Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 7, pp. 2093-2098, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00252-2

Functionalized Chiral γ-Butyrolactones as C5 Building Units: A Straightforward Formal Synthesis of (+)- *exo*- and (+)-*endo*-Brevicomines

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Abstract: A straightforward formal synthesis of the insect pheromones (+)-*exo*-brevicomin **3** and (+)-*endo*-brevicomin **4** starting from homochiral functionalized γ-butyrolactones **1** and **2** as C5 building units is presented.

Chiral γ-butyrolactones functionalized at the ring carbon are useful as building blocks in natural product syntheses.[1] Recent investigations in this laboratory have achieved the stereoselective synthesis of both enantiomers of *cis*-4-hydroxy-5-(iodomethyl)-4,5-dihydro-2-(3*H*)-furanones **1** and *ent*-**1** and of *trans*-4-*tert*-butyldimethylsiloxy-5-(hydroxymethyl)-4,5-dihydro-2-(3*H*)-furanones **2** and *ent*-**2**.[2] Indeed, these γ-butyrolactones have been demonstrated to have significant utility as versatile synthons in chiral synthesis of a variety of biologically active compounds containing the γ-butyrolactone ring system.[2,3] To investigate the scope of this work, we postulated the functionalized γ-butyrolactones **1** and **2** as equivalents of C5 *syn*- and *anti*-1,2-diol units (A and B), respectively (Chart 1). In order to exemplify their possible application, the concise formal synthesis is reported herein of the title pheromones: (+)-*exo*-brevicomin **3**, [4] the aggregation pheromone of the western pine beetle (*Dendroctonus brevicomis Le Conte*), and (+)-*endo*-brevicomin **4**,[5] the pheromone of the southern pine beetles (*Dendroctonus frontalis* and *Dryocoetes autographus*) (Chart 2).

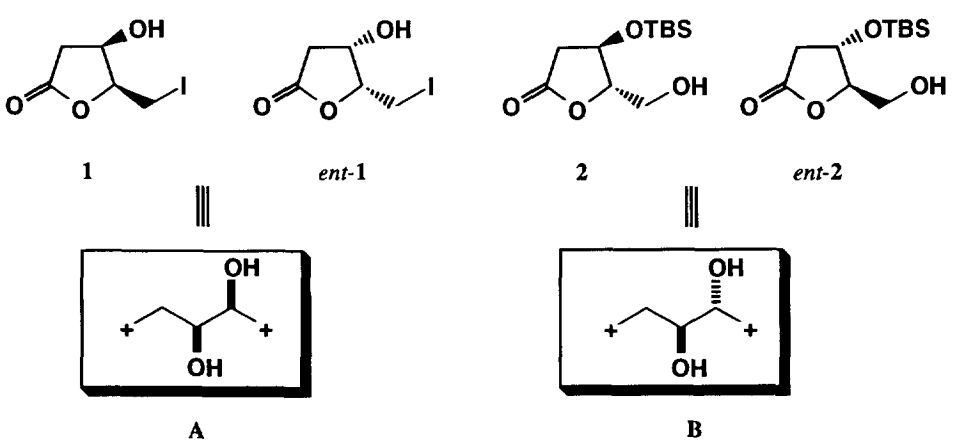
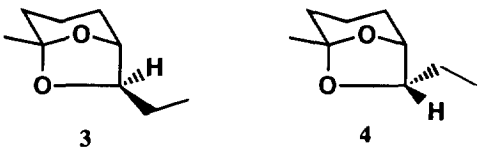


