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SYNTHESIS OF BREVICOMIN, PRINCIPAL SEX ATTRACTANT IN THE FRASS OF THE FEMALE WESTERN PINE BEETLE

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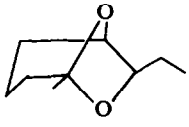
Abstract—The sex attractant, brevicomin [*exo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (**1**)] from the frass of the western pine beetle, *Dendroctonus brevicomis*, was synthesized through acid catalyzed hydrolysis and cyclization of the *cis*-epoxide (**8**). The *endo*-isomer (**2**), also present in frass but inactive, was formed on cyclization of the *trans*-epoxide (**9**).

BREVICOMIN has been identified as the principal component of the sex attractant produced in the frass of the female western pine beetle, *Dendroctonus brevicomis*, boring in ponderosa pine.[1]

Brevicomin is *exo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (**1**). The corresponding *endo* isomer (**2**) was also identified, but was inactive. This ring system is an unusual structure for a natural product; it is represented in the literature only by several anhydro sugars. Very recently, Naya[2] reported the isolation from hop oil of the analogous 7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane.

The synthetic sequence described here was designed to confirm the assigned structures and to furnish material for laboratory and field bioassays.



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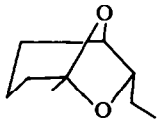

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The following sequence yielded both isomeric bicyclic ketals **1** and **2**.

6-Bromohexane-2-one (**3**) was prepared[3] from 1,3-dibromopropane and ethyl acetoacetate, and by the addition of HBr to allylacetone. The carbonyl group of **3** was blocked by conversion to the ethylene ketal (**4**), which on treatment with triphenylphosphine gave the phosphonium salt (**5**). A Wittig condensation with phenyllithium and propionaldehyde yielded a mixture of *cis*- and *trans*-non-6-en-2-one ethylene ketal (**6** and **7** respectively), which on treatment with *m*-chloroperbenzoic acid yielded a mixture of *cis*- and *trans*-6,7-epoxynonan-2-one ethylene ketal (**8** and **9** respectively).

Whereas the *cis*- and *trans*-olefins (**6** and **7**) showed the same retention time on a Carbowax 20 M and on an Apiezon column, the *cis*- and *trans*-epoxides (**8** and **9**) were readily separated on a Carbowax 20 M column. The NMR relative shift positions

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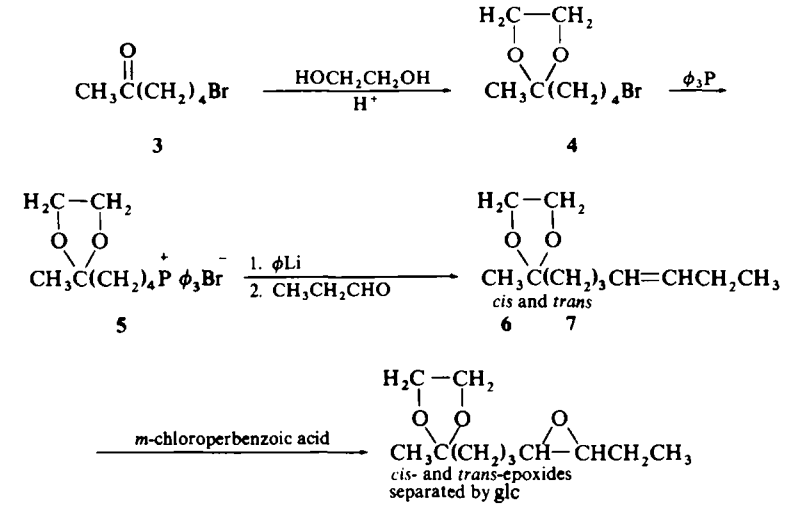
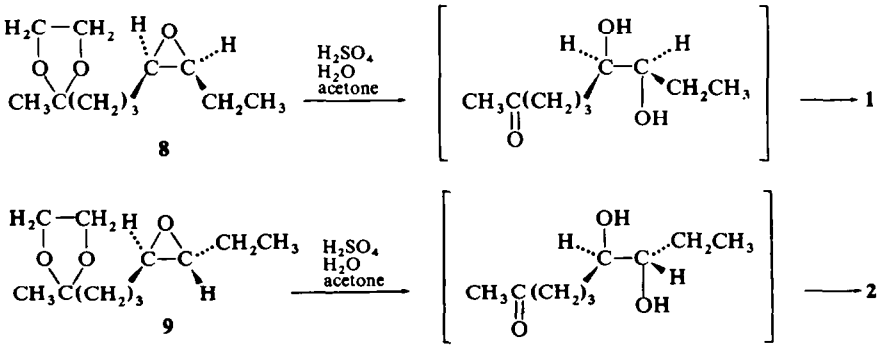
of the epoxide protons determined the configuration assigned[4] (*cis* protons multiplet at $\tau \sim 7{\cdot}28$, *trans* protons at $\tau \sim 7{\cdot}50$). The *cis*-epoxide on acid hydrolysis led directly to the *exo*-bicyclic ketal, and the *trans*-epoxide to the *endo*-product.

