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ENANTIOSELECTIVE SYNTHESES OF *endo*- AND *exo*-BREVICOMIN VIA α-ALKOXYSTANNANES

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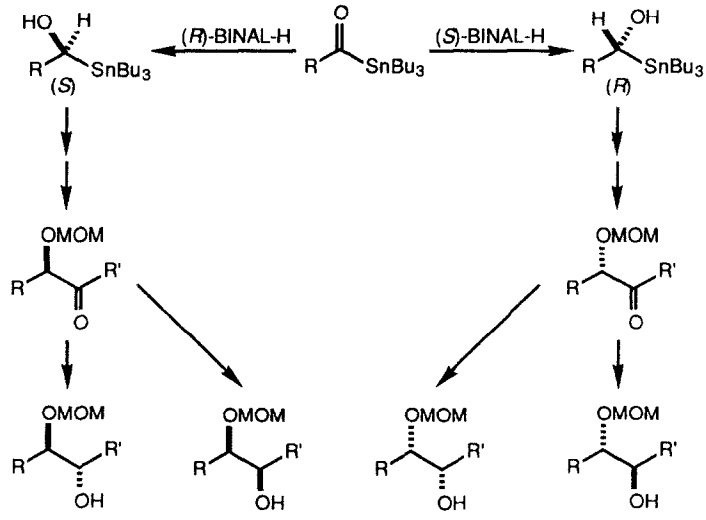
Abstract

Enantioselective syntheses of (+)-endo-brevicomin (1) and (-)-exo-brevicomin (2) from the same enantiomerically-enriched α-alkoxyorganostannane are described. Reduction of 3 with (S)-BINAL-H gave (R)-4 in 98% ee. Transmetalation of (R)-4 with n-BuLi and reaction with N,N-dimethylamide 5 afforded α-alkoxyketone 6 with complete retention of configuration. Further manipulation of 6 efficiently provided either (+)-1 or (-)-2.

Recently, we described the asymmetric reduction of acylstannanes using 2,2'-dihydroxy-1,1'-binaphthyl-modified lithium aluminum hydride (BINAL-H) reagents as the first practical route to enantiomerically-enriched α-alkoxystannanes.[1] α-Alkoxystannanes undergo tin-lithium exchange at low temperatures with retention of configuration, giving rise to configurationally stable α-alkoxyorganolithium reagents.[2] Thus, homochiral α-alkoxystannanes serve as convenient precursors to stereodefined α-alkoxyorganolithium reagents. It was envisaged that one possible application of these reagents would be in the preparation of 1,2-diols of defined absolute and relative stereochemistry. Specifically, it was anticipated that conversion of an α-alkoxyorganolithium to an α-alkoxyketone[3] followed by selective Cram or chelation-controlled reduction[4] would provide the *syn*- or *anti*-1,2-diol, respectively. Moreover, since the absolute stereochemistry of the α-alkoxystannane is defined, this approach would allow one to selectively prepare any of the four possible stereoisomeric 1,2-diols (Scheme I). To test the validity of this approach, in particular to ascertain whether preparation of the α-alkoxyketones proceeds with retention of configuration and whether diastereoselective reductions could be achieved, we undertook enantioselective syntheses of *endo*- and *exo*-brevicomin.

The brevicomins are components of a pheromone system found in several economically important bark beetle species.[5] For example, (+)-*endo*-brevicomin [(+)-**1**] (Scheme II) is an aggregation pheromone for *Dryocetes autographus* which attacks Norway spruce trees.[6] It is also known that (+)-*endo*-brevicomin markedly enhances the aggregation response of southern pine beetles (*Dendroctonus frontalis*) to "Frontalure" (a mixture of racemic frontalin and α-pinene) whereas its

