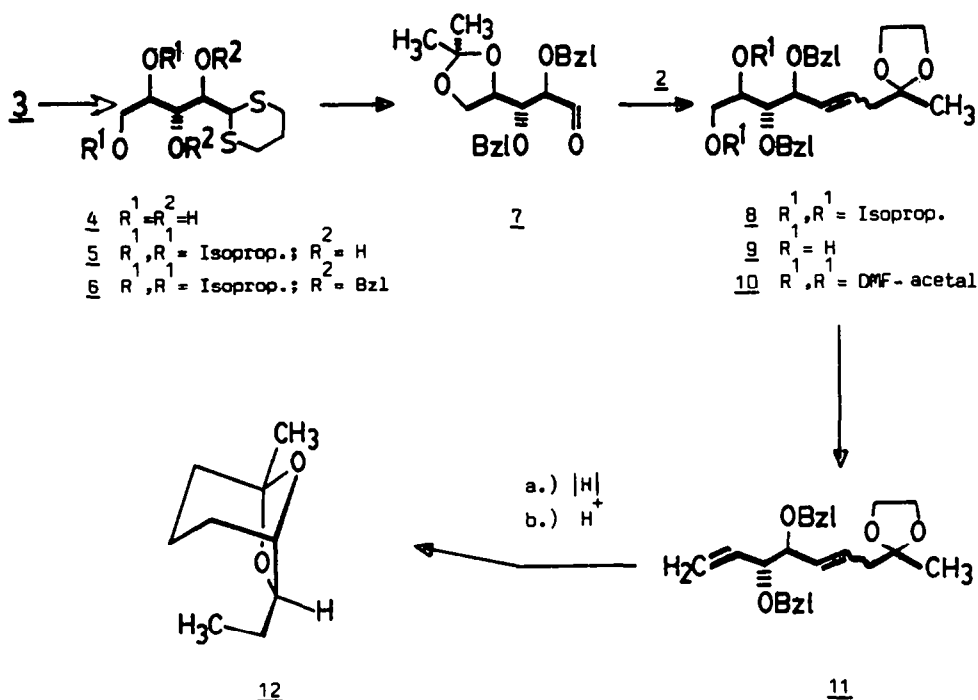
While in earlier field tests racemic endo-brevicomín elicited complex dosage-dependent reactions, recent investigations showed that the activity of the female produced aggregation pheromone, frontalin, is strongly enhanced by (1R,5S,7S)-(+)-endo-brevicomín, while its antipode inhibits response⁶. These results strongly indicate the high demand for optically pure enantiomers of endo-brevicomín for a successful pest management.

Synthesis: The subject of our study on the synthesis of (+)- and (-)-endo-brevicomín⁷⁻¹³ was the use of versatile chiral building units, readily available from carbohydrates.

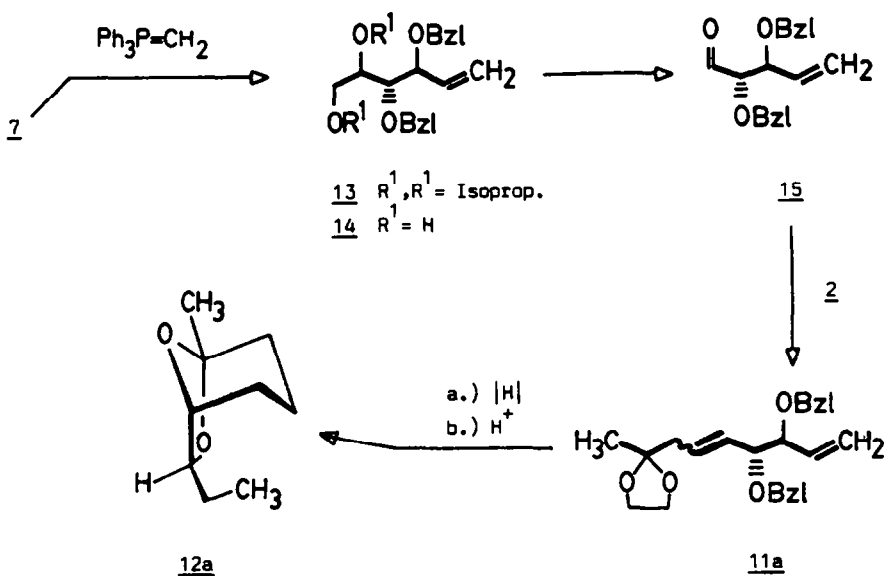
Retrosynthesis:



