# Stereoselective Synthesis of the Macrocycle Segment of Verrucarin J

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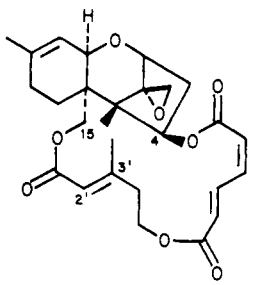
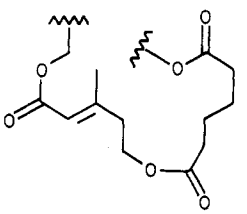
The ester acid **5**, corresponding to the chain of verrucarin J, has been synthesized from 4-hydroxy-2-butanone (**8**). The tetrahydropyranyl ether **9** was converted via a Wittig reaction to hydroxy ester **20**. A Horner–Emmons condensation of phosphonate **22**, derived from the bromoacetate **21**, with malaldehydic acid (**7**) gave **6**, with a 2*E*,7*E*,9*Z* configuration, in 80% yield. A similar sequence proceeding from **8**, via anhydromevalonolactone (**12**), afforded the (*Z*)-phosphonate **16**, which underwent a Horner–Emmons reaction with **7** to yield **5**. Comparison of $^1$H NMR spectra of **5** and **6** with data reported for verrucarin J confirms the revised 2*E* geometry assigned to the natural product.

The verrucarins, roridins, and baccharins comprise a family of naturally occurring macrolides in which a sesquiterpene diol of the trichothecane group is esterified with an $\alpha,\omega$-dicarboxylic acid.[2] Certain of these macrolides are known to possess powerful antibiotic, antifungal, and especially antileukemic activity, but, unfortunately, they have been found to be far too toxic for chemotherapeutic development.[3] Verrucarin J (**1**), a metabolite of *Myrothecium verrucaria*, is characterized by a macro ring containing a 2′,3′ double bond which conventionally has been represented with *Z* configuration.[4] However, a partial synthesis of tetrahydroverrucarin J (**2**), in which the cis,trans muconate segment of **1** was replaced by adipate, afforded NMR evidence in favor of a revised E configuration for the 2′,3′ linkage.[5]

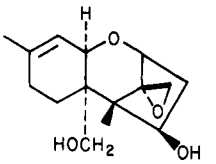


**1**

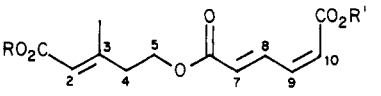


**2**

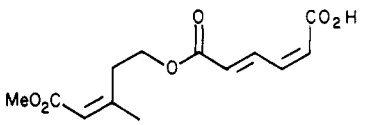
In addition to studies directed toward a synthesis of verrucarol (**3**),[6] the terpenoid nucleus of **1**, we have also pursued approaches to the intact chains of these macrolides in the expectation that they can be attached to the C-4 and C-15 hydroxyl groups of verrucarol through a regioselective esterification.[7] Further, the chains themselves have intrinsic interest as centers of biological activity, and our hope is that structural variation in this segment will influence binding of the verrucarins at the ribosomal subunit where inhibition of protein synthesis takes place.[8] The dicarboxylic acid **4** and derivatives which permit chemical differentiation of the chain ends play a pivotal role in this strategy; we now describe syntheses of **5** and **6**, having unambiguously defined stereochemistries which parenthetically confirm that



**3**



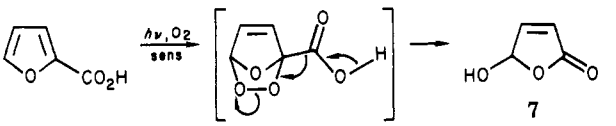
**4**, R = R′ = H
**6**, R = Me; R′ = H
**23**, R = R′ = Me



**5**

verrucarin J possesses 2′,3′-*E* configuration.

The projected key step in the approach to **5** and **6** involved a Horner–Emmons reaction of a phosphonate with malaldehydic acid (**7**), a process which has been previously shown to yield muconic acid half-esters.[9] Several attempts to reproduce a published preparation of **7**[10] gave a low yield of impure material. However, it was found that photooxygenation of 2-furoic acid afforded crystalline **7** in excellent yield[11] and that this material could be utilized directly in condensation [e.g., with ethyl (di-*o*-ethylphosphono)acetate] with highly satisfactory results.