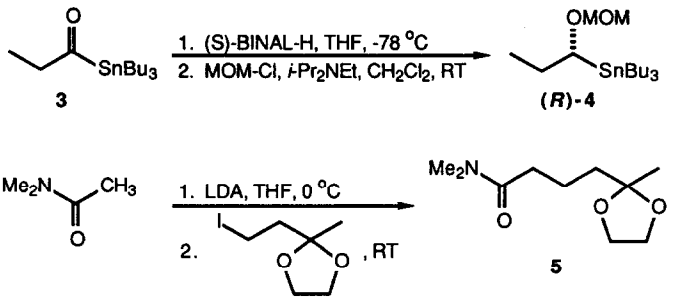
Scheme I



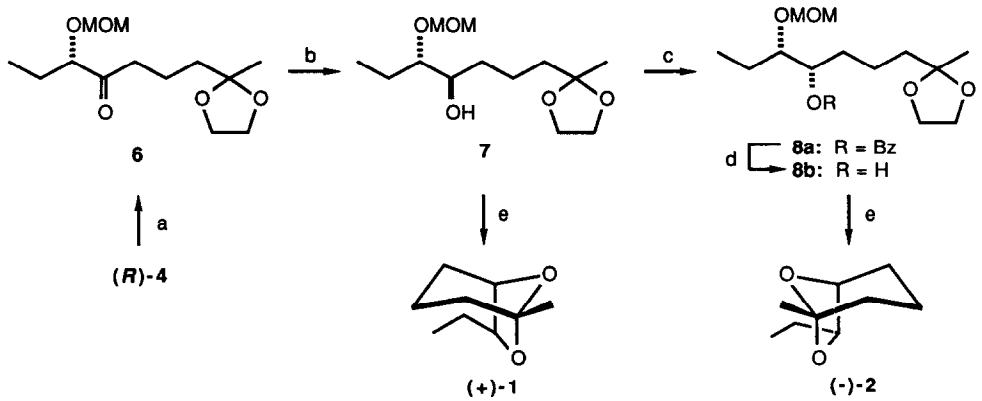
(-)-enantiomer inhibits it.[7] The diastereomeric (+)-*exo*-brevicomin [(+)-**2**] (but not (-)-**2**) has been shown to attract *Dendroctonus brevicomis*, a serious pest of many Western North American pine trees.[8] It is clear, then, that the absolute and relative stereochemistry of these pheromones can play a significant role in their actions, and therefore stereoselective syntheses would be highly desirable. And, in fact, a great many enantioselective syntheses of these pheromones have been reported.[9,10]

The enantioselective syntheses of *endo*- and *exo*-brevicomins using enantiomerically-enriched α-alkoxystannanes are short and efficient (Scheme II). Acylstannane **3**, prepared[11] from tributylstannylmagnesium chloride and propionaldehyde, was reduced with (*S*)-BINAL-H[12] to the (*R*)-α-hydroxystannane which was immediately converted to the methoxymethyl ether (*R*)-**4**. The high enantioselectivity (98% ee) of the reduction was confirmed by HPLC analysis of the derived (+)-MTPA ester. Transmetalation of (*R*)-**4** to the intermediate α-alkoxyorganolithium species followed by trapping[3] with amide **5** (which was prepared[13] from N,N-dimethylacetamide and 2-(2-iodoethyl)-1,3-dioxolane[14]), gave the α-alkoxyketone **6** in 76% yield. Chelation-controlled reduction[4a,c,f] of **6** with $Zn(BH_4)_2$ then provided **7** with good diastereoselectivity (93% de), as shown by HPLC analysis of the 3,5-dinitrophenylcarbamate derivative. The enantiomeric purity of **7** was also determined by performing the HPLC analysis on a chiral Pirkle D-naphthylalanine column.[15] Since the enantiomeric purities of the starting stannane **4** and alcohol **7** were identical (98% ee), the transmetalation-trapping sequence proceeded with complete retention of configuration.

Finally, (+)-*endo*-brevicomin [(+)-**1**] was synthesized from **7** by deprotection of the acetal and ketal functionalities and concomitant cyclization under acidic conditions. Since no epimerization is expected, the *endo*-brevicomin produced should have the same stereochemical purity as **7**



Scheme II[a]



[a] Reagents: (a) 1. *n*-BuLi, DME, -78 °C; 2. **5**, -78 °C; (b) $Zn(BH_4)_2$, Et_2O, -20 °C; (c) Ph_3P, $PhCO_2H$, DIAD, Et_2O, RT; (d) $LiAlH_4$, Et_2O, 0 °C; (e) cat. 70% $HClO_4$, CH_2Cl_2, 0 °C.

(i.e. *R*:*S* = 96.5:3.5 at C-6, *R*:*S* = 1:99 at C-7). Indeed, the same de (93%) was obtained upon analyzing the ^{13}C NMR of (+)-**1**. The overall yield from (*R*)-**4** over three steps was 50%.