Retrosynthesis of the target molecule reveals the presence of an erythro configured diol, which upon intramolecular acetalization with a carbonyl function in the appropriate distance yields endo-brevicomín: enantiomerically pure erythro configured diols are available from numerous carbohydrates. A chiral diol segment, allowing chain elongation at either side with a carbonyl containing synthon, would be a particularly useful starting material, since only one chiral block would be necessary for the synthesis of both enantiomers. The open chain D-ribose derivative 2 fulfills this synthetical requirement. Compound 4 is easily available from D-ribose 3 by reaction with 1,3-propanedithiol under acidic conditions to form the open chain thioacetal 4. Selective isopropylideneation to the monoisopropylidene derivative 5 and benzylation of the remaining hydroxy groups with NaH/benzyl bromide in the presence of a catalytic amount of methyltriphenylphosphonium iodide yields the totally blocked open chain carbohydrate 6. Cleavage of the thioacetal function by treatment of 6 with methyl iodide/collidine in acetone/water gives the key component 7 in an excellent overall yield.



Reaction of 7 with an excess of the Wittig reagent 2 (a suitable C-4 synthon prepared from the corresponding bromide 1) at carefully controlled reaction conditions (12h, +5 °C in THF) completes the carbon chain to 8, in which the blocked diol segment shows D-configuration. Removal of the isopropylidene group, and transformation of the resulting unblocked diol 9 into the olefin 11 via the DMF-acetal 10 and subsequent hydrogenation of 11 (MeOH, 20 bar; 5% Pd/C) followed by acid treatment yields (1S,5R,7R)-(-)-endo-brevicomin 12.



Reaction of 7 with triphenylmethylenephosphorane yields the olefin 13 which may be transformed to (1R,5S,7S)-(+)-endo-brevicomin 12a: removal of the isopropylidene group gives the diol 14 which upon treatment with lead tetraacetate in acetonitrile at -40 °C generates aldehyde 15. Wittig reaction of 15 with reagent 2 already used in the synthesis of 12, now yields 11a, the enantiomer of 11. The following steps to (1R,5S,7S)-(+)-endo-brevicomin 12a are identical with the analogous sequence leading to 12.

EXPERIMENTAL

All melting points are uncorrected. NMR spectra were recorded at 270 MHz or 400 MHz on WH 270 and WH 400 (Bruker) with TMS as an internal standard. Optical rotations were measured on a Perkin Elmer Polarimeter 243. TLC analysis was carried out with Merck pre-coated plates. Kieselgel 60F₂₅₄. Column chromatography was carried out under pressure (max. 6 bar) through silica gel 60 (230-400 mesh, Woelm). Other apparatus and reagents used in this work are typified in the text.

Analysis: Male *D. frontalis*, collected from infested pine trees near Cleveland, Texas, were subjected to aeration for 20 h while walking in the test chamber of a CLSA-apparatus (Brechtbühler AG, CH-8952 Schlieren, Switzerland). Subsequently, the 5 mg charcoal filter of the CLSA was extracted with methylene chloride, the beetles were dissected and their hindguts removed. The extracts and the dissected hindguts were kept at dry ice temperature until analysis. Samples containing the hindguts of 10 or 200 male beetles were steam-distilled, and the head-space vapour or the CLSA-extract, respectively, was analysed (without further purification or chemical manipulation) by GC on a fused silica capillary column (30m x 0.25mm) coated with nickel(II)bis(3-heptafluorobutanoyl-(1R)-camphorate)¹³ in SE 54. The absolute configuration of the predominant enantiomer, i.e. (1R,5S,7S)-(+)-endo-brevicommin, was assigned via coinjection of a synthetic sample of known absolute configuration. The exo/endo-brevicommin ratio as well as the enantiomeric composition of endo-brevicommin was monitored by GC-(CI)MS/SIM (m/z 157, methane) on a Varian MAT 112 S-system.