**7**

Synthesis of the (*Z*)-phosphonate **16** required for the preparation of **5** began from 4-hydroxy-2-butanone (**8**, Scheme I). The latter was first protected as its tetrahydropyranyl derivative **9**[12] and then condensed with ethyl acetate in the presence of lithium diisopropylamide. The desired hydroxy ester **10** was obtained in 74% yield from **8** by this procedure, which was found to be more convenient that that employed by Ellison and Bhatnagar with the corresponding 4-acetoxy-2-butanone.[13] Treatment of **10** with ethanol containing a catalytic amount of acetyl chloride resulted in removal of the tetrahydropyranyl group to furnish δ lactone **11**. This was dehydrated directly to anhydromevalonolactone (**12**) by distillation in the presence of polyphosphoric acid.[14]

(1) Recipient of a National Institutes of Health Research Career Development Award, 1976–1981.
(2) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63.
(3) Tamm, C. In "Mycotoxins in Human and Animal Health"; Pathotox Publishers: Forest Park South, IL, 1977; pp 209–228.
(4) Fetz, E.; Bohner, B.; Tamm, C. *Helv. Chim. Acta* **1965**, *48*, 1669.
(5) Breitenstein, W.; Tamm, C. *Helv. Chim. Acta* **1978**, *61*, 1975.
(6) White, J. D.; Matsui, T.; Thomas, J. A. *J. Org. Chem.* **1981**, *46*, 3376.
(7) It has been shown that the C-4 hydroxyl group in verrucarol can be selectively esterified.[5]
(8) McLaughlin, C. S.; Vaughan, M. H.; Campbell, I. M.; Wei, C. M.; Stafford, M. E.; Hansen, B. S. In "Mycotoxins in Human and Animal Health"; Pathotox Publishers: Forest Park South, IL, 1977; pp 263–273.
(9) Pattenden, G.; Weedon, B. C. L. *J. Chem. Soc. C* **1968**, 1984.
(10) Gvozdetskaya, V. P.; Kulnevich, V. G.; Lapkova, L. B. *Zh. Prikl. Khim. (Leningrad)* **1974**, *47*, 1366.
(11) Cf.: Perez, F.; Ramos, F.; Victoria, M. Spanish Patent 431 794; *Chem. Abstr.* **1972**, *87*, 22418.
(12) Hoffman, C. H.; Wagner, A. F.; Wilson, A. N.; Walton, E.; Shunk, C. C.; Wolf, D. E.; Holly, F. W.; Folkers, K. *J. Am. Chem. Soc.* **1955**, *79*, 2316.
(13) Ellison, R. A.; Bhatnagar, P. K. *Synthesis* **1974**, 719.
(14) Cornforth, J. W.; Cornforth, R. H.; Popjak, G.; Gore, I. *Biochem. J.* **1958**, *69*, 146.

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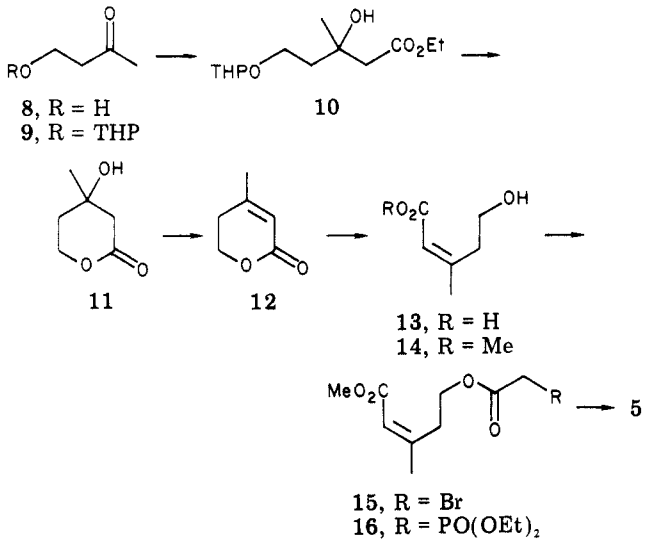
Table I. Proton Chemical Shifts ($\delta$), Multiplicities, and Coupling Constants (Hz) for Synthetic and Natural Verrucarin J Chains