The synthesis of (-)-*exo*-brevicomin [(-)-**2**] required **8b**, the *syn* isomer of **7**. It was hoped that reduction of **6** using a bulky reducing agent would selectively provide **8b**. Unfortunately, reduction of **6** with L-Selectride® (which has proven to be very *syn*-selective in very similar systems[4a,b,c]) gave only very modest selectivity.[16] Ultimately, the *syn* diol **8b** was obtained by performing a Mitsonobu inversion[17] on **7** to give the benzoate ester **8a**, followed by $LiAlH_4$ reduction. The ee and de of **8a** were determined by HPLC analysis of the 3,5-dinitrophenylcarbamate derivative of **8b** and were found to be 98% and 99%, respectively. As expected, the ee of **8b** is identical to that of **7** but the de is higher, presumably due to fortuitous removal of the minor diastereomer during chromatography of **8a**. Acid-catalysed cyclization of **8b** yielded (-)-*exo*-brevicomin [(-)-**2**] in 88% yield. The overall yield of (-)-**2** from (*R*)-**4** was 40% over five steps.

Syntheses of the antipodes of (+)-**1** and (-)-**2** can be easily accomplished by utilizing (*R*)-BINAL-H in the asymmetric reduction of **3**. Thus, in principle, one could use the above methodology to prepare selectively any of the four brevicomins. In a more general sense, the syntheses described above illustrate the utility of α-alkoxystannanes in the synthesis of stereochemically-defined 1,2-diols.

Experimental Section

General. All reactions were carried out with dry glassware under an atmosphere of argon unless otherwise noted. Diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, and toluene were distilled from sodium/benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2. Anhydrous ethanol was distilled from magnesium and stored over 3Å sieves. (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) was prepared from the corresponding acid according to the procedure of Sharpless *et al.*[18] 3,5-Dinitrobenzoyl azide was prepared using the method of Pirkle *et al.*[15] Optically pure (S)-(-)-1,1'-bi-2-naphthol was obtained by enzymatic resolution according to the procedure of Kazlauskas.[19] Other reagents were purchased (Aldrich) and were used without further purification. Thin-layer chromatography was carried out on silica gel 60 F_{254} aluminum sheets (Merck 5554). Developed plates were visualized by staining with a 4% solution of phosphomolybdic acid in ethanol. Flash chromatography was performed using Merck 9385 silica gel 60 (230-400 mesh). Optical rotations were measured on a JASCO DIP-360 digital polarimeter. Infrared spectra were recorded on a Perkin-Elmer 983 infrared spectrophotometer as neat liquids between NaCl plates. ^1H and ^{13}C NMR spectra were recorded using Bruker AC-200 or AM-250 spectrometers using $CDCl_3$ as solvent; tetramethylsilane (^1H, δ 0.0) or $CDCl_3$ (^{13}C, δ 77.0) were used as internal references. Mass spectra were recorded on a Kratos MS890 mass spectrometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

High performance liquid chromatography (HPLC) analyses were conducted on a Waters 600E instrument equipped with a Waters 484 UV-visible detector and a Waters 745 recording integrator. Two methods were used: Method A consisted of a RESOLVE™ Silica Radial-Pak cartridge (5 μm, 8 x 100 mm, Waters), hexane/CH_2Cl_2 82:18 (v/v) as eluant, a flow rate of 2.0 mL/min, and detection at 254 nm; Method B consisted of a Pirkle covalent D-naphthylalanine column (5 μm, 250 mm x 4.6 mm i.d., Regis Chemicals Ltd.), hexane/*i*-PrOH 90:10 (v/v) as eluant, a flow rate of 2.0 mL/min, and detection at 280 nm.

