

## Synthesis of Lateral Root-Inducing Compounds Using an Efficient Coupling Reaction of Chiral Triflates

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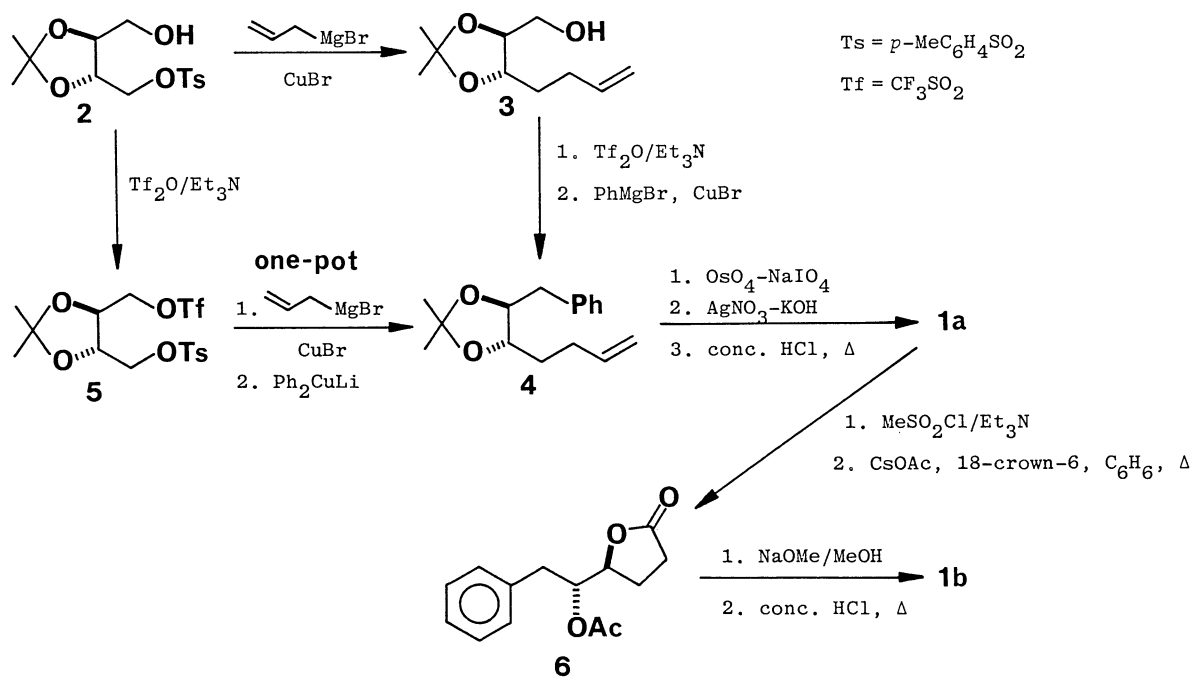
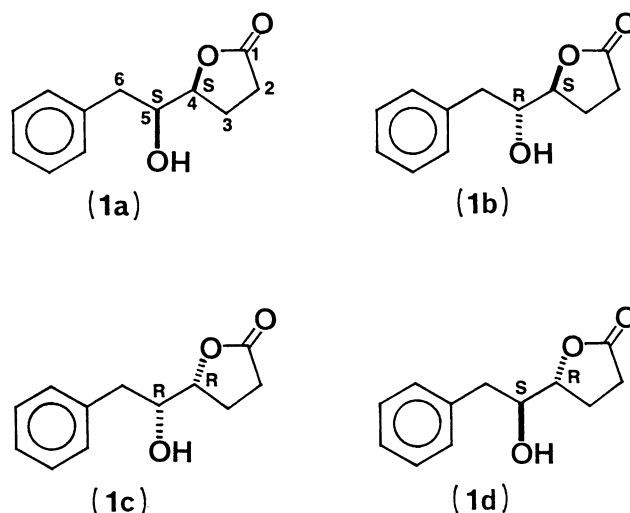
**Synopsis.** Lateral root-inducing compounds, isolated from the bacterium *Erwinia quercina*, have been synthesized by using a coupling reaction of chiral triflates derived from L- or D- tartrates and their biological activities examined.