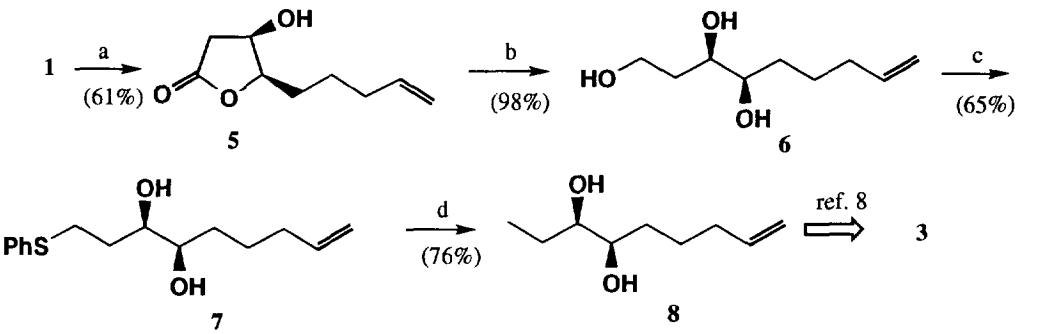
Chart 1



3 4

Chart 2

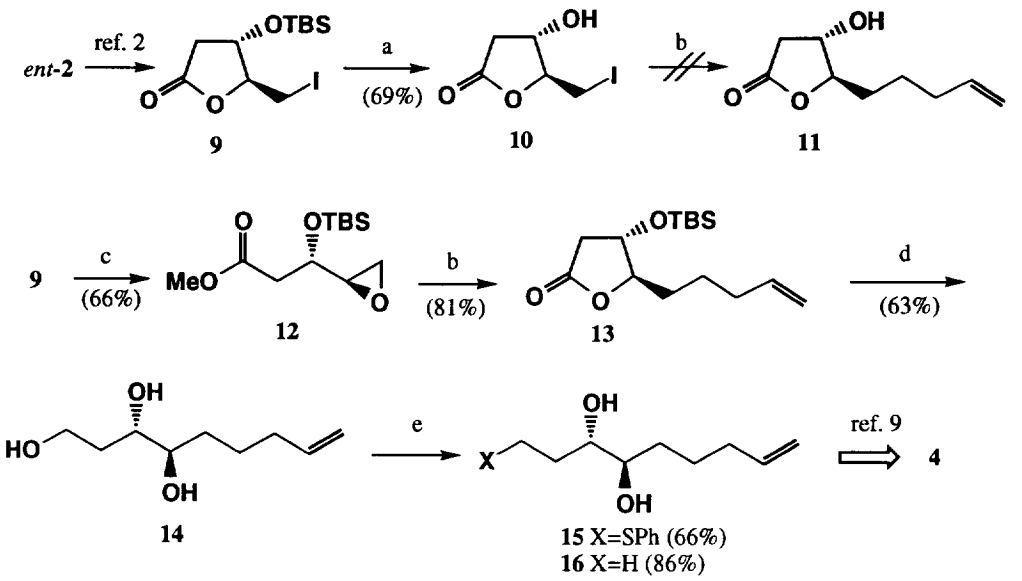
Our synthesis of **3** began with a homologation of the side chain in **1** by use of 1-butenylmagnesium bromide in combination with a cuprous bromide-dimethyl sulfide complex (CuBr-Me_2S) to yield the lactone **5** in 61% yield. Reduction of **5** with lithium aluminum hydride ($LiAlH_4$) gave the triol **6** in 98% yield. Selective sulfenylation of the primary hydroxyl in **6** by Hata's method[6] (PhSSPh/ n-Bu_3P/ pyridine) provided **7** in 65% yield. The diol **7** was desulfenylated with sodium/ammonia to afford the desired synthetic intermediate **8**[7] in 76% yield, which has already been transformed into (+)-*exo*-brevicomin **3** in one step (the Wacker oxidation) by Mori.[8] The spectral data and specific rotation were completely identical with those reported.[8]



(a) 1-butenylmagnesium bromide/CuBr-Me_2S/-20 °C; (b) $LiAlH_4$/0 °C; (c) PhSSPh/n-Bu_3P/pyridine/ reflux; (d) Na/NH_3/-33 °C

Scheme 1

Next, we turned our attention to the formal synthesis of (+)-*endo*-brevicomin **4** by starting from *ent*-**2**. First, with the synthetic method for **3** in mind, the cross-coupling of **10**, prepared from *ent*-**2** in two steps (1; iodination, 2; desilylation), by means of a procedure similar to that described for **5** was examined. Unfortunately, only trace amounts of the desired coupling product **11** were detected, and most of the starting material **10** was recovered. Therefore, **9** was transformed with Na_2CO_3 in methanol into the epoxide **12**, which was cleaved with the Grignard reagent in the presence of CuBr-Me_2S to provide the lactone **13** in 81% yield. Reduction of **13** with $LiAlH_4$ followed by desilylation of the resulting diol afforded the triol **14** in 63% yield. According to the method described for the synthesis of **5**, the sulfenylation of **14** and subsequent desulfenylation were carried out, yielding the desired diol **16** (57%), whose spectral data and specific rotation were identical with those reported.[5e] The conversion of **16** to (+)-*endo*-brevicomin **4** has been performed in one step (the Wacker oxidation) by Mori.[9]



