Tetrahedron. Vol. 30, pp. 4223 to 4227. Pergamon Press 1974. Printed in Great Britain

SYNTHESIS OF *EXO*-BREVICOMIN, THE PHEROMONE OF WESTERN PINE BEETLE, TO OBTAIN OPTICALLY ACTIVE FORMS OF KNOWN ABSOLUTE CONFIGURATION[a]

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(*Received in Japan* 5 *June* 1974; *Received in the UK for publication* 25 *July* 1974)

Abstract—(1*R*:7*R*)-(+)-*exo*-Brevicomin **1** and its antipode **1'** were synthesized from (2*S*:3*S*)-D-(−)-tartaric acid **2** and its antipode, respectively. This establishes the absolute configurations of both enantiomers of *exo*-brevicomin and afforded key materials to clarify the relationship between pheromone activity and chirality.

The attractant pheromone in frass produced by newly emerged western pine beetle, *Dendroctonus brevicomis* Le Conte, boring in ponderosa pine attracts both males and females. From 1·6 kg of frass, about 1·5 mg of a rather volatile active principle was isolated and identified as a unique bicyclic ketal structure: *exo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (**1** or **1'**), named *exo*-brevicomin.[1-3] Several syntheses of racemic *exo*-brevicomin were reported.[4-7]

The pheromone (**1** or **1'**) possesses two asymmetric carbon atoms and therefore is a highly dissymmetric bicyclic compound. However, its 0·05% hexane solution was reported to show no optical rotation between 350 and 250 nm.[1] This means either of the following: (i) the pheromone is racemic or (ii) it has too small a rotation to be measured accurately with such a dilute solution.† Anyway this observation hampered further study on the absolute stereochemistry of the naturally occurring *exo*-brevicomin.

We undertook the synthesis of *exo*-brevicomin in optically active forms of known absolute configuration bearing in mind the following two objectives. The chemical one was to know the sign of the optical rotation of each enantiomer (**1** and **1'**), while the biological one was to test the responses of the insects to **1** or **1'**. It should be added that synthesis of optically active pheromones is of considerable current research interest because it allows the assignment of absolute stereochemistry of pheromones[8,9] and at the same time enables the ability of insects to discriminate between two enantiomers to be tested.[9] This paper describes the realization of the chemical part of our objectives.

The synthesis of an optically active compound can be accomplished in three different manners. One is the resolution of the racemic final product. This was not applicable to the brevicomin synthesis as the racemic bicyclic ketal (**1** + **1'**) could not be resolved by conventional methods. The second is to resolve an appropriate intermediate. This seemed to be the method of choice in view of the reported synthesis and resolution of 3,4-dihydroxyadipic acid starting from butadiene.[10] However, diffculty encountered in the resolution step was so great that it soon proved to be impractical especially when optically pure products were required for biological evaluation. The third method is to employ a readily available optically active compound as the starting material. This was the only successful one as detailed below.

Our starting materials were D-(−)- and L-(+)-tartaric acids (**2** and **2'**) whose absolute configurations had been firmly established as (2*S*:3*S*) and (2*R*:3*R*), respectively.[11] Tartaric acid possesses its vicinal OH groups in *threo*-configuration and therefore affords exclusively the desired *exo*-brevicomin without any contamination of *endo*-brevicomin. This stereoselective conversion of D-(−)-tartaric acid (**2**) into (1*R*:7*R*)-(+)-*exo*-brevicomin (**1**) is shown in the accompanying Scheme. The earlier stages of the synthesis were patterned after the work of Cope and Mehta who prepared **6a'** (antipode of **6a**) from L-(+)-tartaric acid (**2'**) during their study on the absolute configuration of *trans*-cyclooctene.[12]

D-(−)-Tartaric acid (**2**) was esterified by the method of Sugasawa[13] to give the ethyl ester (**3a**). This was methylated with MeI and Ag_2O.[14] The resulting diethyl (2*S*:3*S*)-(−)-2,3-dimethoxysuccinate (**3b**) was reduced with LAH to give (2*R*:3*R*)-(−)-2,3-dimethoxybutane-1,4-diol (**4a**). The crystalline (−)-ditosylate (**4b**) was prepared and converted to the crystalline (−)-dinitrile (**5**) by treatment with NaCN in dry DMSO.[12]‡ The (+)-diester (**6a**) was obtained from the dinitrile (**5**) by methanolysis followed by hydrolysis of the intermediate bis imido ester hydrochloride. Controlled saponification of the (+)-diester (**6a**) with KOH gave the half ester (**6b**). This was treated with B_2H_6 to give a hydroxy ester (**7a**). The oily

[a]Pheromone Synthesis—IV. This constituted a part of the lecture presented at the IXth International Symposium on the Chemistry of Natural Products, Ottawa, June 27, 1974. Part III, K. Mori, *Agr. Biol. Chem.* **38**, 2043 (1974).