Recent studies in our laboratories have revealed that the copper(I)-catalyzed coupling reaction of chiral trifluoromethanesulfonates (triflates) with Grignard reagents is a powerful technique to synthesize optically active natural products.<sup>1)</sup> As an extension of these studies, we herein wish to describe a new versatile strategy towards lateral root-inducing compounds isolated from the bacterium *Erwinia quercina*.<sup>2)</sup> Sims et al. reported that these compounds are a mixture of two diastereomers of 4,5-dihydroxy-6-phenylhexanoic acid; synthetically, they confirmed that all four possible chiral isomers possess biological activity.<sup>2)</sup> However, their synthesis involves a non-stereoselective reduction step and, hence, requires an unavoidable separation stage from the diastereomeric mixture. Compared with this example, our route is of great advantage for deriving these compounds in complete enantioselectivity while providing a rapid means for bioassay.<sup>3)</sup>

A concise route to (4*S*,5*S*)- and (4*S*,5*R*)-isomers (**1a** and **1b**)<sup>4)</sup> is shown in Scheme 1. Utilizing the strategy already developed in these laboratories,<sup>1d)</sup> mono-

*p*-toluenesulfonate (tosylate) **2** was converted into the key intermediate **4** either stepwise or by a one-pot double alkylation method.

Thus, the reaction of **2** with allylmagnesium bromide (7 equiv) in the presence of a catalytic amount of CuBr produced **3** in 83% yield. Triflation followed by treatment with PhMgBr (3 equiv)-CuBr gave the



Scheme 1.

required intermediate **4** in 71% yield. Alternatively, after conversion of **2** into the corresponding tosyl-triflate derivative **5**, one-pot double alkylation first with allylmagnesium bromide (1.1 equiv)-CuBr (at 0°C for 1 h) and secondly with Ph<sub>2</sub>CuLi (3.0 equiv) (at -15°C for 4 h) afforded **4** in 33% yield from **2**. In contrast to the stepwise method, unfortunately, this one-pot double alkylation procedure could not improve so much the overall yield. This, however, does not lose its synthetic superiority from the viewpoint of the experimental simplicity as well as the economical usage of two kinds of alkylating agents.

The double bond in **4** was smoothly oxidized to the corresponding carboxylic acid (OsO<sub>4</sub>-NaIO<sub>4</sub> then AgNO<sub>3</sub>-KOH), which underwent lactonization under acidic conditions to give the (4*S*,5*S*)-isomer (**1a**) {[α]<sub>D</sub><sup>21</sup> +59.8° (*c* 1.04, CHCl<sub>3</sub>); lit.<sup>2)</sup> [α]<sub>D</sub> +49.06° (*c* 1.28, CHCl<sub>3</sub>)} in 91% yield from **4**. Applying the Ikegami's inversion technique,<sup>5)</sup> **1a** was efficiently converted into acetate **6**, which was further treated with NaOMe in MeOH to afford the (4*S*,5*R*)-isomer (**1b**) {[α]<sub>D</sub><sup>20</sup> +34.0° (*c* 0.96, CHCl<sub>3</sub>); lit.<sup>2)</sup> [α]<sub>D</sub> +29.22° (*c* 0.84, CHCl<sub>3</sub>)} in 69% yield from **1a**.

The application of the same synthetic procedure on the enantiomer of **2**, available from D-tartrates, furnished the (4*R*,5*R*)-isomer (**1c**) {[α]<sub>D</sub><sup>21</sup> -60.0° (*c* 0.5, CHCl<sub>3</sub>); lit.<sup>2)</sup> [α]<sub>D</sub> -50.77° (*c* 0.2, CHCl<sub>3</sub>)} and also the (4*R*,5*S*)-isomer (**1d**) {[α]<sub>D</sub><sup>20</sup> -34.2° (*c* 1.20, CHCl<sub>3</sub>); lit.<sup>2)</sup> [α]<sub>D</sub> -29.23° (*c* 0.2, CHCl<sub>3</sub>)} in good overall yields.