(a) PPTS/EtOH/55 °C; (b) 1-butenylmagnesium bromide/CuBr-Me_2S/-20 °C; (c) Na_2CO_3/MeOH/30 °C (d) (1) $LiAlH_4$/0 °C; (2) HCl/EtOH/r.t.; (e) (1) PhSSPh/n-Bu_3P/pyridine/reflux; (2) Na/NH_3/-33 °C

Scheme 2

In summary, we have demonstrated that the readily available γ–butyrolactones **1** and *ent*-**2** serve as chiral C_5 building synthons (A and B) and can be applied to a straightforward formal synthesis of insect pheromones such as (+)-*exo*-brevicomin **3** and (+)-*endo*-brevicomin **4**. This means that both enantiomers of **3** and **4** could be prepared, because both *ent*-**1** and **2** were readily accessible. Further, the synthesis of several additional pheromones starting from the same building blocks **1** and **2** will be reported shortly.

Experimental Section

Melting points are determined using a Yanaco micro melting point apparatus and are uncorrected. Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Infrared spectra (IR) were measured with a Perkin-Elmer 1600 series FTIR spectrophotometer. Proton magnetic resonance (^1H NMR) spectra were recorded either at 300 MHz on a Varian Gemini-300, or 500 MHz on a Varian Unity-500 with $CHCl_3$ (7.26 ppm) as internal standards. Carbon-13 NMR spectra were determined on a Varian Gemini-300, or 500 MHz on a Varian Unity-500instrument with $CDCl_3$ (77.2 ppm) as an internal standard unless otherwise specified. Mass spectra (MS) and high resolution mass spectra (HRMS) were measured on a JEOL JMS D-200 spectrometer. Optical rotations were measured on a JASCO DIP-140 instrument. Column chromatography was performed on silica gel (Fuji-Division BW-200 or Merck 60 (No 9385) with a medium pressure apparatus and a mixture of ethyl acetate/hexane was used as eluant unless otherwise specified. HPLC was performed with a JASCO Intelligent HPLC pump PU-980 using Nakarai Cosmosil , or Daicel Chiralpac AD or AS. The extracts were dried over Na_2SO_4 unless otherwise specified.

(4*R*,5*R*)-4-Hydroxy-5-(4'-pentenyl)-2(3*H*)-dihydrofuranone 5. To a slurry of CuBr-Me_2S (1.73 g, 8.42 mmol) in THF (8.6 mL) was added a 1 M 1-butenyl bromide-THF solution (8.98 mmol) at -78 °C with stirring. After the mixture was stirred for 30 min, a solution of **1** (681 mg, 2.81 mmol) in THF (4.4 mL) was slowly added. The mixture was gradually warmed to -20 °C, stirred for 6 h, and quenched with sat. NH_4Cl. The insoluble materials were filtered off through Celite and the filtrate was washed with an ammonia solution, and extracted with ethyl acetate with three times. The extracts were dried and evaporated. The residue was chromatographed to give **5** (290 mg, 61%) as an oil: bp 140 °C (3 mmHg); $[\alpha]^{25}_D$ +56.2 (*c* 3.37, $CHCl_3$); IR (neat) 3436, 2932, 1766, 1167 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.60-1.89 (6 H, m,), 2.12 (1 H, br s,), 2.55(1 H, d, *J*= 17.7 Hz), 2.79 (1 H, dd, *J* = 17.7, 3.0 Hz), 4.37 (1 H, m), 4.46 (1 H, m), 5.00 (2 H, dd, *J* = 17.1, 10.3 Hz), 5.76-5.84 (1 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.36, 28.26, 33.96, 40.00, 69.64, 85.09, 115.82, 138.52, 175.96 Anal. Calcd for $C_9H_{14}O_3 \cdot 0.2H_2O$: C, 62.19; H, 8.35. Found: C, 62.51; H, 8.35.