1-(Tri-*n*-butylstannyl)propan-1-one (3). To a cold (0 °C), brown solution of Galvinoxyl (0.4 g, 1 mmol) in Et_2O (30 mL) was slowly added *i*-PrMgCl (2 M in Et_2O, 30 mL, 60 mmol). The solution changed to a red colour and then faded to a pale yellow colour. After 10 min, *n*-Bu_3SnH (16.2 mL, 17.4 g, 60 mmol) was added. The colour of the solution turned to orange and again faded to a pale yellow colour. The reaction was then allowed to warm to room temperature and stirred until most of the *n*-Bu_3SnH was consumed (ca. 1-2 h). This was determined by quenching a small amount of the reaction mixture with D_2O and, after standard extractive workup, running the IR spectrum of the product. The intensities of the bands at 1306 cm^{-1} (υ Sn-D) and 1808 cm^{-1} (υ Sn-H) gave the relative amounts of *n*-Bu_3SnD (and hence, by inference, *n*-$Bu_3SnMgCl$) and *n*-Bu_3SnH, respectively.

Propionaldehyde (10 mL, 8.0 g, 140 mmol) was then added slowly to the reaction mixture *via* syringe [**Caution:** *violent reaction*], and the color changed from yellow to orange and then back to yellow. The reaction mixture was heated at reflux temperature for 5 h. It was then cooled to 0 °C, quenched with saturated aqueous ammonium chloride, and then diluted with Et_2O (150 mL). The layers were separated and the organic layer was washed with H_2O (60 mL) and brine (60 mL). Drying ($MgSO_4$) followed by concentration of the organic layer gave the crude product[20] as a dark yellow oil. Vacuum distillation (80 °C, 0.2 torr) through a 15 cm Vigreux column afforded 11 g (53% yield) of the product as a bright yellow oil which was immediately stored under argon and kept in a freezer. Spectral data were identical to that described in the literature.[11d]

(*R*)-1-Methoxymethoxy-1-(tri-*n*-butylstannyl)propane [(*R*)-4]. To a solution of $LiAlH_4$ [1.0 M in THF, 9.0 mL, ca. 10 mmol] in anhydrous THF (25 mL) was added a solution of anhydrous EtOH (461 mg, 10.0 mmol) in THF (2 mL). A THF rinse (1 mL) of the EtOH-containing flask was added. A solution of (S)-(-)-1,1'-bi-2-naphthol (2.86 g, 10.0 mmol) in THF (10 mL) was then *slowly* added *via* syringe. THF rinses (2 x 2.5 mL) of the binaphthol-containing flask were added. If a heavy white precipitate was present at the end of the binaphthol addition, then a "judicious" amount (ca. 0.1 mL increments) of $LiAlH_4$ solution was added until a thin slurry was obtained.[21] (The selectivity is *lowered dramatically* if either too *much* or too *little* $LiAlH_4$ is added). The resulting milky mixture was stirred at room temperature for 3-4 h and then cooled to -78 °C. A THF solution (5.0 mL) of acylstannane **3** (1.23 g, 3.54 mmol) was slowly added. A THF rinse (2.5 mL) of the acylstannane-containing flask was added. After 3 h, the reaction mixture was quenched with saturated NH_4Cl solution and was allowed to warm to room temperature. Water (500 mL) was added and the mixture was extracted with Et_2O (3 x 250 mL). The combined organic extract was washed with H_2O (75 mL) and brine (25 mL), and was then dried ($MgSO_4$) and concentrated (room temperature bath, 20 torr). Petroleum ether (10 mL) was added to precipitate the binaphthol (to be recycled), and the mixture was filtered through anhydrous Na_2SO_4 in a Pasteur pipette. Concentration of the filtrate (room temperature bath, 20 torr) gave 1.25 g of the α-hydroxystannane as a yellow oil.

A small amount (ca. 25 mg) of the intermediate α-hydroxystannane was converted to the Mosher ester using standard conditions [(*R*)-(+)-MTPA-Cl, Et_3N, cat. DMAP, CH_2Cl_2] for analysis of ee by ^1H NMR and by HPLC. Integration of the protons due to the -OMe group in the 250 MHz ^1H NMR spectrum of the Mosher ester provided the diastereomeric ratio, which was ca. >20:1. The ratio by HPLC analysis using Method A [elution times: (*R*)-isomer, 9 min; (S)-isomer, 13 min] was shown to be *R*:*S* = 95-100:1 (98% de). Thus, the enantiomeric purity of the α-hydroxystannane was 98% ee.