A comparison of the specific rotation of our samples with literature data showed a higher optical purity for all of our chiral isomers. These results prompted us to reexamine the structure-activity relationship of these molecules.<sup>6)</sup> However, we found that all of our compounds were active at 10<sup>-5</sup> M (1 M=1 moldm<sup>-3</sup>), with only a slight difference between isomers.<sup>7)</sup> These results are compatible with previous evidence.<sup>2)</sup> Apparently, the stereochemistry of the compounds is not critical to the activity. One possibility is that the chirality is changed or destroyed by metabolism in the carrot discs; a bioassay required 10 days to complete. Further experiments are required to clarify this observation and to identify the actual active compound.

### Experimental

All melting points are uncorrected. The NMR spectra were recorded on a Hitachi R-90H spectrometer (90 MHz for <sup>1</sup>H NMR analysis and 22.6 MHz for <sup>13</sup>C NMR analysis). All NMR spectra were taken in a CDCl<sub>3</sub> solution and tetramethylsilane was used as an internal standard. The IR spectra were measured with a JASCO Model FT/IR-5000 Fourier Transform Infrared spectrometer. High-resolution mass spectra were obtained with a JEOL HX-100 spectrometer. Optical rotations were measured on a Union PM-101 polarimeter. Thin-layer chromatography was conducted by using Merck precoated Kieselgel 60F-254 plates (0.25 mm). Column chromatography was carried out on a Wakogel C-300, and for flash chromatography, Merck Kieselgel (230-400 mesh) was employed.

All solvents were dried immediately before use. Et<sub>2</sub>O, C<sub>6</sub>H<sub>6</sub> and tetrahydrofuran (THF) were distilled from sodium diphenylketyl; dichloromethane and triethylamine were distilled from CaH<sub>2</sub>. All Grignard and organolithium reagents were titrated before use according to methods de-

scribed in the literature.<sup>8)</sup> All reactions were carried out in a nitrogen or argon atmosphere.

**Preparation of 3 from 2.** To an ice-cooled suspension of CuBr (65 mg, 0.45 mmol) in 1.5 ml of dry Et<sub>2</sub>O was added 0.39 M of an allylmagnesium bromide/Et<sub>2</sub>O solution (5.4 ml, 2.1 mmol), followed by the introduction of an Et<sub>2</sub>O solution (1.5 ml) of monotosylate **2** (95 mg, 0.3 mmol); the mixture was then stirred for 1 h. During the reaction a black insoluble substance was gradually formed. The reaction was quenched by the addition of aqueous NH<sub>4</sub>Cl-aqueous NH<sub>3</sub> (9:1); the mixture was then filtered through Celite. The filtrate was extracted with Et<sub>2</sub>O, and the combined extracts were washed with aqueous saturated NaHCO<sub>3</sub> and brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave a crude product which was purified by column chromatography (C-300; from hexane/Et<sub>2</sub>O=2:1 to 1:1) to give 46 mg (83%) of **3** as a colorless oil.

**3:** *R*<sub>f</sub> 0.49 (Et<sub>2</sub>O); [α]<sub>D</sub><sup>23</sup> -27.1° (*c* 1.1, CHCl<sub>3</sub>); IR (neat) 3500, 1644, 1054, 913, and 855 cm<sup>-1</sup>; <sup>1</sup>H NMR δ=1.41 (6H, s), 1.5-1.8 (2H, m), 1.88 (1H, s), 2.05-2.4 (2H, m), 3.5-4.0 (4H, m), 4.98 (1H, brd, *J*=10.0 Hz), 5.02 (1H, brd, *J*=17.2 Hz), 5.84 (1H, ddt, *J*=17.2, 10.0, 6.5 Hz); <sup>13</sup>C NMR δ=27.03, 27.33, 29.98, 32.30, 62.06, 76.39, 81.42, 108.56, 114.87, 137.64. Found: *m/z* 186.1248. Calcd for C<sub>10</sub>H<sub>18</sub>O<sub>3</sub>: M, 186.1256.