D-Ribose trimethylene dithioacetal (4)

To a suspension of D-ribose **3** (15g, 0.1 mol) in chloroform (10 ml) 1,3-propanedithiol (10.6 ml, 0.098 mol) is added. The heavily stirred mixture is acidified with concentrated hydrochloric acid (10 ml). After 2-2.5 h (tlc toluene/ethanol 3:1) the reaction is quenched by dropwise addition of concentrated aqueous ammonia. The mixture is concentrated in vacuo and the residue is evaporated twice from toluene. To remove the salts, **3** is acetylated in pyridine (150 ml) with acetic anhydride (150 ml) (tlc toluene/ethanol 6:1). The mixture is concentrated in vacuo and the residue is evaporated twice from toluene. The crude residue is dissolved in chloroform and washed with diluted sulfuric acid and water. The organic layer is concentrated and the resulting sirup is purified by column chromatography (silica gel 3.5 kg, ether/petroleum ether 1:1). The acetates are removed by Zemplen deacetylation. yield: 21g (87%); $[\alpha]_D^{20}$ -1.3° (c 1.0 methanol), m.p. 94 °C. - C₈H₁₆O₄S₂ (240.34); calc. C, 39.98; H, 6.71; S, 26.68; found C, 38.90; H, 6.68, S, 26.62%.

4,5-D-Isopropylidene-D-ribose trimethylene dithioacetal (5)

At 0°C isopropenyl methyl ether (0.286 ml, 3.06 mmol = 1.6eq) is added to a solution of **4** (460mg, 1.91 mmol) in dry dimethylformamide (50 ml). After 5 min p-toluenesulfonic acid H₂O (92mg, dissolved in 0.25 ml DMF) is added. After 1 h (tlc ether) the reaction is stopped by adding concentrated ammonia. The solvent is removed in vacuo, the residue is evaporated twice from toluene. To remove the salts, the residue is dissolved in chloroform and filtered. Evaporation of the solvent yields crude product **5**, which can be purified by column chromatography (silica gel, ether/petroleum ether 3:2). yield: 477mg (89%); $[\alpha]_D^{20}$ +13.0° (c 1.0 methanol). - C₁₅H₂₄O₄S₂ (364.48 acetate); calc. C, 49.43; H, 6.64; S, 17.59; found C, 49.77; H, 6.82; S, 17.43 %. ¹H-NMR (CDCl₃/TMS_{int}): δ = 2.01, 2.10 (2s, 6 H, 2 OAc), 3.80 (dd, J_{4,5} = 6.4Hz, J_{5,5} = 8.6Hz, 1 H, 5-H), 3.99 (d, J_{1,2} = 10.6Hz, 1 H, 1-H), 4.09 (dd, J_{4,5} = 6.0Hz, 1 H, 5-H), 4.40 (ddd, J_{3,4} = 7.5Hz, 1 H, 4-H), 5.67 (dd, J_{2,3} = 2.2Hz, 1 H, 3-H), 5.78 ppm (dd, 1 H, 2-H).

2,3-Di-O-benzyl-4,5-D-isopropylidene-D-ribose trimethylene dithioacetal (6)

To a solution of **5** (280 mg, 1 mmol) in THF (4 ml) under N₂, NaH (72 mg, 3 mmol) and methyl triphenylphosphonium iodide (40 mg, 0.1 mmol) is added. After 2 h of stirring at room temperature benzyl bromide (376 mg, 2.2 mmol) is added. The mixture is stirred for 12 h. After adding a trace of water the solution is filtrated and concentrated. The crude residue is chromatographed on silica gel (2.5 bar pressure) using t-butyl-methyl ether/petroleum ether b.p. 50-70 °C (1:10, containing 1% triethylamine) as the eluent. yield: 438 mg (95%) $[\alpha]_D^{20}$ +26.0° (c 1.4 methanol), m.p. 86-91 °C. - C₂₅H₃₂O₄S₂ (460.7); calc. C, 65.18; H, 7.00; S, 13.93; found C, 65.18; H, 7.09; S, 13.94 %. ¹H-NMR (CDCl₃/TMS_{int}): δ = 1.33 and 1.42 (s, 6 H, isoprop.); 2.15-1.79 (m, 2 H, -S-CH₂-CH₂-CH₂-S-); 2.92-2.64 (m, 4 H, -S-CH₂-CH₂-CH₂-S-); 3.68 (dd, 1 H, 2-H, J_{2,3} = 4.8Hz); 3.80 (dd, 1 H, 5-H, J_{4,5} = 6.7Hz, J_{5,5} = 8.0Hz); 3.95 (dd, 1 H, 5-H, J_{4,5} = 7.2Hz); 4.09 (dd, 1 H, 3-H, J_{3,4} = 3.8Hz); 4.40 (ddd, 1 H, 4-H); 4.42 (d, 1 H, 1-H, J_{1,2} = 5.7Hz); 4.92-4.63 ppm (m, 4 H, -CH₂-Ph); 7.5-7.1 (m, 10 H, arom. prot.).