(3*R*,4*R*)-1-Phenylthio-8-nonene-3,4-diol 7. To a suspension of $LiAlH_4$ (80.8 mg, 2.13 mmol) in THF (3.1 mL) was added a solution of **5** (242 mg, 1.42 mmol) in THF (4.3 mL) at 0 °C. After being stirred for 30 min, water (0.1 mL) and subsequent methanol (0.2 mL) were added to the reaction mixture. The insoluble materials were filtered off through Celite and the filtrate was evaporated to leave an oil **6** (242 mg, 98%). Without further purification, Bu_3P (334 μL, 1.34 mmol) was added to a mixture of **6**, diphenyl disulfide (292 mg, 1.34 mmol), and pyridine (1.34 mL) and the reaction mixture was refluxed for 18 h. After addition of 10% H_2O (10 mL) and AcOEt (20 mL) to the mixture, the organic phase was separated. The organic solvent was washed sat. citric acid (20 mL), dried, and evaporated to leave the residue, which was chromatographed to yield **7** (235 mg, 65 %) as an oil; bp 155 °C (0.9 mmHg); $[\alpha]_D^{25}$ + 45.4 (*c* 1.05, $CHCl_3$); IR (neat) 3385, 2934, 1438, 738, 691 cm^{-1}; ^{1}H-NMR (500MHz $CDCl_3$) δ 1.40-1.60 (4 H, m), 1.81 (2 H, m), 2.07 (2 H, m), 2.27 (1 H, br s), 3.06 (1 H, m), 3.15 (1 H, m), 3.42 (1 H, m), 3.63 (1 H, m), 4.99 (2 H, m), 5.79 (1 H, m), 7.18-7.37 (5 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 24.94, 30.34, 32.99, 33.09, 33.75, 73.27, 74.43, 115.00, 126.24, 129.43, 136.26, 138.59; Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32. Found: C, 67.36; H, 8.31.

(3*R*,4*R*)-8-Nonene-3,4-diol 8. To a mixture of Na (102 mg, 4.43 mmol) in NH_3 (30 mL) was injected a solution of **7** (118 mg, 0.443 mmol) in THF (1.5 mL). After being stirred for 30 min, the reaction was quenched with sat. NH_4Cl. Excess ethyl acetate was added to the mixture and the organic layer was separated. The organic solvent was dried and evaporated to leave the residue, which was chromatographed to yield **8** (54 mg, 76%) as an oil; $[\alpha]_D^{25}$ + 25.3 (*c* 1.0, $CHCl_3$), lit. [8] $[\alpha]^{19}_D$ +27.8 (*c* 1.01, $CHCl_3$); IR (neat) 3404, 2936 cm^{-1}; ^{1}H NMR (500 Mz, $CDCl_3$) δ 1.00 (3 H, t, *J*=7.5 Hz), 1.43-1.65 (4 H, m), 1.66 (2 H, m), 2.10 (4 H, m), 3.37 (1 H, m), 3.45 (1 H, m), 5.00 (2 H, m), 5.82 (1 H, m); ^{13}C NMR (125 Mz, CDCl3) δ 10.16, 25.06, 26.12, 33.18. 33.84, 74.14, 76.08, 114.93, 138.75.

(3*S*,4*R*)-Methyl 4,5-epoxy-3-[(*tert*-butyldimethylsily)oxy]-pentanoate 12. A mixture of **9** (6.02 g, 16.90 mmol) and Na_2CO_3 (1.97 g, 18.58 mmol) in MeOH (116 mL) was stirred for 24 h at 30 °C. The solvent was evaporated to leave the residue, to which were added water and ether. The organic solvent was separated, washed with brine, dried, and evaporated to leave the residue, which was chromatographed to yield **12** (2.90g, 66%) as an oil; $[\alpha]_D^{25}$ - 5.28 (*c* 2.59, $CHCl_3$); IR (neat) 2857, 1741, 1252, 838 cm^{-1}; ^{1}H-NMR (500MHz $CDCl_3$) δ 0.01 (3 H, s), 0.03 (3 H, s), 0.82 (9 H, s), 2.51 (1 H, dd, *J* = 14.9, 8.1 Hz), 2.57 (1 H, dd, *J* = 14.9, 4.4 Hz), 2.64 (1 H, dd, *J* = 5.2, 2.6 Hz), 2.71 (1 H, dd, *J* = 5.4, 3.8 Hz), 2.93-2.95 (1 H, m), 3.65 (3 H, s), 3.99-4.03 (1 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -7.173, -4.433, 18.091, 25.721, 40.506, 45.332, 51.724, 54.090, 69.079, 171.443; HRMS. Calcd for $C_{12}H_{24}O_4Si$: 261.1522. Found: 261.1535.