Enantiomer of **3**: [α]<sub>D</sub><sup>19</sup> +27.3° (*c* 1.1, CHCl<sub>3</sub>).

**Preparation of 4 from 3.** To a mixture of alcohol **3** (520 mg, 2.8 mmol) and Et<sub>3</sub>N (1.2 ml, 8.6 mmol) in 9 ml of dry CH<sub>2</sub>Cl<sub>2</sub> was added dropwise a CH<sub>2</sub>Cl<sub>2</sub> solution (3 ml) of (CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>O (710 μl, 4.2 mmol) at -15°C; the mixture was then stirred for 20 min. After dilution with CH<sub>2</sub>Cl<sub>2</sub>, the mixture was treated conventionally. The crude product was dried azeotropically with toluene and used in the following step.

To an ice-cooled suspension of CuBr (80 mg, 0.56 mmol) in 6 ml of dry THF was added 1.6 M of PhMgBr/Et<sub>2</sub>O solution (5.3 ml, 8.5 mmol) followed by the introduction of a THF solution (12 ml) of the triflate (obtained as mentioned above); the mixture was then stirred at 0°C for 8 h. The reaction was quenched by the addition of aqueous NH<sub>4</sub>Cl-aqueous NH<sub>3</sub> (9:1), the mixture filtered through Celite. After removing the solvent, the residue was extracted with Et<sub>2</sub>O. After the usual workup, the crude product was purified by column chromatography (flash silica gel; hexane/Et<sub>2</sub>O=50:1) to give 495 mg (72%) of **4** as a colorless oil.

**4:** *R*<sub>f</sub> 0.60 (hexane/Et<sub>2</sub>O=2:1); [α]<sub>D</sub><sup>23</sup> -28.0° (*c* 2.0, CHCl<sub>3</sub>); IR (neat) 2988, 2936, 1642, 1497, 1456, 1375, 1058, and 913 cm<sup>-1</sup>; <sup>1</sup>H NMR δ=1.36 (6H, s), 1.2-1.6 (2H, m), 1.9-2.3 (2H, m), 2.81 (1H, dd, *J*=14.0, 5.3 Hz), 2.94 (1H, dd, *J*=14.0, 5.7 Hz), 3.55-4.0 (2H, m), 4.8-5.1 (1H, m), 5.75 (1H, ddt, *J*=17.1, 9.6, 6.1 Hz), 7.24 (5H, s); <sup>13</sup>C NMR δ=27.27, 27.39, 30.05, 32.12, 39.38, 79.87, 80.99, 108.04, 114.72, 126.33, 128.19(×2), 129.23(×2), 137.49, 137.86. Found: *m/z* 246.1601. Calcd for C<sub>16</sub>H<sub>22</sub>O<sub>2</sub>: M, 246.1620.

Enantiomer of **4**: [α]<sub>D</sub><sup>22</sup> +28.4° (*c* 2.0, CHCl<sub>3</sub>).

**Preparation of 5 from 2.** To a mixture of monotosylate **2** (116 mg, 0.37 mmol) and Et<sub>3</sub>N (155 μl, 1.1 mmol) in 2 ml of dry CH<sub>2</sub>Cl<sub>2</sub> was added dropwise a CH<sub>2</sub>Cl<sub>2</sub> solution (1 ml) of (CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>O (95 μl, 0.56 mmol) at -15°C; the mixture was then stirred for 20 min. After dilution with CH<sub>2</sub>Cl<sub>2</sub>, the mixture was treated conventionally and the crude tosyl-triflate **5** was used in the following step, as described above.

**Preparation of 4 from 5.** To an ice-cooled suspension of CuBr (10 mg, 0.07 mmol) in 1.5 ml of dry Et<sub>2</sub>O was added a 0.39 M allylmagnesium bromide/Et<sub>2</sub>O solution (1 ml, 0.39 mmol), followed by the introduction of an Et<sub>2</sub>O solution (0.5 ml) of tosyl-triflate **5** (obtained as mentioned above); the mixture was then stirred at 0°C for 1 h. During the reaction, a black insoluble substance was gradually formed.