Dichloromethane (2 mL) and *i*-Pr_2NEt (1.55 mL, 8.90 mmol) were added to the remainder of the crude α-hydroxystannane, and the mixture was cooled to 0 °C. Chloromethyl methyl ether (0.450 mL, 5.92 mmol) was added and the reaction mixture was stirred at 0 °C for 3 h, and then at room temperature for 16 h. The mixture was diluted with Et_2O (175 mL) and washed with H_2O (4 x 10 mL), and brine (10 mL). Drying ($MgSO_4$), followed by concentration yielded 1.36 g of a yellow oil. Flash chromatography (60 g silica, petroleum ether/ether 100:1) afforded 786 mg (57% yield) of the desired product as a pale yellow oil: $[\alpha]_D^{24}$ -38° (c 1.3, $CHCl_3$); IR (film) 2949, 2919, 2865, 2812, 2761, 1658, 1456, 1412, 1392, 1371, 1335, 1288, 1268, 1245, 1210, 1179, 1143, 1097, 1034, 958, 919, 873, 687, 662 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.58 (AB q, 2H, J = 6.6 Hz, $\Delta\upsilon_{AB}$ = 13.9 Hz, $OC\underline{H}_2O$), 4.00 (t, 1H, J = 6.6 Hz, $OC\underline{H}CH_2$), 3.35 (s, 3H, $OC\underline{H}_3$), 1.85 (dq, 2H, J = 6.6, 7.3 Hz, $OCHC\underline{H}_2CH_3$), 1.20-1.60 (m, 18H, $C\underline{H}_2$'s of *n*-Bu), 0.97 (t, 3H, J = 7.3 Hz, $C\underline{H}_3CH_2$); 0.90 (t, 9H, J = 7.3 Hz, $C\underline{H}_3$'s of *n*-Bu); ^{13}C NMR (50 MHz, $CDCl_3$) δ 96.34 [$^3J(^{13}C\text{-}Sn)$ = 20 Hz], 75.61 [$^1J(^{13}C\text{-}^{117/119}Sn)$ = 193, 202 Hz], 55.37, 29.21 [$^3J(^{13}C\text{-}Sn)$ = 20 Hz], 27.88, 27.51 [$^2J(^{13}C\text{-}Sn)$ = 54 Hz], 13.66, 12.36, 9.17 [$^1J(^{13}C\text{-}^{117/119}Sn)$ = 291, 304 Hz]; m/z 337(M^+-C_4H_9, 63.7), 291(84.8), 265(8.2), 235(73.6), 179(100), 149(7.1), 121(27.3). Anal. Calcd for $C_{17}H_{38}O_2Sn$: C, 51.93; H, 9.74. Found: C, 51.98; H, 9.57.

N,N-Dimethyl-5-oxohexanamide ethylene ketal (5). To a cold (0 °C) stirred solution of *i*-Pr_2NH (3.8 g, 38 mmol) in THF (300 mL) was slowly added *n*-BuLi (1.6 M in hexanes, 23 mL, 37 mmol) and the resulting pale yellow solution stirred for 10 min. N,N-Dimethylacetamide (3.0 g, 34 mmol) was then added and the reaction mixture was stirred at 0 °C for 20 min. 2-Methyl-2-(2-iodoethyl)-1,3-dioxolane[14] (9.1 g, 38 mmol) was then added and the reaction was allowed to warm to room temperature. After 2 h, water (10 mL) followed by CH_2Cl_2 (500 mL) were added. The organic layer was separated and washed with water (10 mL). Drying ($MgSO_4$), followed by concentration yielded ca. 9 g of a mixture of LiI needles and the crude product.

The crude mixture was taken up in Et_2O (300 mL) and washed with water (20 mL). The aqueous layer was extracted with Et_2O (150 mL) and the combined organic layer was dried and concentrated to afford 6.0 g of a light yellow oil. Vacuum distillation (108-117 °C, 0.8 torr) yielded 4.3 g of the product as a colourless liquid. Flash chromatography (26 g silica, CH_2Cl_2/MeOH 20:1) of the stillpot residue, which also contained product, furnished an additional 1.0 g of the product as a pale yellow oil. The combined yield was 76%: IR (film) 2977, 2935, 2879, 1646, 1495, 1458, 1396, 1375, 1330, 1307, 1260, 1219, 1154, 1123, 1102, 1061, 948, 861, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.93 (m, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.00 (s, 3H, $C\underline{H}_3N$), 2.94 (s, 3H, $C\underline{H}_3N$), 2.34 (t, 2H, J = 6.8 Hz, $COC\underline{H}_2CH_2$), 1.65-1.82 (m,

4H, $C\underline{H}_2C\underline{H}_2$), 1.32 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.31, 109.44, 64.17, 38.17, 36.82, 34.87, 32.80, 23.37, 19.33; m/z 201(M^+, 8), 186(49), 158(36), 141(23), 114(22), 99(73), 91(87), 87(100), 72(69), 65(41), 55(56). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.58; H, 9.36; N, 6.85.