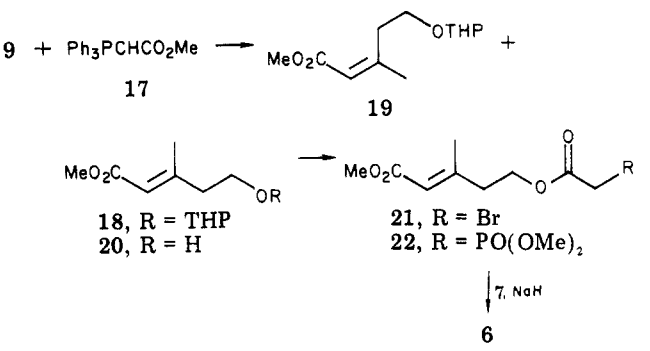
| compd | chemical shift | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $H_2$ | $CH_3C$ | $H_4$ | $H_5$ | $H_7$ | $H_8$ | $H_9$ | $H_{10}$ |
| 5 | 5.88 (m) | 2.03 (d, 1.5) | 2.45 (t, 6) | 4.43 (t, 6) | 6.20 (d, 16) | 8.42 (dd, 11, 16) | 6.80 (t, 11) | 6.06 (d, 11) |
| 6 | 5.76 (m) | 2.20 (d, 1.5) | 2.43 (t, 6) | 4.34 (t, 6) | 6.16 (d, 16) | 8.38 (dd, 11, 16) | 6.75 (t, 11) | 6.01 (d, 11) |
| 1[a] | 5.85 (d, 1.5) | 2.28 | 2.50 (t, 6) | 3.82 (t, 6) | 6.05 (d, 16) | 8.12 (dd, 11, 16) | 6.60 (t, 11) | 6.10 (d, 11) |
| 2[b] | 5.77 | 2.21 | | | | | | |

[a] Data from ref 4. [b] Data from ref 5.

Scheme I




Scheme II




Saponification of **12**, followed by careful acidification with HCl, afforded (2*Z*)-anhydromevalonic acid (**13**), which was promptly converted to its methyl ester **14** with diazomethane. Acylation of **14** with $\alpha$-bromoacetyl bromide gave bromo ester **15**, and, upon exposure to hot triethyl phosphite, this substance yielded the phosphonate diester **16** in quantitative yield.[15]

The (*E*)-phosphonate **22** was also obtained from **8**, in this case via a Wittig reaction with phosphorane **17** catalyzed by benzoic acid[16] (Scheme II). A 3:2 mixture of *E* and *Z* $\alpha,\beta$-unsaturated esters **18** and **19** was produced which, without separation, was treated with methanolic HCl. Following removal of the THP group in this reaction, the *Z* isomer **19** underwent spontaneous lactonization to **12** and could thus be removed in a facile chromatographic separation from the desired hydroxy ester **20**. The latter was converted to bromoacetate **21** and thence phosphonate **22** via a sequence analogous to that used for **13**.

The enolate anion generated from **16** with sodium methoxide in THF underwent Horner–Emmons condensation with **7** to furnish **5** in 84% yield. In contrast, exposure of **7** and **22** to the same conditions gave only the half methyl ester of muconic acid, resulting from methanolysis of **22** and a Horner–Emmons reaction. The use of sodium hydride as the base removed this obstacle and led to **6** in 80% yield. The proton NMR spectra of **5** and **6** clearly revealed that each possessed a 7-trans,9-cis configuration of the muconate segment, with coupling constants in close agreement with data reported for natural verrucarin J[4] (see Table I). As expected, **5** and **6** exhibited a significant difference (ca. 0.2 ppm) in the chemical shifts of their C-3 methyl signals, with that of the *E* isomer being downfield due to the deshielding effect of the proximal ester carbonyl. The similar 3′-methyl chemical shifts of verrucarin J (**1**) and **6** confirm the assignment of *E* configuration made by Tamm to the 2′,3′ double bond of this macrocycle.