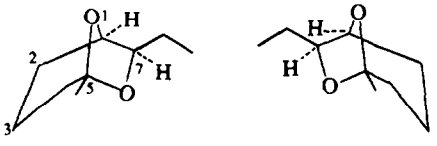
†Professor Silverstein mentioned this possibility in his private communication dated February 14, 1974.

‡The corresponding isopropylidene derivative (**4b**, Me_2C: instead of 2Me's yielded no dinitrile (**5**, Me_2C: instead of 2Me's) under this condition.

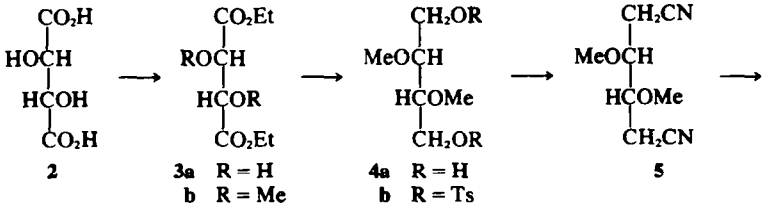
tosylate (**7b**) was prepared and reduced with LAH to give (3*R*:4*R*)-(+)-alcohol (**8a**).* The corresponding tosylate (**8b**) was treated with LiBr in acetone to yield the (+)-bromide (**9**). In order to complete the carbon skeleton of *exo*-brevicomin, the bromide (**9**) was reacted with ethyl acetoacetate. The resulting keto ester (**10**) was heated in the presence of $Ba(OH)_2$ soln. The product was purified by chromatography over alumina to give (+)-dimethoxy ketone (**11a**).

The only remaining task was to remove the Me protecting groups. The Me group is known to be too stable to be used for the routine protection of alcohols.[15] Use of the more common isopropylidene ketal protecting group was unsuccessful as mentioned earlier at the stage of preparation of the dinitrile (**5**). After fruitless experimentation including the use of BCl_3, we finally found that the CrO_3 oxidation of the methyl ether (**11a**) provided the formate (**11b**) in a low but tolerable yield. This unmasking method was first reported by Harrison[16] and later employed by Angyal[17] in carbohydrate field. If the substrate had no other moiety vulnerable to CrO_3 oxidation, this demethylation was apparently of greater

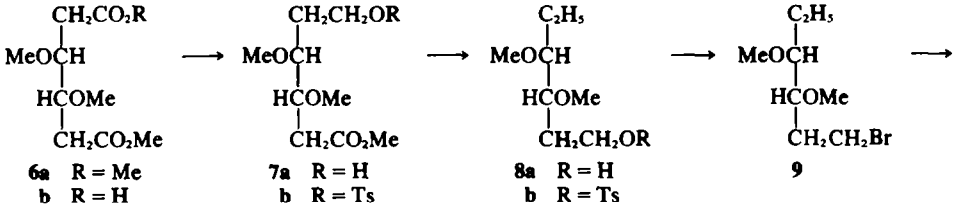
*This alcohol (**8a**) could also be prepared by the following route. The diester (**6a**) was reduced with LAH to a diol (i). This was tosylated with 1 eq of tosyl chloride. The resulting crude tosylate (ii) was treated with LAH. The product was purified by chromatography over Al_2O_3 to give **8a** identical with a sample prepared *via* **7a** on the basis of IR, NMR, TLC and $[\alpha]_D$ values. This excluded the possibility of racemization of **6a** during the alkaline hydrolysis by elimination-addition of the methoxide anion.