(3*S*)-3-Methoxymethoxy-4,8-nonanedione 8-ethylene ketal (6). To a cold (-78 °C), stirred solution of (***R***)-**4** (1.20 g, 3.07 mmol) in DME (30 mL) was added *n*-BuLi (1.64 M in hexanes, 1.85 mL, 3.03 mmol), and the solution was stirred for 15 min. Amide **5** (609 mg, 3.02 mmol) was added and the reaction mixture was stirred at -78 °C for 1 h. After being quenched with MeOH (1 mL) and being allowed to warm to room temperature, the reaction mixture was diluted with Et_2O (300 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic extract was dried ($MgSO_4$) and concentrated to yield 1.8 g of a mixture of two immiscible oils. Flash chromatography (50 g silica, petroleum ether/ethyl acetate 4:1) provided 566 mg (72% yield) of **6** as a pale yellow oil: $[\alpha]_D^{24}$ -44° (c 1.1, $CHCl_3$); IR (film) 2937, 2881, 2823, 1712, 1457, 1401, 1375, 1305, 1254, 1216, 1152, 1101, 1040, 947, 919, 871 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.64 (AB q, 2H, J = 6.9 Hz, $\Delta\upsilon_{AB}$ = 9.8 Hz, $OC\underline{H}_2O$), 3.93 [m, 5H, $OC\underline{H}_2C\underline{H}_2O$, $C\underline{H}(OCH_2OCH_3)$], 3.37 (s, 3H, $OC\underline{H}_3$), 2.54 (t, 2H, J = 6.8 Hz, $COC\underline{H}_2CH_2$), 1.62-1.73 (m, 6H, $C\underline{H}_2C\underline{H}_2$, $CH_3C\underline{H}_2$), 1.32 (s, 3H, $C\underline{H}_3$), 0.96 (t, 3H, J = 7.4 Hz, $C\underline{H}_3CH_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.29, 109.78, 96.27, 83.44, 64.58, 55.88, 38.37, 38.30, 25.17, 23.66, 17.73, 9.57; m/z 245 (M^+-CH_3, 8), 202(3), 157(61), 127(11), 113(12), 99(52), 87(100), 71(7), 55(21). Anal. Calcd for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.91; H, 9.16.

(6*R*,7*S*)-6-Hydroxy-7-methoxymethoxy-2-nonanone ethylene ketal (7). To a cold (-20 °C), stirred solution of **6** (518 mg, 1.99 mmol) in dry Et_2O (20 mL) was added $Zn(BH_4)_2$[22] (ca. 0.2 M in Et_2O, 18.5 mL, 4.07 mmol). After 3 h, the reaction was quenched carefully with H_2O and allowed to warm to room temperature. The mixture was taken up in Et_2O (200 mL) and washed with H_2O (50 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated to afford 604 mg of a slightly cloudy, pale yellow oil. Flash chromatography (20 g silica, petroleum ether/ether 2:1) gave 480 mg (92% yield) of the product as a pale yellow oil: $[\alpha]_D^{24}$ +22° (c 1.1, $CHCl_3$); IR (film) 3475, 2939, 2879, 1460, 1376, 1308, 1213, 1146, 1131, 1098, 1038, 947, 916, 869 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.70 (AB q, 2H, J = 6.8 Hz, $\Delta\upsilon_{AB}$ = 19.1 Hz, $OC\underline{H}_2O$), 3.94 (m, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.60 [br m, 1H, $C\underline{H}(OH)$], 3.44 [m, 1H, $C\underline{H}(OCH_2OCH_3)$], 3.42 (s, 3H, $OC\underline{H}_3$), 2.73 [br d, 1H, J = 6.8 Hz, $CH(O\underline{H})$], 1.39-1.70 (m, 8H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$, $CH_3C\underline{H}_2$), 1.32 (s, 3H, $C\underline{H}_3$), 0.95 (t, 3H, J = 7.4 Hz, $C\underline{H}_3CH_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 110.00, 97.20, 85.45, 72.65, 64.55, 55.69, 39.12, 31.61, 23.69, 23.16, 20.74, 10.41; m/z 247(M^+-CH_3, 5), 215(3), 201(4), 185(5), 159(83), 141(22), 127(15), 115(33), 97(58), 87(100), 71(56), 59(52). Anal. Calcd for $C_{13}H_{26}O_5$: C, 59.52; H, 9.99. Found: C, 59.65; H, 10.05.