The geometry of the bicyclic compounds isolated had been tentatively assigned because additional splitting of the 1- and 7-protons was predicted and observed for the *endo*-isomer. In the *exo*-isomer, the 1- and 7-protons are effectively decoupled from each other because they form approximately a 90° angle.

In the following synthesis, *cis*-non-6-en-2-one ethylene ketal (**6**) was prepared by catalytic hydrogenation[5] of non-6-yn-2-one ethylene ketal (**10**), which was prepared from 1-butyne and 5-bromopentan-2-one ethylene ketal (**11**) derived from 2-acetylbutyrolactone (**12**).[6]

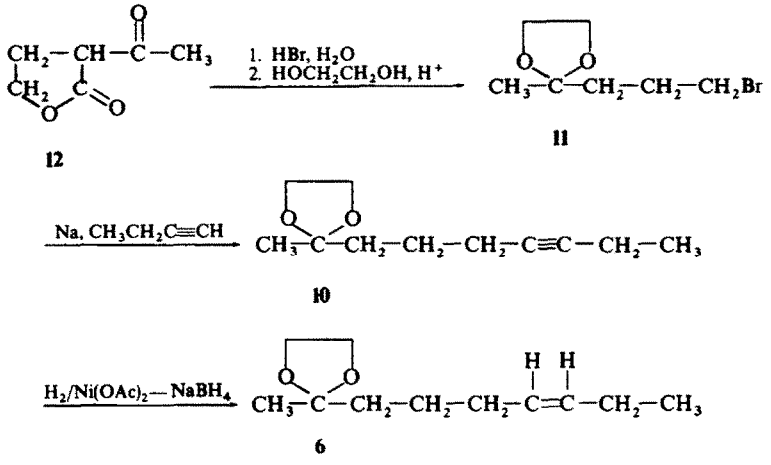




Professor H. H. Wasserman and E. H. Barber,* in a study of [3.2.1] ring systems, have independently synthesized brevicomin by epoxidation of *cis*-non-6-en-2-one followed by cyclization. Spectra and biological activity of this compound and ours are in complete agreement.

* H. H. Wasserman, private communication. We are indebted to Dr. Wasserman for a sample of his product for comparison.

Note added in proof: H. H. Wasserman and E. H. Barber, *J. Am. Chem. Soc.* **91**, 3674 (1969).



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EXPERIMENTAL

6-Bromohexan-2-one ethylene ketal (**4**). A. To a cooled, stirred soln of 5·47 g (0·238 g atoms) of Na in 80 ml EtOH was added sequentially 32·5 g (0·25 mole) ethyl acetoacetate and 47 g (0·232 mole) 1,3-dibromopropane. On cautious heating, an exothermic reaction started (at about 60°) with precipitation of NaBr. When the reaction moderated, the mixture was refluxed for 1 hr. The cooled soln was filtered, and the solvent was removed *in vacuo*. An ether soln of the residue was washed with water, dried ($MgSO_4$), and concentrated. The oily residue, cooled in an ice bath, was treated with 75 ml 48% HBr. On cautious heating, gas evolution started at about 25°. The mixture was slowly heated, held at 60° for 30 min, cooled, and poured onto ice. The oil that separated was extracted with ether; the ethereal extract was washed free of acid with water, dried ($MgSO_4$), concentrated, and distilled at 20 mm giving 20 g 1,3-dibromopropane (66–67°) and 9·6 g (40% based on recovered 1,3-dibromopropane) of 3 (105–106°); IR (film, μ) 5·83 (C=O); NMR (neat, 60 MHz, τ), 6·45 (3H, distorted t, $BrCH_2$—), 7·52 (3H, distorted t, —CH_2C=O), 7·89 (3H, s, CH_3C=O), ~8·2 (4H, m, —CH_2CH_2—).

