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

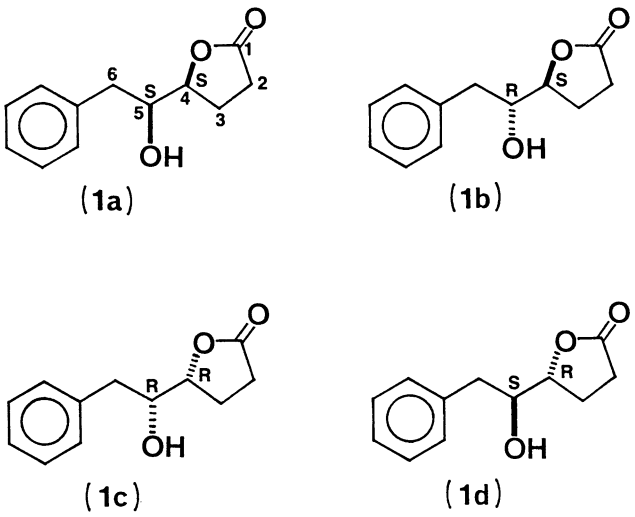
Hiyoshizo KOTSUKI,* Aya MIYAZAKI, Masamitsu OCHI, and James J. SIMS†
Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780
†Department of Plant Pathology, University of California, Riverside, CA 92521, U.S.A.
(Received October 1, 1990)

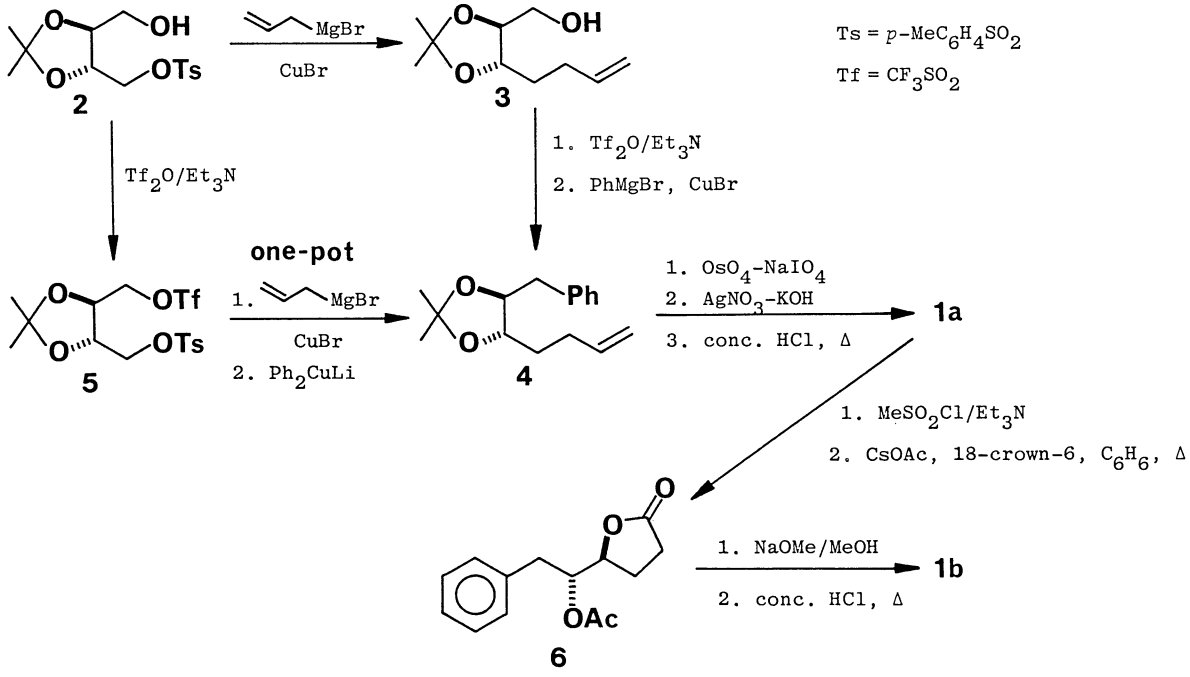
Synopsis. Lateral root-inducing compounds, isolated from the bacterium *Erwinia quercina*, have been synthesized by using a coupling reaction of chiral triflates derived from L- or D- tartrates and their biological activities examined.