(15) Wadsworth, W. S. *Org. React.* **1977**, *25*, 73.
(16) Keller-Schierlein, W.; Widmer, J.; Maurer, B. *Helv. Chim. Acta* **1972**, *55*, 198.

## Experimental Section

Infrared spectra (IR) were recorded on a Perkin-Elmer 727B spectrophotometer. $^1H$ nuclear magnetic resonance spectra (NMR) were recorded on a Varian EM-360A or HA-100 spectrometer, and $^{13}C$ spectra were measured on a Varian FT-80A spectrometer. Chemical shifts are reported in parts per million ($\delta$) with tetramethylsilane as the internal standard. Coupling constants (*J*) are given in hertz; the abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Mass spectra were obtained on a Varian MAT CH-7 spectrometer, and exact masses were measured by using a CEC-110B spectrometer at an ionization potential of 70 eV. Combustion analyses were performed by Micro-Tech Laboratories. Analytical thin-layer chromatography (TLC) was done on Merck TLC sheets precoated with silica gel 60 F-254 (0.2 mm thick). Preparative layer chromatography was done on Analtech precoated silica gel GF-259 plates (1 mm thick). Merck silica gel 60 (0.06–0.02 mm, activity 2–3) was used for column chromatography. All boiling points (bp) and melting points (mp) are uncorrected. Dry tetrahydrofuran (THF) was obtained by distillation, under nitrogen, from sodium–benzophenone ketyl. Hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) were dried by distillation from calcium hydride at reduced pressure. Other solvents were purified by using standard procedures.

**5-Hydroxy-2(5*H*)-furanone (Malaldehydic Acid, 7).** A solution of 2.00 g (0.018 mol) of 2-furoic acid and 50 mg of Rose Bengal in 110 mL of methanol at 25 °C was swept with a stream of oxygen and irradiated with a 450-W Hanovia medium-pressure mercury lamp through a Pyrex filter. After 4 h the solution was filtered through Norite, and the solvent was removed at <50 °C to leave 1.80 g (100%) of virtually pure **7** as a semicrystalline solid: $^1H$ NMR ($CDCl_3$) $\delta$ 7.33 (1 H, dd, $J$ = 6, 1.5 Hz), 6.25 (1 H, br s), 6.18 (1 H, m), 5.69 (1 H, br a, OH). This material was used promptly without purification, but, if necessary, it could be crystallized from ether (with loss of material) to give a colorless

solid: mp 51–54 °C (lit.[17] mp 50–53 °C).

**4-[(2-Tetrahydropyranyl)oxy]butan-2-one (9).** A solution of 13.0 g (0.147 mol) of 4-hydroxybutan-2-one, 15.0 mL (0.194 mol) of dihydropyran, and 700 mg of *p*-toluenesulfonic acid in 150 mL of dichloromethane was stirred at 0 °C under nitrogen for 1 h. Solid sodium bicarbonate (10 g) was added, and the mixture was stirred at room temperature for 0.5 h. The mixture was filtered through Celite, the filtrate was evaporated, and the residue was distilled to give 24.0 g (92%) of **9**: bp 65 °C (0.2 mm); IR (film) 1710, 1450, 1370, 1125, 1070, 1030 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.62 (1 H, br s), 3.70 (5 H, m), 2.70 (2 H, t, $J$ = 7 Hz), 2.20 (3 H, s), 1.60 (6 H, m).

**Ethyl 3-Hydroxy-3-methyl-5-[(2-tetrahydropyranyl)-oxy]pentanoate (10).** To a solution of 33 mL (0.24 mol) of distilled diisopropylamine in 200 mL of dry tetrahydrofuran at 0 °C was added 150 mL of 1.6 M (0.24 mol) butyllithium via syringe. After 0.5 h at 0 °C, the solution was cooled to −78 °C, and 21.2 g (23.5 mL, 0.24 mol) of ethyl acetate was added dropwise followed, after 0.5 h, by 39.2 g (0.23 mol) of **9**. After 0.5 h at −78 °C, 60 mL of 20% hydrochloric acid was added, and the mixture was poured into 500 mL of water. The solution was extracted three times with 250 mL of ether, and the combined ether extract was washed with saturated sodium chloride and dried ($MgSO_4$). Filtration followed by removal of the solvent gave 46.2 g (80%) of **10** as a viscous, sweet-smelling oil which was virtually pure: IR (film) 3500, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.64 (1 H, br s), 4.20 (2 H, q, $J$ = 8 Hz), 3.93 (2 H, s), 3.30–4.10 (2 H, m), 2.60 (2 H, s), 1.94 (2 H, t, $J$ = 6 Hz), 1.64 (6 H, m), 1.34 (3 H, s), 1.30 (3 H, t, $J$ = 8 Hz); mass spectrum, $m/e$ 176 ($M^+ - C_3H_8O$).