(4*S*,5*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-(4'-pentenyl)-2(3*H*)-dihydrofuranone 13. To a slurry of CuBr-Me_2S (554 mg, 2.69 mmol) in THF (4.6 mL) was added a solution of **12** (699 mg, 2.69 mmol) in THF (1.6 mL) at - 20 °C. To the mixture was slowly added a 1 M 1-butenyl bromide-THF solution (6.74 mmol) over 30 min at -20 °C with stirring. The reaction mixture was stirred for 2 h at the same temperature and quenched with sat. NH_4Cl. The mixture was extracted with ether three times. The extracts were successively washed with sat. NH4Cl, water, and brine. The solvent was dried and evaporated to leave the residue, which was chromatographed to yield **13** (677 mg, 81%) as an oil; $[\alpha]_D^{25}$ + 37.2 (*c* 4.29, $CHCl_3$); IR (neat) 3077, 2930, 1785 cm^{-1}; ^1H NMR (500 Mz, $CDCl_3$) δ 0.08 (3 H, s), 0.09 (3 H, s), 0.89 (9 H, s), 1.54-1.65 (4 H, m), 2.11 (2 H,, dd, *J* = 7.5, 1.1 Hz), 2.45 (1 H, dd, *J* = 17.5, 4.7 Hz), 2.75 (1 H, dd, *J* = 17.5, 6.8 Hz), 4.16-4.19 (1 H, m), 4.24-4.27 (1 H, m), 4.98-5.05 (2 H, m), 5.75-5.81 (1 H, m); ^{13}C NMR (125 Mz, CDCl3) δ -4.713, -4.530, 18.039, 24.644, 25.765, 32.392, 33.351, 38.375, 72.477, 87.767, 115.425, 137.979, 174.996; HRMS. Calcd for $C_{15}H_{28}O_3Si$: 284.1808. Found: 284.1821.

(3*S*,4*R*)-1-Phenylthio-8-nonene-3,4-diol 15. To a suspension of $LiAlH_4$ (100 mg, 2.64 mmol) in THF (6 mL) was added a solution of **13** (501 mg, 1.76 mmol) in THF (7 mL) at 0 °C. After being stirred for 30 min, water (0.1 mL) , 2N NaOH (0.3 mL), and water (0.3 mL)were successively added to the reaction mixture. After addition of excess THF, the mixture was dried. The insoluble materials were filtered off through Celite and the filtrate was evaporated to leave the diol as an oil (401 mg). Without further purification, 10% HCl (0.5 mL) was added to a solution of the diol in methanol (6 mL). The mixture was stirred at room temperature for 3 h and evaporated to leave the residue. After addition of toluene to the residue, the solvent was evaporated to leave the residue, which was chromatographed to yield **14** (227 mg, 94%) as a white solid; $[\alpha]_D^{25}$ -1.75 (*c* 1.80, MeOH); ^1H-NMR (500MHz $CDCl_3$) δ 1.40-1.77 (6 H, m), 2.06-2.14 (2 H, m), 3.64 (1 H, br s), 3.68-3.85 (4 H, br s), 4.95-5.04 (2 H, m), 5.77-5.85 (1 H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 25.464, 31.491, 32.436, 33.827, 61.156, 74.381, 74.527, 114.971, 138.668; HRMS. Calcd for $C_9H_{18}O_3$: 174.1256. Found: 174.1255. According to the analogous procedure described for **7**, a mixture of **14** (59 mg, 0.338 mmol), pyridine (0.4 mL), PhSSPh (73 mg, 0.338 mmol), and Bu_3P (84 μL, 0.338 mmol) gave **15** (59 mg, 66%) as a white solid; mp 78-82 °C; $[\alpha]_D^{25}$ -29.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3320 cm^{-1}; ^1H NMR (500 Mz, $CDCl_3$) δ 1.38-1.85 (6 H, m), 2.05-2.09 (3 H, m), 2.36 (1 H, br s), 3.01-3.07 (1 H, m), 3.15-3.21 (1 H, m), 3.62-3.64 (1 H, br s), 3.77-3.81 (1 H, br s), 4.95-5.04 (2 H, m), 5.75-5.83 (1 H, m), 7.18-7.37 (5 H, m); ^{13}C NMR (125 Mz, $CDCl_3$) δ 25.303, 30.180, 30.642, 31.169, 33.776, 73.436, 74.674, 115.030, 126.226, 129.126, 129.368, 136.185, 138.565; Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32. Found: C, 67.86; H, 8.35.