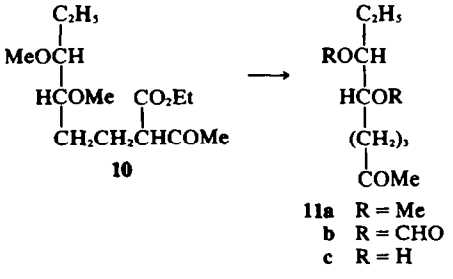
1 **1'**



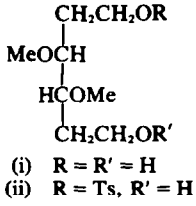
2 **3a** R = H; **b** R = Me; **4a** R = H; **b** R = Ts; **5**



6a R = Me; **b** R = H; **7a** R = H; **b** R = Ts; **8a** R = H; **b** R = Ts; **9**



10 **11a** R = Me; **b** R = CHO; **c** R = H; **1** (1*R*:7*R*)



(i) R = R' = H
(ii) R = Ts, R' = H

utility than that with BCl_3 which inevitably yielded some chlorine containing materials. The formate (**11b**) was hydrolysed to **11c** which in turn was treated with acid to give (1*R*:7*R*)-*exo*-brevicomin (**1**). Its IR, NMR and mass spectra were completely identical with those of the natural *exo*-brevicomin (**1**).[2] GLC analysis also confirmed the purity of our synthetic material with no observable contamination of *endo*-brevicomin (**1**, α-Et at C-7 instead of β-Et). This excluded the possibility of racemization in the course of the synthesis. Random racemization should have yielded a certain amount of thermodynamically more stable *erythro*-isomer of **11c**, the precursor of *endo*-brevicomin. In entirely the same manner, (1*S*:7*S*)-*exo*-brevicomin (**1'**) was synthesized from L-(+)-tartaric acid (**2'**).

The rotation measurement revealed that (1*R*:7*R*)-product (**1**) was dextrorotatory, $[\alpha]_D^{26}+84{\cdot}1°$ (c = 2·2, ether), while (1*S*:7*S*)-product (**1'**) was levorotatory, $[\alpha]_D^{24}-80{\cdot}0°$ (c = 1·6, ether). This firmly established the correlation between the optical rotation and the absolute stereochemistry of two enantiomers of *exo*-brevicomin. The absolute configuration of the natural *exo*-brevicomin, however, remains unsolved until enough material for rotation measurement is re-isolated from frass later.

The biological study with our synthetic products (**1** and **1'**) is in progress by Professor David L. Wood, University of California, Berkeley, and will be published elsewhere.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films unless otherwise specified and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded at 60 or 100 MHz with TMS as an internal standard. Optical rotations were measured on a Jasco DIP-4 polarimeter. GLC analyses were performed on a Yanaco G 80 gas chromatograph.

Diethyl (2S:3S)-(−)-2,3-*dimethoxysuccinate* (**3b**). Freshly prepared and powdered dry Ag_2O (166 g) was added portionwise to a soln of diethyl (2*S*:3*S*)-(−)-tartrate [**3a**, $[\alpha]_D^{19}-9{\cdot}42°$ (c = 1·05, EtOH), 49 g] in MeI (300 g) with vigorous stirring and water-cooling. After stirring for 30 min with water-cooling (10 ~ 35°), the mixture was stirred and heated under reflux for 2 h and filtered. The solid was washed with ether. The combined organic soln was concentrated *in vacuo*. The residue was distilled to give 53 g (95%) of **3b**, b.p. 106 ~ 108°/4 mm, n_D^{23} 1·4270; $[\alpha]_D^{17}-86{\cdot}7°$ (c = 2·6, EtOH); ν_{max} 2960 (m), 2910 (m), 2800 (m), 1750 (vs), 1725 (s), 1270 (s), 1180 (vs), 1140 (s), 1100 (vs), 1020 (s), 920 (w), 850 (w) cm^{-1}. (Found: C, 50·88; H, 7·63. $C_{10}H_{18}O_6$ requires: C, 51·27; H, 7·75%). In the same manner (2*R*:3*R*)-(+)-**3b'**, $[\alpha]_D^{16}+85{\cdot}4°$ (c = 2·3, EtOH), was obtained.

