Asymmetric Synthesis of exo-Isobrevicomin and exo-Brevicomin via Conjugated Addition of Primary Alkyl Iodides to $\alpha,\beta$-Unsaturated Ketones

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(-)-exo-Isobrevicomin (1) e (+)-exo-brevicomin (2) são substâncias voláteis produzidas pelos besouros machos Dendroctonus ponderosae, os quais habitam árvores do gênero Pinus encontradas no hemisfério norte, frequentemente causando a morte dos hospedeiros. Objetivando a obtenção desses feromonônicos de agregação, que apresentam a estrutura 6,8-dioxabicyclo[3.2.1]octano, as estratégias sintéticas utilizadas nesse trabalho tiveram como etapas-chaves a di-hidroxilação assimétrica de Sharpless e a adição conjugada, promovida pela liga Zn(Cu) em meio aquoso e acelerada por ultra-som. A adição conjugada dos acetonídeos 13 e 14 às respectivas cetonas insaturadas (metil-vinil-cetona e etil-vinil-cetona) gerou os adutos 15 e 16. A ciclização intramolecular catalisada dos compostos 15 e 16 com ácido fosfotungstico (H$_3$PW$_{12}$O$_{40}$) forneceu a exo-isobrevicomin (1) e a exo-brevicomin (2).

Keywords: Isobrevicomin, brevicomin, 6,8-dioxabicyclo[3.2.1]octane, aggregation pheromones, conjugate addition

Introduction

Mountain pine beetles, Dendroctonus ponderosae, are destructive pests which cause damage to coniferous forests in the northern hemisphere. The interest in chemical communication systems of insect species, coupled with their economic influence, has stimulated biological activity and synthetic studies.¹

The isolation and the first synthesis of (-)-exo-isobrevicomin (1), (1S,5R,7S)-5-ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]octane, and the respective hydroxylated derivatives were reported by Francke and co-workers² in 1996. Further alternative strategies for the preparation of this compound were reported by Mori and co-workers³ in 1997, and by Taniguchi and co-workers⁴ in 1998. Compound 1 is a new naturally occurring isomer of (+)-exo-brevicomin (2), with opposite absolute configuration at the stereogenic centers, produced by males of the beetles Dendroctonus ponderosae.

As the major volatile component of several bark beetle species, (+)-exo-brevicomin (2), (1R,5S,7R)-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane, prepared by diverse synthetic methodologies, has been described quite frequently in the literature.¹,⁵ The strategy most commonly used for the syntheses of compounds 1 and 2 involves the conversion of E-7-nonen-3-ones and E-6-nonen-2-ones into their chemical equivalent intermediates (epoxy or dihydroxy derivatives) by means of enzymatic or enantioselective transformations, followed by intramolecular acetalization.¹,² Despite compound 2 existing in nature as a pure enantiomer, it has been shown that its racemate is potent enough for practical applications.¹,⁴
Our interest in the preparation of bicyclic acetal (1) arose from its recent isolation and syntheses. We have been involved with the syntheses of some acyclic pheromones from acyl-cyclopentanones. The acetylenic ester, obtained as the key intermediate, can be transformed into the natural product (Scheme 1).

Although the route described in Scheme 1 had involved inexpensive starting materials and could have led to homochiral products, it was quite long. Therefore, we have developed a new sequence which is shorter and leads to optically active products (Scheme 2).

In this alternative path, the conjugate addition reactions (paths f and g) were definitely considered as key steps in furnishing the desired products 1 and 2.

**Experimental**

Unless otherwise specified, all reagents and solvents were used as received from the commercial suppliers. Organic extracts were dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure on a rotatory evaporator. Chromatographic purifications were conducted by flash or "dry-column" flash chromatography on silica gel (Merck, 60 Å, 230-400 mesh). Melting points were determined on a Kofler block and are uncorrected. A Branson ultrasonic cleaner (Model 1210; 47 ± 6 KHz) was used to conduct heterogeneous reactions. Infrared spectra of liquid samples (neat films) and solids (KBr disks) were recorded on a Bomem Hartmann & Braun (MB-100) spectrometer. Routine $^1$H NMR spectra were obtained on a VARIAN EM-390 (90 MHz) spectrometer, while the high resolution $^1$H and $^{13}$C NMR spectra were registered on a Bruker ARX200 (200/50 MHz) spectrometer and on a Bruker ARX400 (400/100 MHz) spectrometer. Chemical shifts ($\delta$) are given in ppm and coupling constants ($J$) in Hz. GC-EIMS (70 eV) analyses were carried out on a PERKIN ELMER Q-MASS 910 spectrometer, containing the DB-17 capillary column (30 m).