**5,6-Dihydro-4-methyl-α-pyrone (Anhydromevalonolactone, 12).** To a solution of 0.3 mL of acetyl chloride in 300 mL of dry ethanol was added 42.1 g (0.16 mol) of **10**, and the mixture was allowed to stand at room temperature overnight. The mixture was concentrated in vacuo and the residue was distilled at 0.3 mm. The fraction with a boiling point of 120–125 °C was collected to yield ca. 22 g of mevalonolactone (**11**). To this distillate was added 0.5 mL of polyphosphoric acid, and the mixture was redistilled, giving 18.1 g (89% from **10**) of **12**, bp 65 °C (0.4 mm), with spectral properties identical with those reported.[14]

**Methyl (*Z*)-5-Hydroxy-3-methylpent-2-enoate (14).** A mixture of 0.50 g (4.5 mmol) of **12** in 5 mL of 1 N sodium hydroxide was refluxed for 10 min. The mixture was then cooled in ice, and 5 mL of 1 N hydrochloric acid was added followed by saturated ammonium chloride solution. The mixture was extracted several times with ether and the combined extract was treated with an ethereal solution of diazomethane until the yellow color persisted. The solution was dried ($Na_2SO_4$) and the solvent was removed to leave 0.44 g (76%) of virtually pure **14**: IR (film) 3440, 1710, 1645 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.80 (1 H, br s), 3.78 (2 H, t, $J$ = 7 Hz), 3.69 (3 H, s), 2.87 (2 H, t, $J$ = 7 Hz), 1.96 (3 H, br s); $^{13}C$ NMR ($CDCl_3$) $\delta$ 167.6 (C-1), 157.8 (C-3), 117.5 (C-2), 61.0 ($OCH_3$), 51.05 (C-5), 36.80 (C-4), 25.6 ($CCH_3$). This material underwent conversion to **12** upon heating or prolonged storage.

**Methyl (*Z*)-5-(2-Bromoacetoxy)-3-methylpent-2-enoate (15).** To a solution of 0.20 g (1.40 mmol) of **14** in 10 mL of dry ether containing 0.5 mL of pyridine at 0 °C was added 0.15 mL (1.67 mmol) of α-bromoacetyl bromide. The mixture was allowed to stand at 0 °C for 0.5 h, was diluted with 25 mL of water, and was extracted with ether. The ethereal extract was dried ($MgSO_4$), and the solvent was removed to give 0.36 g (96%) of the unstable diester **15** as a viscous oil: IR (film) 1720–1745 (br), 1645 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 5.83 (1 H, br s), 4.38 (2 H, t, $J$ = 7 Hz), 3.88 (2 H, s), 3.70 (3 H, s), 3.03 (2 H, t, $J$ = 7 Hz), 2.00 (3 H, d, $J$ = 2 Hz).

**Methyl (*Z*)-5-[(Di-*O*-ethylphosphono)acetoxy]-3-methylpent-2-enoate (16).** A mixture of 0.36 g (1.36 mmol) of **15** and 0.33 g (2.0 mmol) of triethylphosphite was heated at 100 °C for 1 h. Excess triethyl phosphite was removed in vacuo, and the residue was chromatographed on silica (hexane–ethyl acetate eluent) to yield 0.41 g (97%) of **16** as an oil: IR (film) 1715–1740 (br), 1645, 1260, 1030 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 5.81 (1 H, br s), 4.33 (2 H, t, $J$ = 7 Hz), 4.23 (2 H, q, $J$ = 7 Hz), 4.17 (2 H, q, $J$ = 7 Hz), 3.70 (3 H, s), 3.02(2 H, t, $J$ = 7 Hz), 2.99 (2 H, d, $J$ = 22 Hz), 2.00 (3 H, d, $J$ = 2 Hz), 1.35 (6 H, t, $J$ = 7 Hz); mass spectrum, $m/e$ 322 ($M^+$). Anal. Calcd for $C_{13}H_{23}O_7P$: C, 48.45; H, 7.14. Found: C, 48.21; H, 6.88.