A small amount (ca. 5 mg) of **7** was converted to the 3,5-dinitrophenylcarbamate derivative (3,5-dinitrobenzoyl azide, toluene, reflux) for analysis of ee and de by HPLC. Using Method B, the elution times of the isomers of **7** were as follows: (6*R*,7*R*), 20.12 min; (6*S*,7*R*), 20.14 min; (6*S*,7*S*), 21.50 min; (6*R*,7*S*), 27.44 min. The ee and de were determined to be 98% and 93%, respectively.

(6*S*,7*S*)-6-Hydroxy-7-methoxymethoxy-2-nonanone ethylene ketal benzoate (8a). To an Et_2O (15 mL) solution of **7** (471 mg, 1.79 mmol), Ph_3P (711 mg, 2.71 mmol), and $PhCO_2H$ (243 mg, 1.99 mmol) was added diisopropyl azodicarboxylate (DIAD, 0.530 mL, 2.69 mmol). The mixture was stirred at room temperature for 48 h. The resulting white precipitate of Ph_3P=O was removed by filtration and washed with petroleum ether. Removal of the solvent gave 1.6 g of a thick yellow oil. Flash chromatography (50 g silica, petroleum ether/ether 4:1) afforded 567 mg (86% yield) of **8a**: $[\alpha]_D^{24}$ -12° (c 2.2, $CHCl_3$); IR (film) 3063, 2937, 2883, 2823, 1718, 1601, 1584, 1490, 1451, 1376, 1314, 1272, 1218, 1110, 948, 920, 863, 806, 786, 713, 688, 670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.04-8.10 (m, 2H, Ar $\underline{H}$), 7.39-7.60 (m, 3H, Ar $\underline{H}$), 5.29 [ddd, 1H, J = 5.0, 6.2, 6.2 Hz, $C\underline{H}(OBz)$], 4.70 (AB q, 2H, J = 6.8 Hz, $\Delta\upsilon_{AB}$ = 13.4 Hz, $OC\underline{H}_2O$), 3.89 (m, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.65 [ddd, 1H, J = 5.3, 5.3, 6.8 Hz, $C\underline{H}(OCH_2OCH_3)$], 3.38 (s, 3H, $OC\underline{H}_3$), 1.43-1.82 (m, 8H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$, $CH_3C\underline{H}_2$), 1.28 (s, 3H, $C\underline{H}_3$), 0.98 (t, 3H, J = 7.4 Hz, $C\underline{H}_3CH_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.07, 132.81, 130.33, 129.60, 128.28, 109.79, 96.49, 79.47, 74.77, 64.52, 55.77, 38.87, 29.89, 23.67, 23.27, 20.12, 9.84; m/z 351(M^+-CH_3, 4.5), 203(1.3), 149(38), 105(80), 87(100). Anal.

Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.65; H, 8.17. The same reaction using diethyl azodicarboxylate (DEAD) gave only 50% of the product.