**Scheme 1.** Synthesis of exo-Isobrevicomin (1) from ethanoyl-cyclopentanone

**Scheme 2.** Synthesis of exo-Isobrevicomin (1) and exo-Brevicomin (2)

- a) p-TsCl, KOH, Et$_2$O, -10 °C, 1.5 h; b) NaI, acetone, 25 °C, 16 h; c) AD-mix-$\alpha$, MeSO$_2$NH$_2$, NaHCO$_3$, t-BuOH:H$_2$O (1:1), 0 °C, 15 h; d) AD-mix-$\beta$, MeSO$_2$NH$_2$, NaHCO$_3$, t-BuOH:H$_2$O (1:1), 0 °C, 15 h; e) 2,2-dimethoxy-propane, PPTS, 25 °C, 5 h; f) EVK, Zn(Cu), EtOH:H$_2$O (7:3), ultrasound, 25 °C, 2 h; g) MVK, Zn(Cu), EtOH:H$_2$O (7:3), ultrasound, 25 °C, 2 h; h) H$_3$PW$_{12}$O$_{40}$ cat., CH$_2$Cl$_2$, 25 °C, 4h.
m x 0.25 mm x 0.25 mm). GC analyses were carried out on a VARIAN STAR 3400 CX, utilizing DB-WAX and Chirasil-DEX CB capillary columns (30 m x 0.25 mm x 0.25 mm).

(E)-But-2-en-1-yl p-toluenedisulfonate (7)

To a stirred solution of the (E)-but-2-en-1-ol (5) (3.4 mL, 40 mmol), p-toluenedisulfonyl chloride (9.6 g, 50 mmol) in dry ether (40 mL), cooled at -10 °C and under anhydrous conditions, was added pulverized potassium hydroxide 85% (4.5 g, 80 mmol). The reaction mixture was stirred for 1-2 h, diluted with brine (20 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined extract was washed with water (30 mL), diluted HCl (30 mL) and a saturated solution of NaHCO₃ (3 x 30 mL). The combined extracts were washed with brine, dried and evaporated of solvent to afford a brownish liquid (5.98 g, 95%). IR ν_{max}/cm⁻¹ 3027, 1655, 961 (film); 1H NMR (90 MHz, CDCl₃) δ 0.99 (t, J 7.5 Hz, 3H), 1.57-2.35 (m, 2H), 3.60-4.00 (m, 2H), 5.20-6.00 (m, 2H).

(2R,3S)-1-Iodo-but-2-3-diol (11)

AD-mix-α® (4.2 g) was added to a solution of (E)-1-iodo-but-2-ene (9) (0.55 g, 3 mmol), methanesulfonylamine (0.29 g, 3 mmol) and sodium bicarbonate (0.76 g, 9 mmol) in i-butanol:water (1:1, 30 mL), and stirred at 0 °C for 15 h. The reaction was quenched with sodium sulfite (4.5 g), stirred for 15 min at 0 °C and for 10 min at room temperature, and then extracted with CH₂Cl₂ (3 x 25 mL). The combined extracts were washed with brine, dried and concentrated to furnish a yellowish solid. The crude solid was recrystallized from n-hexane:ethyl acetate (4:1) and purified by “dry-column” flash chromatography (n-hexane:ethyl acetate, 3:1), yielding a white solid (0.49 g, 76%); m.p. 61-63 °C; IR ν_{max}/cm⁻¹ 3311, 1145, 1050 (KBr); 1H NMR (200 MHz, CDCl₃) δ 1.15 (d, J 6.0 Hz, 3H), 3.40-3.46 (m, 2H), 3.80 (d, J 6.0 Hz, 3H), 3.90-4.10 (m, 2H), 7.63 (d, J 9.0 Hz, 2H).