***Z* Ester 5.** To a solution of 1.00 g (3.10 mmol) of **16** in 20 mL of dry tetrahydrofuran stirred at room temperature under nitrogen was added simultaneously and separately from two motor-driven syringes a solution of sodium methoxide (prepared from 0.15 g, 6.5 mmol, of sodium) in 10 mL of methanol and a solution of 0.36 g (3.50 mmol) of **7** in 10 mL of tetrahydrofuran. Addition of the reagents by this means took ca. 1 h, after which the mixture was stirred for a further 45 min. The mixture was diluted with water, and sufficient 10% hydrochloric acid was added to bring the pH to 2. The mixture was extracted three times with ether, and the combined extracts were dried ($MgSO_4$). Evaporation of the solvent gave 0.75 g (90%) of virtually pure **5** which solidified at ca. 10 °C. An analytical sample was prepared by thick-layer chromatography on silica gel: IR (film) 2500 (br), 1690–1730 (br), 1645, 1610 $cm^{-1}$; $^{13}C$ NMR $\delta$ 169.2, 166.7, 165.5, 159.0, 142.0, 138.7, 129.0, 124.4, 116.4, 66.2, 51.9, 29.2, 22.9. Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 57.89; H, 5.91.

**Methyl (*E*)- and (*Z*)-3-Methyl-5-[(2-tetrahydropyranyl)oxy]pent-2-enoate (18 and 19).** A solution of 3.90 g (0.023 mol) of **9**, 7.50 g (0.022 mol) of **17**, and 0.05 g (0.41 mmol) of benzoic acid in 10 mL of toluene was heated at reflux for 3 days. The solvent was removed in vacuo, and the solid residue was triturated with hexane. The hexane extract was filtered, and the filtrate was evaporated to leave a viscous oil which was chromatographed on silica gel. Elution from the column with hexane–acetone (9:1) afforded 2.11 g (42%) of a mixture of **18** and **19**. The $^1H$ NMR spectrum of this mixture exhibited two doublets ($J$ = 1.5 Hz) at 2.20 and 1.98, corresponding to the $CCH_3$ signals of **18** and **19**, respectively, in a ratio of ca 3:2. All attempts at separation of these *E*/*Z* isomers failed.

**Methyl (*E*)-5-Hydroxy-3-methylpent-2-enoate (20).** A solution of 2.11 g (9.25 mmol) of the mixture of **18** and **19**, prepared as above, and 0.5 mL of 2 M hydrochloric acid in 25 mL of methanol was allowed to stand at room temperature for 1 h. The mixture was concentrated in vacuo, ethyl acetate was added, and the organic layer was separated, washed with saturated sodium bicarbonate, and dried ($MgSO_4$). The solvent was removed by evaporation, and the residue was chromatographed on silica gel. Elution with hexane–ethyl acetate gave 0.91 g (68%) of **20** as an oil: IR (film) 3400, 1710, 1645 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.70 (1 H, br s), 3.73 (2 H, t, $J$ = 7 Hz), 3.70 (3 H, s), 2.36 (2 H, t, $J$ = 7 Hz), 2.19 (3 H, d, $J$ = 1.5 Hz); mass spectrum, $m/e$ 144 ($M^+$). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.54; H, 8.10.

**Methyl (*E*)-5-(2-Bromoacetoxy)-3-methylpent-2-enoate (21).** To a solution of 0.30 g (2.08 mmol) of **20** in 5 mL of tetrahydrofuran containing 0.17 g of pyridine cooled to 0 °C was added 0.42 g (2.10 mmol) of α-bromoacetyl bromide. After 0.5 h at 0 °C, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated cupric sulfate solution and water and was dried ($Na_2SO_4$). Evaporation of the solvent gave 0.49 g (88%) of virtually pure **21** as an oil: $^1H$ NMR ($CDCl_3$) $\delta$ 5.74 (1 H, br s), 4.34 (2 H, t, $J$ = 7 Hz), 3.82 (2 H, s), 3.70 (3 H, s), 2.52 (2 H, t, $J$ = 7 Hz), 2.22 (3 H, d, $J$ = 1.5 Hz); mass spectrum, $m/e$ 264.266 (1:1, $M^+$). This material was converted promptly to **22**.