2,3-Di-O-benzyl-4,5-D-isopropylidene-D-ribose (7)

To a solution of **6** (460 mg, 1 mmol) in acetone/water (10 ml, 4:1 v/v) s-collidine (882 mg, 7 mmol) and methyl iodide (0.5 ml) is added. The mixture is warmed to 40°C for approx. 4 h. After removal of the solvents the residue is dissolved in ether and washed with water. The organic layer is dried and concentrated; the residue is evaporated in high vacuum. The oily residue is

chromatographed on silica gel (2.5 bar pressure) using *t*-butyl-methyl ether/petroleum ether (1:5) as the eluent. yield: 337 mg (91%); $[\alpha]_D^{20} +66.3^\circ$ (c 0.72 methanol). - $C_{22}H_{26}O_5$ (370.5); calc. C, 71.33; H, 7.07; found C, 71.36; H, 7.07%. ^1H-NMR ($CDCl_3/TMS_{int}$): δ = 1.30 and 1.31 (s, 6 H, isoprop.); 3.71 (dd, 1 H, 3-H, $J_{2,3} = 1.8Hz$, $J_{3,4} = 8.4Hz$); 3.86 (dd, 1 H, 5'-H, $J_{4,5'} = 4.2Hz$, $J_{5,5'} = 8.8Hz$); 4.07 (dd, 1 H, 5-H, $J_{4,5} = 6.4Hz$); 4.11 (dd, 1 H, 2-H, $J_{1,2} = 1.2Hz$); 4.34 (ddd, 1 H, 4-H); 4.54 (q, 2 H, $-CH_2-Ph$); 4.78 (q, 2 H, $-CH_2-Ph$); 7.5-7.2 (m, 10 H, arom. prot.); 9.70 ppm (d, 1 H, 1-H).

6,7-Di-O-benzyl-8,9-O-isopropylidene-1,3,4,5-tetra-deoxy-D-ribo-non-4-eno-2-ulose ethylene acetal (8)

a) Refluxing of equimolar amounts of the bromoacetal¹⁴ 1 and triphenylphosphane in 1-propanol yields 50-55% of the phosphonium bromide, m.p. 155-157 °C from chloroform/ethyl acetate. If the protecting group is partially lost during the reaction (controlled by ^1H-NMR after removal of the solvent) it is easily regained by azotropic reacetalization of the crude product.

b) The protected aldehyde, 7, (358 mg, 1mmol) is added to a solution of the Wittig reagent 2 (generated from 1.37 g, 3mmol of the respective triphenylphosphonium bromide with *n*-butyllithium in hexane at -20 to -10 °C) in THF (7.5ml) at -20 °C under N_2 . The reaction mixture is stored at +5 °C for 12 h and after the addition of acetone (1 ml) it is concentrated in vacuo. Most of the salts are removed by crystallization from ether at -5 - 0° C and filtration over celite. After evaporation of the solvent, the oily residue is chromatographed on a silica gel column (2.5 bar pressure) using *t*-butyl-methyl ether/petroleum ether (1:4) as the eluent. yield: 310 mg (66%); $[\alpha]_D^{20} +54.3^\circ$ (c 1,2 methanol). - $C_{28}H_{36}O_6$ (468.6); calc. C, 71.77; H, 7.74; found C, 71.33; H, 7.73%. ^1H-NMR ($CDCl_3/TMS_{int}$): δ = 1.30 (s, 3 H, $-CH_3$); 1.38 and 1.32 (6 H, isoprop.); 2.49-2.26 (m, 2 H, 3- CH_2); 4.14-3.69 (m, 8 H); 4.44-4.36 (m, 1 H); 4.51 (q, 2 H, $-CH_2-Ph$); 4.77 (q, 2 H, $-CH_2-Ph$); 5.89-5.60 (m, 2 H, olef. prot.); 7.44-7.21ppm (m, 10 H, arom. prot.).