(E)-Pent-2-en-1-yl p-toluenedisulfonate (8)

It was prepared from (E)-pent-2-en-1-ol (6), as described in the above method, giving a colorless liquid (7.7 g, 80%), which was utilized in the next reaction without further purification; IR ν_{max}/cm⁻¹ 3033, 1671, 1598, 1359, 1189 (film); 1H NMR (90 MHz, CDCl₃) δ 1.70-2.10 (m, 2H), 2.39 (s, 3H), 4.30 (d, J 6.0 Hz, 2H), 5.08-5.88 (m, 2H), 7.21 (d, J 9.0 Hz, 2H), 7.63 (d, J 9.0 Hz, 2H).

(E)-1-Iodo-but-2-ene (9)

Anhydrous sodium iodide (6.0 g, 40 mmol) was added to (E)-but-2-en-1-yl p-toluenedisulfonate (7) (7.7 g, 34 mmol) in anhydrous acetone (40 mL). After stirring at room temperature for 16 h, the mixture was diluted with ice/water (10 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The organic phase was washed with dilute solution of Na₂S₂O₅ (30 mL), saturated solution of NaHCO₃ (2 x 30 mL) and brine (30 mL). Drying and evaporation of solvent furnished a crude dark brown liquid that was purified by “dry-column” flash chromatography, eluting with petroleum ether, to afford a brownish liquid (5.9 g, 95%); IR ν_{max}/cm⁻¹ 3024, 1658, 961 (film); 1H NMR (90 MHz, CDCl₃) δ 1.61 (t, J 3H), 3.50-4.00 (m, 2H), 5.30-5.90 (m, 2H); GC/EIMS (70 eV) m/z 182 (M⁺, 13.8%), 127 (34), 55 (100).

(4R,5S)-4-Iodomethyl-2,2,5-trimethyl-[1,3]-dioxolane (13)

To a solution of compound 11 (0.86 g, 4 mmol) in anhydrous CH₂Cl₂ (30 mL) under argon was added 2,2-dimethoxy-propane (0.5 mL, 4 mmol) and pyridinium p-toluenedisulfonate (0.1 g, 0.4 mmol). After stirring for 5 h at room temperature, the reaction mixture was diluted with CH₂Cl₂ (20 mL) and washed with brine (20 mL). Drying and evaporating afforded a colorless liquid that was purified by “dry-column” flash chromatography, eluting with n-hexane/ethyl acetate (9:1), to obtain a colorless liquid (1.0 g, 98%); IR ν_{max}/cm⁻¹ 1455, 1379, 1241, 1097 (film); 1H NMR (200 MHz, CDCl₃) δ 1.35 (d, J 6.0 Hz, 3H), 1.42 (d, J 0.6 Hz, 3H), 1.43 (d, J 0.6 Hz, 3H), 3.25 (d, J 5.2
Hz, 1H), 3.26 (d, J 5.2 Hz, 1H), 3.56 (dt, J 5.2 and 7.5 Hz, 1H), 3.88 (dq, J 6.0 and 7.5 Hz, 1H); \(^{1}C\) NMR (50 MHz, CDCl\(_{3}\)) \(\delta\) 5.0, 18.5, 27.2, 27.5, 77.4, 81.0, 108.6; GC/EIMS (70 eV) \(m/z\) 241 (M-CH\(_{3}\), 100%), 181 (11), 127 (9), 85 (27).

(4R,5S)-4-Ethyl-5-iodomethyl-2,2-dimethyl-[1,3]-dioxolane (14)

Starting from compound 12 (0.92 g, 4 mmol) and using the same conditions described in the previous method, compound 14 was prepared as a colorless liquid (1.07 g, 99%); IR \(\nu_{max}/cm^{-1}\) 1458, 1379, 1238, 1033 (film); \(^{1}H\) NMR (400 MHz, CDCl\(_{3}\)) (200 MHz, CDCl\(_{3}\)) \(\delta\) 0.6, 1.24 (d, J 6.5 Hz, 3H), 1.41 (d, J 0.6 Hz, 3H), 1.44 (d, J 0.6 Hz, 3H), 1.55-1.78 (m, 2H), 3.13-3.34 (m, 2H), 3.62-3.78 (m, 2H); \(^{13}C\) NMR (50 MHz, CDCl\(_{3}\)) d 6.3, 10.0, 26.4, 27.4, 27.6, 79.4, 82.6, 108.9; GC/EIMS (70 eV) \(m/z\) 255 (M-CH\(_{3}\), 100%), 195 (53), 85 (88), 59 (49).