(2*R*:3*R*)-(−)-2,3-*Dimethoxybutane*-1,4-*diol* (**4a**). A soln of **3b** (53 g) in dry ether (400 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (22·5 g) in dry ether (560 ml). The mixture was stirred and heated under reflux for 4 h and left to stand overnight at room temp. Then it was ice-cooled and decomposed by successive addition of H_2O (23 ml), 15% NaOH soln (23 ml) and H_2O (70 ml). After stirring for 4 h at room temp, the mixture was filtered, the filter cake was washed several times with acetone and combined filtrates were evaporated to dryness. The residual oil was distilled to give 24·2 g (70%) of **4a**, b.p. 108 ~ 110°/0·5 mm, $[\alpha]_D^{16}-9{\cdot}04°$ (c = 1·8, EtOH); ν_{max} ~3350 (vs), 2920 (s), 2810 (s), 1090 (vs), 1040 (vs) cm^{-1}. (Found: C, 47·01; H, 9·33. $C_6H_{14}O_4$ requires: C, 47·98; H, 9·40%). In the same manner (2*S*:3*S*)-(+)-**4a'**, $[\alpha]_D^{16}+8{\cdot}79°$ (c = 1·8, EtOH)[lit.[12] $[\alpha]_D^{25}+6{\cdot}06$ (c = 8·23. EtOH)], was obtained. The oily diol crystallized after storage in a refrigerator.

(2*R*:3*R*)-(−)-2,3-*Dimethoxybutane*-1,4-*diol di-p-toluenesulphonate* (**4b**). To a soln of **4a** (24·0 g) in dry pyridine (120 ml) cooled at 0 ~ 5° was added *p*-TsCl (74 g) with stirring. The mixture was left to stand overnight at room temp then poured into ice-water and extracted with ether. The ether soln was washed with dil HCl, $NaHCO_3$ soln and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo to give* 57·6 *g* (79%) of crystalline **4b**. Recrystallization from ether yielded prisms, m.p. 63°, $[\alpha]_D^{17}-9{\cdot}63°$ (c = 5·4, $CHCl_3$); TLC (silica gel G, ether): R_f 0·50; ν_{max} 1600 (m), 1360 (s), 1190 (s), 1175 (vs), 1100 (s), 960 (s), 810 (s) cm^{-1}. (Found: C, 52·44; H, 5·71. $C_{20}H_{26}O_8S_2$ requires: C, 52·38; H, 5·72%). In the same manner (2*S*:3*S*)-(+)−**4b'**, $[\alpha]_D^{17}+9{\cdot}50°$ (c = 4·0, $CHCl_3$) [lit.[12] $[\alpha]_D^{27\cdot5}+9{\cdot}02$ (c = 4·635, $CHCl_3$)], was obtained.

(3*R*:4*R*)-(−)-3,4-*Dimethoxyhexane*-1,6-*dinitrile* (**5**). To a stirred soln of **4b** (136 g) in dry DMSO (750 ml) was added powdered NaCN (36·1 g) in small portions over a period of 3 days at 20°. At the end of 6 days the clear brown soln was poured into H_2O (2 l) and extracted with CH_2Cl_2(1·2 l × 3). The extract was washed with H_2O (400 ml × 3), dried ($MgSO_4$) and concentrated to give 35·5 g (66·5%) of **5**. Recrystallization from C_6H_6-ether yielded needles, m.p. 69 ~ 70°, $[\alpha]_D^{19}-15{\cdot}0°$ (c = 6·73, acetone); ν_{max} (nujol) 2260 (m), 1240 (m), 1200 (m), 1190 (m), 1135 (s), 1090 (s), 1050 (m), 1015 (m), 930 (s), 850 (w), 835 (m) cm^{-1}. (Found: C, 57·25; H, 7·14; N, 16·73. $C_8H_{12}N_2O_2$ requires: C, 57·13; H, 7·19; N, 16·66%). In the same manner (3*S*:4*S*)-(+)-**5'**, $[\alpha]_D^{20}+15{\cdot}7°$ (c = 6·52, acetone) [lit.[12] $[\alpha]_D^{27\cdot5}$·15·81° (c = 8·415, acetone)] was obtained.