6,7-Di-O-benzyl-1,3,4,5-tetra-deoxy-D-ribo-non-4-eno-2-ulose ethylene acetal (9)

A solution of 8 (470 mg, 1 mmol) in acetic acid (80%, 2.5 ml containing 1% trifluoroacetic acid) is stored for 1 h at room temperature. The solvent is evaporated in vacuo by co-distillation with toluene. For analytical purpose a purification is necessary. yield: 411 mg (96%); $[\alpha]_D^{20} +3.2^\circ$ (c 0.95 methanol). - $C_{25}H_{32}O_6$ (428.6); calc. C, 70.07; H, 7.53; found C, 69.82; H, 7.40; ^1H-NMR ($CDCl_3/TMS_{int}$) Diacetate: δ = 1.29 (s, 3 H, $-CH_3$); 2.00 (s, 6 H, acetate); 2.48-2.21 (m, 2 H, $-CH_2-$); 3.77 (dd, 1 H, 7-H, $J_{6,7} = 5.0$, $J_{7,8} = 5.0Hz$); 3.97-3.82 (m, 4 H, $-OCH_2-CH_2-O-$); 4.25 (dd, 1 H, 6-H, $J_{5,6} = 9.4$, $J_{4,6} = 0.6Hz$); 4.48 (dd, 1 H, 9-H, $J_{8,9} = 2.6Hz$); 4.51 (q, 2 H, $-CH_2-Ph$); 4.66 (q, 2 H, $-CH_2-Ph$); 5.25 (ddd, 1 H, 8-H); 5.62 (m, 1 H, 5-H); 5.86 (m, 1 H, 4-H); 7.4-7.2 ppm (m, 10 H, arom. prot.).

6,7-Di-O-benzyl-1,3,4,5,8,9-hexa-deoxy-D-erythro-non-4,8-dieno-2-ulose ethylene acetal (11)

a) Preparation of the *N,N*-dimethylformamide acetal 10: According to the procedure of Hanessian¹⁵ to a solution of 9 (429 mg, 1 mmol) in dichloromethane (4 ml) *N,N*-dimethylformamide di-methyl acetal (1.4 ml, approx. 10 mmol) is added. After 1 h the reagent and the solvent is evaporated.

b) The crude 10 is dissolved in 10 ml toluene and methyl iodide (6:4) and stored at room temperature for 1-2 h. The mixture is subsequently refluxed for approx. 30 min. After removal of the main part of the solvents in vacuo the crude material is directly chromatographed on silica gel (2.5 bar pressure, ether/petroleum ether 1:2, containing 1% triethylamine). yield: 120-240 mg (30-60%) (the reaction showed no const. yields); $[\alpha]_D^{20} +8.5^\circ$ (c 1.7 methanol). - $C_{25}H_{28}O_4$ (392.5); calc C, 76.50; H, 7.19; found C, 76.43; H, 7.27%. ^1H-NMR ($CDCl_3/TMS_{int}$): δ = 1.30 (s, 3 H, $-CH_3$); 2.47- 2.21 (m, 2 H, $-CH_2-$); 4.0 - 3.8 (m, 5 H, $-CH_2-CH_2-, -CH-OR-$); 4.24 (o, 1 H); 4.46 (q, 2 H, $-CH_2-Ph$); 4.47 (q, 2 H, $-CH_2-Ph$); 5.36-5.20 (m, 2 H, olef. prot.); 5.52-5.51 (m, 1 H, olef. prot.); 5.98-5.71 (m, 2 H, olef. prot.); 7.4-7.2 ppm (m, 10 H, arom. prot.).

(1S,5R,7R)-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane, (-)-endo-brevicomine (12)

A solution of 11 (392 mg, 1mmol) in methanol (5 ml) is hydrogenated (H_2 , 5% Pd/C, 20 bar). After removal of the catalyst by filtration, the solution is acidified with *p*-toluenesulfonic acid H_2O (50 mg), stirred for 1 h and subsequently extracted with pentane. To remove traces of water and acid, the pentane extract is dried over magnesium sulfate containing some potassium carbonate. After filtration, the pentane is evaporated under normal pressure; subsequent Kugelrohr distillation (bath: 100 °C) gives a colorless liquid. A gas chromatogramm of the crude distillate (50m glas capillary coated with WC 11, 100 °C) showed the presence of 5% of *exo*-brevicomine and traces of higher boiling impurities. The product was further purified by preparative gas chromatography on SE as a stationary phase, yielding 50 mg (32%) of pure 12. Gas chromatographic and mass spectroscopic properties of the final product, as well as its ^1H-NMR spectrum, proved to be identical with those of an authentic racemic sample. Both enantiomers of *exo*- and *endo*-brevicomine may be simultaneously separated on nickel(II)bis(3-heptafluorobutanoyl-(1R,2S)-pinen-4-onate)¹⁶; the order of elution is (+)-*exo*-, (-)-*exo*-, (+)-*endo*- and (-)-*endo*-brevicomine. It could be shown that the *exo*-brevicomine formed during the reaction sequence was almost racemic, while *endo*-brevicomine 12

proved to be 98% enantiomerically pure. The purified **12** showed a rotation value of $[\alpha]_D^{22} -79.5^\circ$ (c 1.17 Et₂O). -