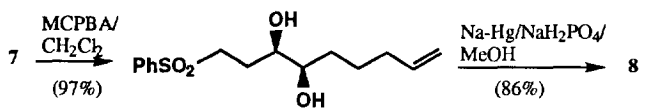
(3*S*,4*R*)-8-Nonene-3,4-diol 16. By means of a procedure similar to that described for **8**, the reaction of **15** (59 mg, 0.222 mmol) with Na (51 mg, 2.22 mmol) in NH_3 (15 mL) gave **16** (30 mg, 86%) as a white solid; mp 82-84 °C, lit.[9] mp 81-2 °C; $[\alpha]^{25}_D$ +11.5 (*c* 0.74, $CHCl_3$), lit. [9] $[\alpha]^{21}_D$ +11.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 Mz) δ 1.005 (3 H, t, *J*=7.4 Hz), 1.41-1.71 (6 H, m), 1.98 (2 H, br s), 2.07-2.18 (2 H, m), 3.53-3.55 (1 H, br s), 3.63 (1 H, br s), 4.96-5.05 (2 H, m), 5.78-5.86 (1 H, m); ^{13}C NMR (125 Mz, $CDCl_3$) δ 10.607, 24.388, 25.435, 30.708, 33.864, 74.439, 76.402, 114.934, 138.748.

Acknowledgments

This work was supported in part by the Chemical Materials Research and Development Foundation. The generous gift of lipase from Amano Pharmaceutical Co. is gratefully acknowledged.

REFERENCES AND NOTES

1. For syntheses of chiral γ-butyrolactones, see: Koch, S. S.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725 and refs cited therein.
2. Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1994**, *59*, 7201.
3. (a) Takahata, H.; Uchida, Y.; Momose, T. *Tetrahedron Lett.* **1994**, *35*, 4123; (b) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1995**, *60* , 5628.
4. Isolation: (a) Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; Browne, L. E. *Science* **1968**, *159*, 889; Recent previous syntheses of (+)-*exo*-brevicomin: (b) Soderquist, J. A.; Rane, A. M. *Tetrahedron Lett.* **1993**, *34*, 5031; (c) Turpin, J. A.; Weigel, L. O. *Tetrahedron Lett.* **1992**, *33*, 6563; (d) Myles, D. C.; Andrulis, P. J., III; Whitesides, G. M. *Tetrahedron Lett.* **1991**, *32*, 4835.
5. Isolation: (a) ref.4a; (b) Kohnle, U.; Vité, J. P. *Naturwiss* **1984**, *71*, 47. Recent previous syntheses of (+)-*endo*-brevicomin: (c) Kim, M.-J.; Choi, G.-B.; Kim, J.-Y.; Kim, H.-J. *Tetrahedron Lett.* **1995**, *36*, 6253; (d) Gypser, A.; Flasche, M.; Scharf, H.-D. *Liebigs Ann. Chem.* **1994**, 775; (e) Mori, K.; Kiyota, H.. *Liebigs Ann. Chem.* **1992**, 989; (f) Pedrocchi-Fantoni, G.; Servi, S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1764.
6. Nakagawa, I; Hata, T. *Tetrahedron Lett.* **1975**, 1409.
7. The diol **8** was also prepared from **7** by an alternative procedure shown below.



8. Mori, K.; Seu, Y.-B. *Liebigs Ann. Chem.* **1986**, 205.
9. Mori, K.; Seu, Y.-B. *Tetrahedron* **1985**, *41*, 3429.

(*Received in Japan* 7 *May* 1996)