Then,  $\text{Ph}_2\text{CuLi}$  (prepared from  $\text{CuI}$  (211 mg, 1.11 mmol) and 1.19 M of  $\text{PhLi}/\text{Et}_2\text{O}$  solution (1.9 ml, 2.26 mmol) in dry  $\text{Et}_2\text{O}$  (3 ml)) was introduced at  $-15^\circ\text{C}$ ; the mixture was then stirred at this temperature for 4 h. The reaction was quenched by the addition of aqueous  $\text{NH}_4\text{Cl}$ -aqueous  $\text{NH}_3$  (9:1) and the mixture filtered through Celite. After the usual workup, the crude product was purified by column chromatography (flash silica gel; hexane/ $\text{Et}_2\text{O}$ =50:1) to give 30 mg (33%) of **4** as a colorless oil.

**Preparation of 1a from 4.** The starting material **4** (74 mg, 0.3 mmol) was dissolved in 9 ml of  $\text{THF}/\text{H}_2\text{O}$  (5:4) and an  $\text{Et}_2\text{O}$  solution of  $\text{OsO}_4$  (5 mg in 0.5 ml) was added at room temperature. After stirring for 10 min,  $\text{NaIO}_4$  (330 mg, 1.5 mmol) was added and the mixture stirred for 0.5 h. The mixture was then quenched by the addition of brine, and the conventional treatment gave a crude aldehyde which was subjected to the next reaction.

To a stirred solution of the aldehyde obtained above in 2.5 ml of  $\text{MeOH}$  were successively added  $\text{AgNO}_3$  (102 mg, 0.6 mmol) in 1.5 ml of  $\text{H}_2\text{O}$  and  $\text{KOH}$  (67 mg, 1.2 mmol) in 1 ml of  $\text{H}_2\text{O}$ . After stirring for 0.5 h at  $0^\circ\text{C}$ , the mixture was acidified with concentrated  $\text{HCl}$  and heated at  $50^\circ\text{C}$  for 0.5 h. After removing the insoluble substance by filtration through Celite, the filtrate was concentrated in vacuo. The usual treatment of the residue gave a crude product which was purified by column chromatography (flash silica gel; from hexane/ $\text{Et}_2\text{O}$ =1:2 to  $\text{Et}_2\text{O}$  only) to give 56 mg (91%) of **1a** as a colorless oil.

**1a:**  $R_f$  0.26 ( $\text{Et}_2\text{O}$ );  $[\alpha]_D^{21} +59.8^\circ$  ( $c$  1.04,  $\text{CHCl}_3$ ); IR (neat) 3500, 1769, and  $1191\text{ cm}^{-1}$ ;  $^1\text{H NMR}$   $\delta$ =2.0–2.4 (2H, m), 2.4–2.7 (2H, m), 2.58 (1H, s), 2.91 (2H, d,  $J$ =7.0 Hz), 3.80 (1H, dt,  $J$ =6.8, 3.1 Hz), 4.42 (1H, dt,  $J$ =7.1, 3.3 Hz), 7.27 (5H, s);  $^{13}\text{C NMR}$   $\delta$ =23.92, 28.55, 39.89, 74.26, 81.21, 126.61, 128.53( $\times 2$ ), 129.26( $\times 2$ ), 137.19, 177.43. Found:  $m/z$  206.0932. Calcd for  $\text{C}_{12}\text{H}_{14}\text{O}_3$ : M, 206.0943.

**1c**, enantiomer of **1a**:  $[\alpha]_D^{21} -60.0^\circ$  ( $c$  0.5,  $\text{CHCl}_3$ ).

**Preparation of 1b from 1a.** To an ice-cooled mixture of alcohol **1a** (65 mg, 0.32 mmol),  $\text{Et}_3\text{N}$  (88  $\mu\text{l}$ , 0.63 mmol) and a catalytic amount of 4-(dimethylamino)pyridine in 3.0 ml of dry  $\text{CH}_2\text{Cl}_2$  was added methanesulfonyl chloride (30  $\mu\text{l}$ , 0.39 mmol); the mixture was then stirred at room temperature for 1 h. The usual workup gave a crude methanesulfonate which was used without further purification in the following step.