A soln of 3·93 g (0·022 mole) of **3**, 3·00 g (0·048 mole) ethylene glycol, and 28 mg *p*-toluenesulfonic acid in 25 ml benzene was refluxed for 2 hr under a Dean–Stark trap, then cooled and washed 5 times with a 1% Na_2CO_3 aq. The benzene soln was dried (K_2CO_3), concentrated *in vacuo*, and the residue was distilled at 125–127°/24 mm, yield 2·94 g (60%). An analytical sample was obtained by GLC (4% Carbowax 20 M on Chromosorb G 60/80, 6 ft × ¼ in Al, 60 cm^3/min, 155°); NMR (neat, 60 MHz, τ), 6·18 (4H, s, —OCH_2CH_2O—), 6·65 (3H, distorted t, —CH_2Br), ~8·0–8·7 (6H, —$(CH_2)_3$—), 8·76 (3H, s, $-\overset{O}{\overset{|}{C}}-\overset{O}{\overset{|}{C}}H_3$). (Found: C, 43·19; H, 6·96. Calc. for $C_8H_{15}BrO_2$: C, 43·07; H, 6·78%).

6-Bromohexan-2-one ethylene ketal (**4**). B. A stream of anhyd HBr was bubbled for 30 min through an irradiated (Hanovia 67A36) soln of 29 g (0·295 mole) allylacetone in 1·5 l. pentane, following which the lamp was removed, and the soln was purged with dry N_2, washed with water until neutral, dried ($MgSO_4$), and concentrated. The residue was converted directly to **4** by refluxing with 30 g ethylene glycol and 250 mg *p*-toluenesulfonic acid in 250 ml benzene for 8 hr under a Dean–Stark trap. The product was worked up as under the previous paragraph and distilled. The ethylene ketal of the unreacted allylacetone distilled at 60–70°/24 mm (9·6 g), and **4** distilled at 125–127°/24 mm (31·2 g, 64% based on recovered allylacetone). The NMR spectrum showed no evidence for the presence of the 5-bromo-isomer.

Non-6-en-2-one ethylene ketal [cis (**6**) *and* trans (**7**)]. A soln of 8·25 g (0·0369 mole) of **4**, 9·72 g (0·0372 mole) triphenylphosphine in 50 ml toluene was refluxed for 38 hr. The solvent was decanted from the glassy phosphonium salt,* which was washed four times with benzene. Ether (80 ml) was added, followed by 14 ml 2·14 M phenyllithium in benzene–ether. The phosphonium salt slowly dissolved giving a deep red soln. After 2 hr, 1·84 g (0·0318 mole) propanal in 15 ml ether was added over 10 min to the ylid soln, stirred and cooled in an ice bath. The soln was allowed to warm to room temp, refluxed for 2 hr, and cooled and

* In a later experiment, the phosphonium salt was obtained crystalline on standing under ethyl acetate in the refrigerator for 10 days.

filtered. The filtrate was diluted with 30 ml hexane, refiltered, washed 3 times with 1% Na_2CO_3 aq, dried ($MgSO_4$), and concentrated. The residue was distilled, giving 1·6 g (23·5%) of the desired product, b.p. 110–116°/22 mm. An analytical sample was obtained by GLC (4% Carbowax 20 M on Chromosorb G, 6 ft × ¼ in Al); NMR (CCl_4, 100 MHz, τ), 4·72 (2H, m, —CH=CH), 6·18 (4H, s, —OCH_2CH_2O—), 8·81 (3H, s, —C(O)O—CH_3), 9·05 (3H, t, C$\underline{H}_3CH_2$—). (Found: C, 71·73; H, 10·73. Calc. for $C_{11}H_{20}O_2$: C, 71·70; H, 10·94%).