(6*S*,7*S*)-6-Hydroxy-7-methoxymethoxy-2-nonanone ethylene ketal (8b). To a cold (0 °C) suspension of $LiAlH_4$ (125 mg, 3.29 mmol) in dry Et_2O (24 mL) was added an Et_2O (8 mL) solution of **8a** (567 mg, 1.55 mmol). The reaction mixture was stirred at 0 °C for 2 h and was then quenched (carefully!) with H_2O. The mixture was diluted with Et_2O (60 mL) and washed with H_2O (60 mL). The aqueous phase was extracted with more Et_2O (4 x 50 mL) and the combined organic layer was dried ($MgSO_4$) and concentrated to give 599 mg of a pale yellow oil. Flash chromatography (20 g silica, petroleum ether/ether 2:1) afforded 323 mg (80% yield) of **8b** as a pale yellow oil: $[\alpha]_D^{24}$ +12° (c 1.1, $CHCl_3$); IR (film) 3480, 2945, 2881, 1462, 1377, 1214, 1144, 1102, 1037, 948, 919, 871 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.70 (s, 2H, $OC\underline{H}_2O$), 3.94 (m, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.53 [br m, 1H, C<u>H</u>(OH)], 3.41 (s, 3H, $OC\underline{H}_3$), 3.30 [ddd, 1H, J = 6, 6, 11.6 Hz, C<u>H</u>(OCH_2OCH_3)], 2.84 [br d, 1H, J = 3.8 Hz, CH(O<u>H</u>)], 1.43-1.72 (m, 8H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$, $CH_3C\underline{H}_2$), 1.32 (s, 3H, $C\underline{H}_3$), 0.93 (t, 3H, J = 7.4 Hz, $C\underline{H}_3CH_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 109.92, 96.81, 83.93, 72.02, 64.45, 55.63, 39.00, 33.20, 23.57, 23.53, 20.13, 9.38; m/z 247(M^+-CH_3, 2.3), 215(2.0), 201(2.3), 159(63.4), 141(12.7), 127(9.0), 115(18.6), 97(33.0), 87(100), 71(34.2), 59(27.1). Anal. Calcd for $C_{13}H_{26}O_5$: C, 59.52; H, 9.99. Found: C, 59.33; H, 9.73.

A small amount (ca. 5 mg) of **8b** was converted to the 3,5-dinitrophenylcarbamate derivative. The ee and de were determined to be 98% and 99%, respectively, as shown by HPLC analysis using Method B.

(+)-*endo*-Brevicomin [(+)-1]. To a cold (0 °C) CH_2Cl_2 (3.0 mL) solution of **7** (125 mg, 0.475 mmol) was added 70% $HClO_4$ (10 μL). The mixture was stirred for 10 min and then quenched with powdered $NaHCO_3$. Concentration (0 °C bath, 20 torr) followed by a short (Pasteur pipette) column chromatography (CH_2Cl_2 as eluant) gave 58.0 mg (75% yield) of **(+)-1**. Spectral data were identical to that described in the literature.[23] $[\alpha]_D^{24}$ +62° (c 1.2, Et_2O). {Literature values: $[\alpha]_D^{23}$ +58.2° (c 1.17, Et_2O), 80% ee[10a]; $[\alpha]_D^{22}$ +79.8° (c 1.05, Et_2O), 99% ee[10g]; $[\alpha]_D^{25}$ +64.2° (c 2.3, Et_2O), 82% ee[24]; $[\alpha]_D^{20}$ +80.0° (c 1.3, Et_2O), >98% ee[23]; $[\alpha]_D^{25}$ +96.6° (c 0.98, Et_2O), "enantiomerically pure"[26]; $[\alpha]_D^{21}$ +78.8° (c 0.5, Et_2O), 96-97% ee[6]; $[\alpha]_D^{26}$ +74.6° (c 1.06, Et_2O)[27]; $[\alpha]_D^{20}$ +74° (c 2.2, Et_2O)[30].}

(-)-*exo*-Brevicomin [(-)-2]. The *exo*-isomer was prepared (88% yield) from **8b** in a similar manner as the *endo*-isomer. Spectral data were identical to that described in the literature.[2,3] $[\alpha]_D^{24}$ -72° (c 1.0, Et_2O). {Literature values: $[\alpha]_D^{23}$ -41.9° (c 2.1, Et_2O), 63% ee[10a]; $[\alpha]_D^{20}$ -69.7° (c 3.6, Et_2O), >99% ee[23]; $[\alpha]_D^{25}$ -80.3° (c 2.23, Et_2O), "enantiomerically pure"[26]; $[\alpha]_D^{25}$ -66.5° (c 1.112, Et_2O)[27]; $[\alpha]_D$ -73° (c 2, Et_2O)[28]; $[\alpha]_D^{27}$ -60.6° (c 2.3, $CHCl_3$)[29]; $[\alpha]_D^{20}$ -66° (c 2, Et_2O)[30]; $[\alpha]_D^{24}$ -80.0° (c 1.6, Et_2O)[31].}

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