Dimethyl (3*R*:4*R*)-(+)-3,4-*dimethoxyadipate* (**6a**). A stirred soln of **5** (36·5 g) in MeOH (1 l) was saturated with dry HCl at room temp. The mixture was stirred and heated under reflux for 2 h. About half of the MeOH was removed *in vacuo*, H_2O (160 ml) was added, and the soln was left overnight at room temp. Then it was diluted with H_2O and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give an oily residue. A soln was prepared by adding $SOCl_2$ (20 ml) with stirring to MeOH (130 ml) cooled to −78° and kept below −20° during the addition. The oil obtained above was added and the mixture was allowed to warm to 0° and then kept overnight in a refrigerator. Then it was concentrated *in vacuo* and the residue was dissolved in ether. The ether soln was washed with $NaHCO_3$ soln and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 39·7 g (84%) of **6a**, b.p. 120 ~ 122°/0·5 mm, n_D^{20} 1·4350; $[\alpha]_D^{20}+24{\cdot}2°$ (c = 4·17, acetone); ν_{max} 2940 (m), 2830 (m), 1740 (vs), 1440 (s), 1380 (m), 1320 (s), 1280 (s), 1210 (vs), 1170 (vs), 1100 (vs), 1075 (m), 1000 (m), 880 (w), 850 (w) cm^{-1}. (Found: C, 51·02; H, 7·64. $C_{10}H_{18}O_6$ requires: C, 51·27; H, 7·75%). In the same manner (3*S*:4*S*)-(−)-**6a**, $[\alpha]_D^{20}-23{\cdot}0°$ (c = 4·13, acetone) [lit.[12] $[\alpha]_D^{27\cdot5}$–23·55° (c = 7·05, acetone)] was obtained.

Methyl hydrogen (3*R*:4*R*)-3,4-*dimethoxyadipate* (**6b**). A soln of KOH (4·0 g) in MeOH (45 ml) was added during 1 h to a stirred soln of **6a** (16·6 g) in MeOH (45 ml) at room temp. The mixture was stirred for an additional 1 h at room temp and concentrated *in vacuo*. The residue was dissolved in H_2O (150 ml) and extracted with ether to remove the unchanged **6a**. The aq layer was saturated with NaCl, acidified with dil HCl to pH2 and extracted with ether. The unchanged **6a** (3·6 g) was treated with KOH (0·8 g) in MeOH (20 ml). The acid fraction was combined, washed with NaCl soln, dried ($MgSO_4$) and concentrated. The residue was dissolved in $CHCl_3$ and cooled to 0°. The crystalline precipitates were collected on a filter. This was shown to be *trans*, *trans*-muconic acid (1·1 g) by IR and m.p. The filtrate was concentrated *in vacuo* to give 11·3 g (72%) of **6b**, ν_{max} ~3400 (m), ~3200 (m), 2930 (m), 2830 (m), 1740 (vs, br.), 1440 (m), 1310 (m), 1270 (m), 1210 (m), 1170 (s), 1100 (s), 1000 (w) cm^{-1}. This was

employed for the next step without further purification. In the same manner (3*S*:4*S*)-**6b**′ was synthesized.

Methyl (3*R*:4*R*)-(+)-3,4-*dimethoxy*-6-*hydroxyhexanoate* (**7a**). A soln of B_2H_6 in THF (0·935 M soln, 38 ml) was added during 20 min to a soln of **6b** (11·3 g) in dry ether (170 ml) with stirring and ice-cooling under N_2. A small amount of yellow and voluminous precipitate resulted. The mixture was stirred for 30 min at room temp, poured into ice-NaCl soln and extracted with ether. The ether extract was washed with $NaHCO_3$ soln and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 5·7 g (54%) of **7a**, b.p. 118 ~ 120°/0·5 mm, n_D^{16} 1·4437; $[\alpha]_D^{23}$ + 39·4°(c = 2·13, EtOH); ν_{max} ~ 3400 (m), 2920 (s), 2820 (m), 1740 (vs), 1445 (s), 1380 (m), 1300 (m), 1205 (m), 1170 (s), 1100 (vs), 1010 (m), 895 (w), 840 (w) cm^{-1}; δ (60 MHz, CCl_4) 1·60 (2H, m), 2·33 (2H, t, J = 6 Hz), 2·66 1H, (1H, br, s, –OH), 3·32 (3H, s), 3·35 (3H, s), 3·60 (3H, s), ~3·48 – ~4·00 (4H, m), (Found: C, 51·46; H, 8·28. $C_9H_{18}O_5$ requires: C, 52·41; H, 8·80%). In the same manner (3*S*:4*S*)-(–)-**7a**′, $[\alpha]_D^{23}$ – 38·6° (c = 2·07, EtOH), was obtained.