5,6-Dideoxy-3,4-di-O-benzyl-1,2-O-isopropylidene-L-ribo-hex-5-enitol (13)

13 is synthesized according to the procedure described for compound **8**, now using triphenylmethylenephosphorane as the reagent. yield: 313 mg (85%); $[\alpha]_D^{20} +59.2^\circ$ (c 1.2 methanol). - C₂₃H₂₈O₄ (368.5); calc. C, 74.97; H, 7.66; found C, 75.03; H, 7.72%. ¹H-NMR (CDCl₃/TMS_{int}): δ = 1.33 and 1.38 (s, 6 H, isoprop.); 3.74 (q, 1 H); 4.18-3.88 (m, 4 H); 4.53 (q, 2 H, -CH₂-Ph); 4.77 (q, 2 H, -CH₂-Ph); 5.41-5.28 (m, 2 H, olef. prot.); 5.92 (o, 2 H, olef. prot.); 7.4-7.2 ppm (m, 10 H, arom. prot.).

5,6-Dideoxy-3,4-di-O-benzyl-L-ribo-hex-5-enitol (14)

A solution of **13** (368 mg, 1 mmol) in acetic acid/trifluoroacetic acid/water 15:1:4 (4 ml) is stored for 12 h at room temperature. The solvent is in vacuo and by co-distillation with toluene. For analytical purpose a purification is necessary. yield: 320 mg (97%); $[\alpha]_D^{20} +44.5^\circ$ (c 1.2 methanol). - C₂₀H₂₄O₄ (328.4); calc. C, 73.15; H, 7.37; found C, 73.15; H, 7.34%. ¹H-NMR (CDCl₃/TMS_{int}): δ = 3.64 (q, 1 H); 3.74 (d, 2 H); 3.78 (m, 1 H); 4.09 (q, 1 H); 4.54 (q, 2 H, -CH₂-Ph); 4.66 (q, 2 H, -CH₂-Ph); 5.50-5.37 (m, 2 H, olef. prot.); 5.93 (o, 1 H, olef. prot.); 7.4-7.2 ppm (m, 10 H, arom. prot.).

6,7-Di-O-benzyl-1,3,4,5,8,9-hexaideoxy-L-erythro-non-4,8-dieno-2-ulose (11a)

a) 2,3-Di-O-benzyl-L-erythro-pent-4-enoose (15)

To a solution of **14** (328 mg, 1 mmol) in acetonitrile (8 ml) sodium acetate (1 g, 12 mmol) and lead tetraacetate (1 g, 2.2 mmol) is added at -40°C. The mixture is stirred for ca 20 min and then diluted with ether/toluene 1:1 (100 ml). After the addition of charcoal (5 g) the mixture is pressed through a short column, filled with silica gel. The column is washed with ether. Removal of the solvents in vacuo and drying in high vacuum yields an unstable oil which is directly used for the next step.

b) Aldehyde **15** is treated as described for **8**. Column chromatography is carried out with ether - petroleum ether 1:10, yields 161 mg (41%); $[\alpha]_D^{20} -8.3^\circ$ (c 1.6 methanol). - C₂₅H₂₈O₄ (392.5); calc. C, 76.50; H, 7.19; found C, 76.32; H, 7.04%.

(1R,5S,7S)-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane, (+)-endo-brevicomine (12a)

The final steps of the synthesis from **11a** to **12a** were carried out according to the procedure described above. With regards to the gas chromatographic and spectroscopic data the compound proved to be identical with the enantiomer described above. Gas chromatographic separation of the enantiomers revealed the presence of 1% of the antipode: $[\alpha]_D^{22} +79.8^\circ$ (c 1.05 Et₂O). - The rotation values of our products are in accord with those reported in the literature⁷⁻¹²; they do not, however, corroborate the high values reported by Sato *et al.*¹³.

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