5-Bromopentan-2-one ethylene ketal (**11**). 2-Acetylbutyrolactone (40 g, 0·312 mole) was added dropwise over 3 hr to a refluxing HBr soln (100 ml of 48% HBr and 45 ml of water) in a flask surmounted by a Dean–Stark trap. The product collected in the trap during the course of the reaction Refluxing was continued for 1 hr after the addition was complete. The oily layer of the distillate was washed with water, filtered through $MgSO_4$, and distilled at 79–81°/21 mm (28 g, 55%). This product was refluxed for 4 hr under a Dean–Stark trap with 22 g ethylene glycol and 200 mg *p*-toluenesulfonic acid in 250 ml benzene. The soln was poured into 1% $NaHCO_3$ aq, washed 3 times with 1% $NaHCO_3$ aq, then with water, and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the product was distilled at 103–105°/20 mm (21·3 g, 60%); NMR (neat, 60 MHz, τ), 6·11 (4H, s, —OCH_2CH_2O—), 6·85 (2H, distorted t, —CH_2Br), 7·8–8·5 (4H, m, —CH_2CH_2—), 8·73 (3H, s, —C(O)O—CH_3). (Found: C, 40·30; H, 6·20. Calc. for $C_7H_{13}BrO_2$: C, 40·21; H, 6·26%).

Non-6-yn-2-one ethylene ketal (**10**). An excess (5·4 g, 0·1 mole) butyne was added to a soln of 0·9 g (0·0392 g atoms) of Na in 25 ml liquid ammonia, and the mixture was stirred until the Na dissolved. The ammonia was allowed to evaporate and was replaced with 15 ml of a 7:5 mixture of xylene and dimethylformamide. A soln of 2·4 g (0·0132 mole) of **11** in the same solvent was added, and the mixture was stirred overnight. Water was added, and the organic phase was washed 3 times with water, dried ($MgSO_4$), and the xylene was removed *in vacuo*. The product was distilled at ~80–90°/1 mm in a short-path still (0·4 g, 16·7%).

An analytical sample was obtained by GLC (4% SE 30 on Chromosorb G, 45/60, 144°, 40 cm^3/min); NMR (CCl_4, 60 MHz, τ), 6·17 (4H, s, —OCH_2CH_2O—), 7·9 (4H, broad —$CH_2C{\equiv}CCH_2$—), 8·4 (4H, broad, —CH_2CH_2—), 8·74 (3H, s, —C(O)O—CH_3), 8·90 (3H, distorted t, —$CH_2C\underline{H}_3$). (Found: C, 72·63; H, 10·01. Calc. for $C_{11}H_{18}O_2$: C, 72·49; H, 9·96%).

cis-*Non-6-en-2-one ethylene ketal* (**6**). To a stirred soln of 106 mg nickel acetate tetrahydrate in 10 ml 95% EtOH under H_2 was added 19 mg $NaBH_4$ in 5 ml 95% EtOH. A soln of 266 mg (1·24 mmoles) of **10** in 2 ml 95% EtOH was added, and hydrogenation was allowed to proceed until 25 cm^3 H_2 was consumed. The mixture was filtered, and water was added to the filtrate. Extraction of the aqueous soln with ether, drying ($MgSO_4$), and evaporation of the solvent gave 216 mg (80%) of the product.

Conversion of this isomer to the epoxide by the procedure used to prepare the mixed epoxides (see below) gave only a single product whose GLC retention corresponded to that of the *cis*-epoxide (**8**).

6,7-*Epoxynonan-2-one ethylene ketal* [cis (**8**) *and* trans (**9**)]. To a stirred soln of 0·24 g (0·00131 moles) of **6** and **7** in 25 ml benzene was added 0·42 g of 76% assay (0·00185 mole) *m*-chloroperbenzoic acid. After 5 hr, the soln was washed successively with water, 1% Na_2CO_3 aq, 1% $NaHSO_3$ aq (twice), and water (twice). The benzene soln was dried ($MgSO_4$), and the benzene was removed *in vacuo* at 30°. Analytical GLC (4% Carbowax 20 M on Chromosorb G 60/80, 5 ft × ⅛ in Al, 133°, 30 cm^3/min) showed the major components at 6·4 and 8·5 min in a 1:4 ratio; starting material was absent. (Found: for a GLC cut containing both isomers: C, 65·85; H, 9·80. Calc. for $C_{11}H_{20}O_3$: C, 65·97; H, 10·07%).