(4S,5S’)-6-(2,2,5-Trimethyl-[1,3]-dioxolan-4-yl)-hexan-3-one (15)

Freshly distilled ethyl vinyl ketone (0.4 mL, 3.9 mmol) was added to a suspension of acetonide 13 (0.77 g, 3 mmol), activated zinc\(^{10}\) (Aldrich, 0.248 g, 3.8 mmol) and copper iodide (0.83 g, 4.4 mmol) in ethanol/water (21 mL/9 mL). The reaction mixture was irradiated with ultrasound for 2 h under argon and then diluted with brine (10 mL). After filtration over diatomaceous earth and extracting with CH\(_{3}\)Cl\(_{2}\) (3 x 30 mL), the organic phase was washed with brine. Usual work-up gave a yellowish liquid, which was purified by flash chromatography (n-hexane:ethyl acetate, 9:2) furnishing a colorless liquid (1.07 g, 96%); IR \(\nu_{max}/cm^{-1}\) 1463, 1363, 1239, 1182, 1015 (film); \(^{1}H\) NMR (400 MHz, CDCl\(_{3}\)) \(\delta\) 0.95 (t, J 7.5 Hz, 3H), 1.18 (d, J 6.2 Hz, 3H), 1.47-1.95 (m, 8H), 4.04 (s large, 1H), 4.21 (q, J 6.2 Hz, 1H); \(^{13}C\) NMR (50 MHz, CDCl\(_{3}\)) \(\delta\) 7.3, 17.1, 21.7, 28.1, 30.6, 33.5, 75.6, 80.0, 110.0; GC/EIMS (70 eV) \(m/z\) 156 (M\(^{+}\), 7%), 116 (12), 100 (45), 71 (19), 57 (100).

(1R,5S,7R)-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (1)

Using the same conditions as above, compound 2 was prepared as a pale liquid (0.12 g, 96%); IR \(\nu_{max}/cm^{-1}\) 1461, 1382, 1239, 1174, 1033 (film); \(^{1}H\) NMR (400 MHz, CDCl\(_{3}\)) \(\delta\) 0.90 (t, J 7.4 Hz, 3H), 1.40 (s, 3H), 1.41-1.94 (m, 8H), 3.92 (t, J 6.5 Hz, 1H), 4.12 (s large, 1H); \(^{13}C\) NMR (50 MHz, CDCl\(_{3}\)) \(\delta\) 7.4, 17.1, 25.1, 28.0, 28.6, 35.0, 78.3, 81.2, 107.8; GC/EIMS (70 eV) \(m/z\) 156 (M\(^{+}\), 8%), 114 (100), 98 (46), 85 (96).

Results and discussion

In this novel synthesis of \(E^{\prime}:Z^{\prime}\)-pent-2-en-1-ol (5) and \(E^{\prime}:Z^{\prime}\)-pent-2-en-1-ol 95% (6), purchased from Aldrich as a 95:5 mixture of \(E^{\prime}:Z\) isomers, were converted by the method already described\(^{11}\) into their respective tosylated derivatives 7 and 8 in 85 and 80% yield, respectively. The next step, involving a nucleophilic substitution with NaI in anhydrous acetone permitted, in almost quantitative yields, the preparation of iodide derivatives 9 and 10, whose respective \(E^{\prime}:Z\) compositions (98:2 and 95:5) were characterized by gas chromatography (DB-WAX). The asymmetric catalytic \(cis\)-dihydroxylation of the double
bonds of 9 and 10, mediated by the commercially available Sharpless reagents (AD-mix-ε and AD-mix-β), which have already been used to synthesize the (-)-exo-isobrevicomin (1), (+)-exo-brevicomin (2) and respective endo isomer, furnished the corresponding diols (2,2-dimethoxy-propane and PPTS), were submitted to aqueous medium. For the primary halide compounds, has been discussed as involving a free radical formed in the reaction of these adducts has been applied in some industrial and academic cases.

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