**Methyl (*E*)-3-Methyl-5-[(di-*O*-methylphosphono)acetoxy]pent-2-enoate (22).** A solution of 0.30 g (1.13 mmol) of **21** in 1 mL of trimethylphosphite was heated at 100 °C for 1 h. The excess phosphite was removed in vacuo, and the residue was chromatographed on silica gel, eluting with hexane–ethyl acetate, to yield 0.26 g (81%) of **22** as a viscous oil: IR (film) 1720 (br), 1645, 1260, 1030 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.74 (1 H, br s), 4.34 (2 H, t, $J$ = 7 Hz), 3.78 (6 H, s), 3.71 (3 H, s), 3.01 (2 H, d, $J$ = 22 Hz), 2.53 (2 H, t, $J$ = 7 Hz), 2.22 (3 H, d, $J$ = 1.5 Hz); mass spectrum, $m/e$ 294 ($M^+$). Anal. Calcd for $C_{11}H_{19}O_7P$: C, 44.90; H, 6.46. Found: C, 45.28; H, 6.11.

***Z* Ester 6.** To a stirred mixture of 55.8 mg (1.164 mmol) of sodium hydride (50% dispersion in oil) in 1 mL of dry tetrahydrofuran at 0 °C was added 155.5 mg (0.529 mmol) of **22** in 2 mL of tetrahydrofuran. A yellow solution resulted with the evolution of gas. After 20 min, 52.9 mg (0.529 mmol) of **7** in 2

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mL of tetrahydrofuran was added dropwise, and the reaction mixture was allowed to warm to room temperature. After being stirred for 1 h, the mixture was quenched with 1 mL of water and acidified to pH 2 with 3 N HCl. Saturated ammonium chloride solution (3 mL) was added, and the mixture was extracted with ether. The organic layer was extracted with dilute sodium carbonate solution, the basic extract was acidified to pH 2 with 3 N HCl, and the aqueous layer was extracted with ether. After the ethereal extract was washed twice with water, it was dried ($Na_2SO_4$), and the solvent was removed to yield 114 mg (80%) of **6** as a clear oil: IR (film) 3100 (br), 1720, 1655, 1600 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 217 ($\epsilon$ 15600), 262 (12670); $^{13}C$ NMR $\delta$ 169.7, 166.8, 165.8, 155.2, 142.1, 138.3, 129.0, 124.2, 117.3, 62.7, 50.9, 39.31, 18.50. A small sample of **6** in ether was esterified with an excess of diazomethane, and the product was subjected to rapid chromatography on silica. Elution with ether–hexane (2:3) gave the diester **23** as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 8.35 (1 H, dd, $J$ = 11.16 Hz), 6.58 (1 H, t, $J$ = 11 Hz), 6.03 (1 H, d, $J$ = 16 Hz), 5.92 (1 H, d, $J$ = 11 Hz), 5.70 (1 H, m), 4.30 (2 H, t, $J$ = 7 Hz), 3.74 (3 H, s), 3.66 (3 H, s), 2.52 (2 H, t, $J$ = 7 Hz), 2.22 (3 H, d, $J$ = 1.5 Hz); mass spectrum, $m/e$ 282.112 ($M^+$, calcd for $C_{14}H_{18}O_6$ 282.110).

**Registry No. 5**, 80514-95-0; **6**, 80514-96-1; **7**, 541-57-1; **8**, 590-90-9; **9**, 20705-59-3; **10**, 80514-97-2; **11**, 503-48-0; **12**, 2381-87-5; **14**, 32775-50-1; **15**, 80514-98-3; **16**, 80514-99-4; **17**, 2605-67-6; **18**, 35066-34-3; **19**, 35066-33-2; **20**, 35066-36-5; **21**, 80515-00-0; **22**, 80515-01-1; **23**, 80515-02-2; 2-furoic acid, 88-14-2; ethyl acetate, 141-78-6; $\alpha$-bromoacetyl bromide, 598-21-0; triethyl phosphite, 122-52-1; trimethyl phosphite, 121-45-9.