A mixture of the methanesulfonate (obtained as mentioned above),  $\text{CsOAc}$  (200 mg, 1.0 mmol) and 18-crown-6 (100 mg, 0.38 mmol) was refluxed in dry  $\text{C}_6\text{H}_6$  (9 ml) for 12 h. After dilution with  $\text{Et}_2\text{O}$ , the organic layer was treated conventionally and the crude product was purified by column chromatography (flash silica gel; hexane/ $\text{Et}_2\text{O}$ =1:2) to give 56 mg (71%) of acetate **6** as colorless needles (recrystallized from  $\text{Et}_2\text{O}$ -hexane).

**6:** Mp  $75.0$ – $76.0^\circ\text{C}$ ;  $R_f$  0.40 ( $\text{Et}_2\text{O}$ );  $[\alpha]_D^{19} +43.1^\circ$  ( $c$  0.52,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 1779, 1744, 1236, and  $1044\text{ cm}^{-1}$ ;  $^1\text{H NMR}$   $\delta$ =2.00 (3H, s), 2.1–2.4 (2H, m), 2.4–2.7 (2H, m), 2.91 (1H, dd,  $J$ =14.3, 6.6 Hz), 2.98 (1H, dd,  $J$ =14.3, 6.6 Hz), 4.47 (1H, dt,  $J$ =6.6, 5.1 Hz), 5.28 (1H, dt,  $J$ =6.6, 4.8 Hz), 7.24 (5H, m). Found: C, 67.77; H, 6.51%. Calcd for  $\text{C}_{14}\text{H}_{16}\text{O}_4$ :

C, 67.73; H, 6.50.

Enantiomer of **6**: Mp  $74.5$ – $75.0^\circ\text{C}$ ;  $[\alpha]_D^{19} -41.8^\circ$  ( $c$  1.3,  $\text{CHCl}_3$ ).

**Preparation of 1b from 6.** To a solution of acetate **6** (80 mg, 0.32 mmol) in 5 ml of absolute  $\text{MeOH}$  was added 0.4 M  $\text{NaOMe}/\text{MeOH}$  (1 ml, 0.4 mmol) at  $0^\circ\text{C}$  and the mixture was stirred at the same temperature for 1 h. At the end of the reaction the mixture was acidified with concentrated  $\text{HCl}$  and heated at  $50^\circ\text{C}$  for 0.5 h. After removing most of the organic solvent, the residue was extracted with  $\text{AcOEt}$ . The usual workup gave a crude product which was purified by column chromatography (flash silica gel, hexane/ $\text{Et}_2\text{O}$ =1:4) to afford 64 mg (97%) of **1b** as colorless needles (recrystallized from  $\text{Et}_2\text{O}$ -hexane).

**1b:** Mp  $60.0$ – $61.0^\circ\text{C}$  (lit.<sup>2)</sup>  $59$ – $60^\circ\text{C}$ );  $R_f$  0.30 ( $\text{Et}_2\text{O}$ );  $[\alpha]_D^{20} +34.0^\circ$  ( $c$  0.96,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 3434, 1775, and  $1187\text{ cm}^{-1}$ ;  $^1\text{H NMR}$   $\delta$ =1.8–2.7 (6H, m), 4.10 (1H, ddd,  $J$ =7.7, 5.7, 4.4 Hz), 4.41 (1H, dt,  $J$ =7.0, 4.0 Hz), 7.27 (5H, m);  $^{13}\text{C NMR}$   $\delta$ =21.60, 28.49, 39.01, 72.52, 81.85, 126.64, 128.53( $\times 2$ ), 129.14( $\times 2$ ), 136.94, 177.37. Found: C, 69.89; H, 6.86. Calcd for  $\text{C}_{12}\text{H}_{14}\text{O}_3$ : C, 69.88; H, 6.84.

**1d**, enantiomer of **1b**: Mp  $58.0$ – $60.5^\circ\text{C}$ ;  $[\alpha]_D^{20} -34.2^\circ$  ( $c$  1.20,  $\text{CHCl}_3$ ).

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