Methyl (3*R*:4*R*)-3,4-*dimethoxy*-6-*p*-*toluenesulphonyloxyhexanoate* (**7b**). p-TsCl (16·1 g) was added to an ice-cooled soln of **7a** (14·1 g) in dry pyridine (65 ml) at 0–5°. The mixture was left to stand at room temp for 3 h, poured into H_2O and extracted with ether. The ether soln was washed with H_2O, dil HCl and $NaHCO_3$ soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 20·0 g (81%) of oily **7b**, ν_{max} 2930 (m), 2830 (m), 1740 (vs), 1600 (m), 1450 (m), 1370 (s), 1300 (m), 1200 (vs), 1180 (vs), 1100 (s), 1020 (m), 965 (m), 940 (m), 910 (m), 820 (m), 775 (m) cm^{-1}. This was directly employed for the next step. In the same manner (3*S*:4*S*)-**7b**′ was synthesized.

(3*R*:4*R*)-(+)-3,4-*Dimethoxyhexan*-1-*ol* (**8a**). A soln of **7b** (20 g) in dry ether (150 ml) was added during 30 min to an ice-cooled and stirred suspension of LAH (11·0 g) in dry ether (400 ml). The mixture was left to stand overnight at room temp and then stirred and decomposed with ice-cooling by successive addition of H_2O (11 ml), 20% NaOH soln (11 ml), H_2O (33 ml) and THF (200 ml). The stirring was continued for 1 h and the mixture was filtered. The filter cake was washed with ether. The combined filtrate and washings were dried (K_2CO_3) and concentrated. The residue was distilled to give 6·8 g (75%) of **8a**, b.p. 120 ~ 125°/20 mm, n_D^{24} 1·4330; $[\alpha]_D^{23.5}$ + 48·5° (c = 4·14, EtOH); TLC (silica gel G, ether): R_f 0·46; ν_{max} 3400 (s), 2940 (vs), 2880 (s), 2830 (s), 1470 (m), 1385 (m), 1340 (w), 1195 (m), 1150 (m), 1090 (vs), 1050 (s), 980 (w), 930 (m), 900 (w) cm^{-1}; δ(60 MHz, CCl_4) 0·92 (3H, deformed t, J = 6·5 Hz), 1·2 ~ 1·75 (4H, m), 2·8 ~ 3·2 (2H, m), 3·06 (1H, s, –OH), 3·30 (6H, s), 3·53 (2H, t, J = 7 Hz). (Found: C, 59·46; H, 11·07. $C_8H_{18}O_3$ requires: C, 59·23; H, 11·18%). In the same manner (3*S*:4*S*)-(–)-**8a**′ was obtained in 60% yield: $[\alpha]_D^{24}$ – 50·2° (c = 4·06, EtOH); (Found: C, 58·87; H, 11·06. $C_8H_{18}O_3$ requires: C, 59·23; H, 11·18%). (3*R*:4*R*)-(+)-**8a** synthesized *via* i and ii exhibited $[\alpha]_D^{17}$ + 50·8° (c = 0·95, EtOH).

(3*R*:4*R*)-3,4-*Dimethoxyhexan*-1-*ol* *p*-*toluenesulphonate* (**8b**). *p*-TsCl (10 g) was added to an ice-cooled soln of **8a** (6·8 g) in dry pyridine (28 ml). The mixture was left to stand in a refrigerator for 14 h, poured into ice-dil HCl and extracted with ether. The ether extract was washed with H_2O and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 13·0 g (97%) of **8b**, ν_{max} 3020 (m), 1600 (m), 1460 (m), 1360 (s), 1190 (s), 1180 (s), 1095 (s), 950 (m), 930 (m), 915 (m), 815 (m), 760 (m), 665 (m) cm^{-1}. This was employed for the next step without further purification. In the same manner (3*S*:4*S*)-**8b**′ was obtained.