# Synthetic Routes to 6,8-Dioxabicyclo[3.2.1]octyl Pheromones from D-Glucose Derivatives. 2.‡ Synthesis of (+)-*exo*-Brevicomin

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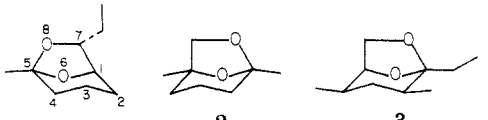
The hydrated, acyclic form of (+)-*exo*-brevicomin indicates that the chirality of the molecule resides in a D-threo glycol segment such as that found at C3 and C4 of D-glucose. Accordingly, "acyclic transfer" of this portion of the sugar into a suitable precursor is required; however, the synthetic route adopted has utilized all six carbons of D-glucose. Thus the C3-hydroxyl group of "diacetone glucose" is benzylated, and the 5,6-*O*-isopropylidene ring is selectively hydrolyzed. The resulting diol is disulfonated, and reductive elimination now gives the hex-5-enofuranose. Acid-induced methanolysis of the 1,2-*O*-isopropylidene ring affords the methyl furanoside, exposing the C2 hydroxyl which is then removed by the Barton–McCombie procedure. Gentle hydrolysis now gives the free furanose which reacts with the ylide from chloroacetone, the crude $\alpha$-enone product being hydrogenated directly. Purification is effected at this stage, upon further treatment with hydrogen, the benzyl group of the saturated ketone is cleaved by hydrogenolysis, and cyclization occurs in situ to give (+)-*exo*-brevicomin.

Sugar derivatives possessing the 6,8-dioxabicyclo-[3.2.1]octyl skeleton, most commonly encountered as 1,6-anhydro-$\beta$-D-hexopyranoses, are readily obtainable,[1-5] and a sizeable body of knowledge about their chemistry exists.[6] However, the first natural products found to contain this ring system were the beetle pheromones *exo*-brevicomin,[7] frontalin,[8] and $\alpha$-multistriatin,[9] shown as their (major) naturally occurring enantiomers **1–3** respectively. The

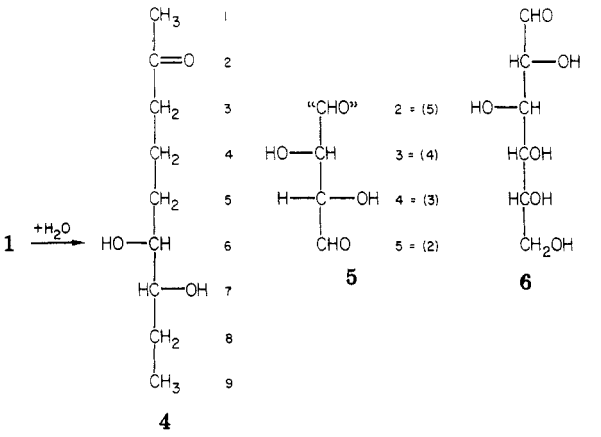


**1** **2** **3**

first of these, *exo*-brevicomin (**1**), was isolated only in 1969 by Silverstein.[7] Subsequently, frontalin (**2**)[8] and multistriatin (**3**)[9] were added. We have studied the preparation of all three from derivatives of D-glucose and now report our results, some of which have appeared in preliminary form.[10,11] In this paper we describe our work on *exo*-brevicomin (**1**), and in the accompanying papers we discuss frontalin (**2**)[12] and $\alpha$-multistriatin (**3**).[13]

*Dendroctonus brevicomins*, the western pine beetle, is a principal pest in timber regions on the western coast of North America. The beetle emits an aggregation pheromone system that attracts other beetles of the same species to the host tree which they inoculate with a pathogenic

Scheme I



**4** **5** **6**

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† From the M.Sc. Thesis of A.E.S. University of Waterloo, 1978.

‡ Reference 10 is considered part 1 of this series.

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