A portion of this product was chromatographed on preparative GLC (8% Carbowax 20 M on Chromosorb G 60/80, 6 ft × ¼ in, 145°, 100 cm^3/min). The *cis*-epoxide (**8**) was collected at 26–30 min NMR (CCl_4, 100 MHz, τ), 6·16 (4H, s, —OCH_2CH_2O—), 7·29 (2H, m, HC(O)CH, *cis*), 8·5 (6H, broad, —$(CH_2)_3$—), 8·76 (3H, s, —C(O)O—CH_3), 8·97 (3H, distorted t, —$CH_2C\underline{H}_3$); mass spectrum: M^+ 200. The *trans* epoxide (**9**) was collected at 19–23 min: NMR (CCl_4, 100 MHz, τ), 6·16 (4H, s, —OCH_2CH_2O –), 7·50 (2H, m, HC(O)CH, trans), 8·50 (6H, broad, —$(CH_2)_3$—), 8·77 (3H, s, —C(O)O—CH_3), 9·03 (3H, distorted t, —$CH_2C\underline{H}_3$); mass spectrum: M^+ 200.

7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]*octane* [exo (**1**) *and* endo (**2**)]. A soln of 1·0 g (0·005 mole) of *cis*-**8** and *trans*-**9** in 20 ml acetone and 7 ml water was treated at room temp with 0·2 ml 1 M perchloric acid. After 1 hr, the soln was poured into 1% $NaHCO_3$ aq, and the mixture was extracted with ether. The ether soln was washed with water, dried ($MgSO_4$), and the ether was distilled through a short packed

column. The residue was distilled at 150–155° (0·71 g, 91%). (Found: C, 69·31; H, 10·37. Calc. for $C_9H_{16}O_2$: C, 69·19; H, 10·32%).

The two isomers were separated by preparative GLC (20% Carbowax 20 M on Chromosorb W, 45/60, 6 ft × $\frac{3}{8}$ in Al, 110°, 60 cm³/min). An analytical GLC established their relative retention times (10% Carbowax 20 M on Chromosorb W, 60/80, 5 ft × $\frac{1}{8}$ in Al, 30 cm³/min, temp programmed from 60° to 100° at 6°/min, retention time for *exo*-isomer 3·5 min, for *endo*-isomer 4·3 min).

Mass, IR, and NMR spectra for the *exo*-isomer and for the *endo*-isomer were congruent with those for the biologically active and inactive components, respectively, isolated from frass.

Since these data for the active component have been published,[1] they serve to describe the *exo*-isomer. The NMR spectrum of the *endo*-isomer is as follows: (CCl_4, 100 MHz, τ), 5·97 (1H, broad, $w_{\frac{1}{2}} \sim 7$ Hz, ), 6·16 (1H, m, ), 8·70 (3H, s, ), 9·03 (3H, t, —$CH_2C\underline{H}_3$).

Small-scale experiments confirmed that the *cis*-epoxide (**8**) gave exclusively the exo-isomer (**1**), and the *trans*-epoxide (**9**) gave exclusively the *endo*-isomer (**2**).

exo-7-*Ethyl*-5-*methyl*-6,8-*dioxabicyclo*[3.2.1]*octane* (**1**). Hydrolysis and cyclization (as described above for the *cis*- and *trans*-epoxides) of the *cis*-epoxide (**8**), prepared by catalytic reduction and epoxidation of 1·77 g of **10**, gave 0·153 g of *exo*-product (**1**) by preparative GLC, which showed less than 2% of the *endo*-product (**2**).

Instrumentation. NMR spectra were obtained on Varian A-60A and HA-100 instruments, mass spectra on a CEC 21-103C and a CEC 21-110. Gas chromatography was carried out on Varian instruments A-90P, 204, and a modified 205-1B.

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