(3*R*:4*R*)-(+)-3,4-*Dimethoxyhexyl bromide* (**9**). Dry LiBr (12 g) was added to a soln of **8b** (13·0 g) in acetone (70 ml) and the mixture was heated under reflux for 2 h. The acetone was distilled off. The residue was diluted with water and extracted with ether. The extract was washed with NaCl soln, dried ($CaCl_2$) and concentrated. The residue was distilled to give 7·4 g (92% from **8a**) of **9**, b.p. 120 ~ 122°/80 mm, n_D^{23} 1·4510; $[\alpha]_D^{23}$ + 61·08° (c = 4·24, $CHCl_3$); ν_{max} 2980 (s), 2940 (s), 2880 (s), 2820 (m), 1465 (m), 1380 (m), 1335 (w), 1280 (m), 1195 (m), 1100 (vs), 1005 (w), 930 (m) cm^{-1}; δ (60 MHz, CCl_4) 0·91 (3H, deformed t, J = 6 Hz), 1·1 ~ 1·7 (2H, m), 1·90 (2H, t), 2·9 ~ 3·9 (2H, m), 3·32 (3H, s), 3·35 (3H, s), 3·43 (2H, t, J = 7 Hz). (Found: C, 42·18; H, 7·58. $C_8H_{17}BrO_2$ requires: C, 42·67; H, 7·61%). In the same manner (3*S*:4*S*)-(–)-**9**′ was prepared in 78% yield from **8a**′: $[\alpha]_D^{23}$ – 58·1° (c = 4·34, $CHCl_3$); (Found: C, 42·07; H, 7·41. $C_8H_{17}BrO_2$ requires: C, 42·67; H, 7·61%).

(3*R*:4*R*)-(+)-6,7-*Dimethoxynonan*-2-*one* (**11a**). $AcCH_2CO_2Et$ (9·6 g) was added to a suspension of NaH (50% NaH, 3·7 g. The mineral oil was removed by washing with dry C_6H_6) in dry C_6H_6 (70 ml) to yield Na-enolate. To this was added with stirring a soln of **9** (7·4 g) in dry C_6H_6 (30 ml). The mixture was stirred and heated under reflux for 16 h. After cooling it was diluted with water and extracted with ether. The extract was washed with water and NaCl soln, dried ($MgSO_4$) and concentrated to give crude **10**, ν_{max} 1740 ~ 1710 (vs), 1635 (m), 1370 (s), 1320 (s), 1300 (s) 1250 (s), 1150 (vs), 1040 (s) cm^{-1}. This was dissolved in 95% EtOH (24 ml) and mixed with $Ba(OH)_2 . 8H_2O$ (22 g) and H_2O (80 ml). The mixture was stirred and heated under reflux for 16 h. After cooling, it was acidified with dil HCl to dissolve $BaCO_3$ and extracted with ether. The extract was washed with $NaHCO_3$ soln and NaCl soln, dried (K_2CO_3) and concentrated. The residue was chromatographed over Woelm neutral Al_2O_3 (Grade II, 80 g, 25 × 2·5 cm) in light petroleum. Elution with light petroleum gave, after 100 ml of forerun containing hydrocarbon, **11a**, 2·4 g (32%), b.p. 120 ~ 121°/9 mm, n_D^{25} 1·4340, n_D^{13} 1·4368; $[\alpha]_D^{25}$ + 16·2° (c = 5·0, $CHCl_3$); ν_{max} 2960 (sh), 2920 (vs), 2860 (sh), 2805 (s), 1710 (vs), 1460 (m), 1410 (w), 1370 (m), 1230 (w), 1160 (m), 1140 (m), 1090 (vs), 970 (w), 920 (w), 890 (w) cm^{-1}; δ (100 MHz, CCl_4) 0·89 (3H, t, J = 7 Hz), 1·1 ~ 1·7 (6H, m), 2·03 (3H, s), 2·35 (2H, t, J = 6 Hz), 3·05 (2H, m), 3·33 (6H, s). (Found: C, 65·08; H, 10·97. $C_{11}H_{22}O_3$ requires: C, 65·31; H, 10·96%). In the same manner (3*S*:4*S*)-(–)-**11a**′ was obtained in 30% yield: $[\alpha]_D^{27}$ –15·6° (c = 5·0, $CHCl_3$), (Found: C, 65·10; H, 10·56. $C_{11}H_{22}O_3$ requires: C, 65·31; H, 10·96%).

(1*R*, 7*R*)-(+)-*exo*-7-*Ethyl*-5-*methyl*-6,8-*dioxabicyclo* [3.2.1] *octane* (*exo*-brevicomin, **1**). A soln of **11a** (2·4 g) in CH_2Cl_2 (5 ml) was added to a stirred and water-cooled suspension of CrO_3 (15 g) in AcOH (150 ml). The mixture was stirred for 2 h at room temp (22 ~ 24°), diluted with water and extracted with CH_2Cl_2. The extract was washed with $NaHCO_3$ soln and NaCl soln, dried ($MgSO_4$) and concentrated to give 1·8 g of crude **11b**, ν_{max} 2930 (m), 1720 (s), 1420 (m), 1360 (m), 1170 (s), 1090 (m) cm^{-1}. This was dissolved in MeOH (5 ml) and mixed with NaOH (0·5 g) in H_2O (2·5 ml) and left to stand at room temp for 20 min to yield **11c**. Then the mixture was acidified with conc HCl using Congo red as an indicator, left for 1 h at room temp and extracted with ether. The ether extract was washed with $NaHCO_3$ soln and NaCl soln, dried (K_2CO_3) and concentrated to give 1·0 g of a crude oil. This was chromatographed over Woelm neutral Al_2O_3 (grade II, 5 g, 4·5 × 1·6 cm) in light petroleum. Elution with light petroleum (90 ml) gave 500 mg of **1** which was purified by distillation to give 215 mg (11%) of pure **1**, b.p. 95 ~ 100°/110 mm, n_D^{26} 1·4370; $[\alpha]_D^{26}$ + 84·1° (c = 2·2, ether): ν_{max} 2940 (s), 2880 (m), 2850 (m), 1470 (m), 1390 (s), 1360 (w), 1340 (w), 1310 (vw), 1280 (w), 1265 (w), 1250 (s), 1200 (m), 1190 (m), 1180 (s), 1140 (w), 1110 (m), 1085 (w), 1080 (w), 1040 (w), 1035 (s), 1020 (m), 1010 (s), 995 (m), 970 (m), 930 (m), 900 (vw), 880 (m), 860 (s), 850 (s), 790 (w) cm^{-1}; δ (100 MHz, CCl_4) 0·86 (3H, t, J = 7 Hz), 1·30 (3H, s), 3·79 (1H, t, J = 7 Hz, C-1 H), 3·99 (1H, s, C-7 H, $\Phi_{1,7}$ = 90°); MS: m/e 41·0370 (C_3H_5, 16%), 43·0171 (C_2H_3O, 100%, base peak), 57·0347 (C_3H_5O, 8%), 67·0554 (C_5H_7, 12%), 68·0618 (C_5H_8, 14%), 71·0489 (C_4H_7O, 10%), 73·0640 (C_4H_9O, 8%), 81·0676 (C_6H_9, 10%), 85·0631 (C_5H_9O, 44%), 86·0698 ($C_5H_{10}O$, 16%), 98·0735 ($C_6H_{10}O$, 16%), 99·0812 ($C_6H_{11}O$, 8%), 127·0736 ($C_7H_{11}O_2$, 6%), 156·1157 ($C_9H_{16}O_2 = M^+$,

4%). This was measured by Hitachi Datalyzer Hi-Res. Mass System at our Department with ionization potential of 70 eV. These spectral data were identical with those of natural *exo*-brevicomin.[2] GLC (Column, 5% LAC 2R-446 on Diasolid L, 1·5 m × 3 mm i.d. at 60°, Carrier gas, N_2, 1·0 kg/cm^2): Rt 5·6 min. In the same manner (1*S*:7*S*)-(−)-brevicomin (1′) was prepared: b.p. 95–96°/100 mm, n_D^{24} 1·4372; $[\alpha]_D^{24}$ −80·0° (c = 1·6, ether). The spectral data were identical with those of 1.

Acknowledgements—I thank Prof. M. Matsui, the Dean, Faculty of Agriculture of this University for encouragements. Prof. R. M. Silverstein, State University of New York, Syracuse, kindly sent me a copy of the NMR spectrum of natural *exo*-brevicomin. Thanks are due to Dr. K. Aizawa and his associates, this Department, for MS and elemental analyses. Help of Mr. T. Takigawa in NMR measurements is acknowledged with thanks.

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