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.[1] 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*.[2] 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.[2] 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.[3]

A concise route to (4*S*,5*S*)- and (4*S*,5*R*)-isomers (**1a** and **1b**)[4] is shown in Scheme 1. Utilizing the strategy already developed in these laboratories,[1d] 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 tosyltriflate derivative **5**, one-pot double alkylation first with allylmagnesium bromide (1.1 equiv)-CuBr (at 0 °C for 1 h) and secondly with Ph_2CuLi (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 loose 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_4-$NaIO_4$ then $AgNO_3$-KOH), which underwent lactonization under acidic conditions to give the (4*S*,5*S*)-isomer (**1a**) {$[\alpha]_D^{21}$ +59.8° (*c* 1.04, $CHCl_3$); lit,[2] $[\alpha]_D$ +49.06° (*c* 1.28, $CHCl_3$)} in 91% yield from **4**. Applying the Ikegami's inversion technique,[5] **1a** was efficiently converted into acetate **6**, which was further treated with NaOMe in MeOH to afford the (4*S*,5*R*)-isomer (**1b**) {$[\alpha]_D^{20}$ +34.0° (*c* 0.96, $CHCl_3$); lit,[2] $[\alpha]_D$ +29.22° (*c* 0.84, $CHCl_3$)} 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**) {$[\alpha]_D^{21}$ −60.0° (*c* 0.5, $CHCl_3$); lit,[2] $[\alpha]_D$ −50.77° (*c* 0.2, $CHCl_3$) and also the (4*R*,5*S*)-isomer (**1d**) {$[\alpha]_D^{20}$ −34.2° (*c* 1.20, $CHCl_3$); lit,[2] $[\alpha]_D$ −29.23° (*c* 0.2, $CHCl_3$) 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.[6] However, we found that all of our compounds were active at 10^{-5} M (1 M=1 mol dm^{-3}), with only a slight difference between isomers.[7] These results are compatible with previous evidence.[2] 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 ^1H NMR analysis and 22.6 MHz for ^{13}C NMR analysis). All NMR spectra were taken in a $CDCl_3$ 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_2O, C_6H_6 and tetrahydrofuran (THF) were distilled from sodium diphenylketyl; dichloromethane and triethylamine were distilled from CaH_2. All Grignard and organolithium reagents were titrated before use according to methods described in the literature.[8] 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_2O was added 0.39 M of an allylmagnesium bromide/Et_2O solution (5.4 ml, 2.1 mmol), followed by the introduction of an Et_2O 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_4Cl-aqueous NH_3 (9:1); the mixture was then filtered through Celite. The filtrate was extracted with Et_2O, and the combined extracts were washed with aqueous saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a crude product which was purified by column chromatography (C-300; from hexane/Et_2O=2:1 to 1:1) to give 46 mg (83%) of **3** as a colorless oil.

3: R_f 0.49 (Et_2O); $[\alpha]_D^{23}$ −27.1° (*c* 1.1, $CHCl_3$); IR (neat) 3500, 1644, 1054, 913, and 855 cm^{-1}; ^1H 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); ^{13}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 $C_{10}H_{18}O_3$: M, 186.1256.

Enantiomer of **3**: $[\alpha]_D^{19}$ +27.3° (*c* 1.1, $CHCl_3$).

Preparation of 4 from 3. To a mixture of alcohol **3** (520 mg, 2.8 mmol) and Et_3N (1.2 ml, 8.6 mmol) in 9 ml of dry CH_2Cl_2 was added dropwise a CH_2Cl_2 solution (3 ml) of $(CF_3SO_2)_2O$ (710 μl, 4.2 mmol) at −15 °C; the mixture was then stirred for 20 min. After dilution with CH_2Cl_2, 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_2O 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_4Cl-aqueous NH_3 (9:1), the mixture filtered through Celite. After removing the solvent, the residue was extracted with Et_2O. After the usual workup, the crude product was purified by column chromatography (flash silica gel; hexane/Et_2O=50:1) to give 495 mg (72%) of **4** as a colorless oil.

4: R_f 0.60 (hexane/Et_2O=2:1); $[\alpha]_D^{23}$ −28.0° (*c* 2.0, $CHCl_3$); IR (neat) 2988, 2936, 1642, 1497, 1456, 1375, 1058, and 913 cm^{-1}; ^1H 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); ^{13}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 $C_{16}H_{22}O_2$: M, 246.1620.

Enantiomer of **4**: $[\alpha]_D^{22}$ +28.4° (*c* 2.0, $CHCl_3$).

Preparation of 5 from 2. To a mixture of monotosylate **2** (116 mg, 0.37 mmol) and Et_3N (155 μl, 1.1 mmol) in 2 ml of dry CH_2Cl_2 was added dropwise a CH_2Cl_2 solution (1 ml) of $(CF_3SO_2)_2O$ (95 μl, 0.56 mmol) at −15 °C; the mixture was then stirred for 20 min. After dilution with CH_2Cl_2, the mixture was treated conventionally and the crude tosyltriflate **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_2O was added a 0.39 M allylmagnesium bromide/Et_2O solution (1 ml, 0.39 mmol), followed by the introduction of an Et_2O 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, Ph_2CuLi (prepared from CuI (211 mg, 1.11 mmol) and 1.19 M of PhLi/Et_2O solution (1.9 ml, 2.26 mmol) in dry Et_2O (3 ml)) was introduced at −15 °C; the mixture was then stirred at this temperature for 4 h. The reaction was quenched by the addition of aqueous NH_4Cl-aqueous 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/Et_2O=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 THF/H_2O (5:4) and an Et_2O solution of OsO_4 (5 mg in 0.5 ml) was added at room temperature. After stirring for 10 min, $NaIO_4$ (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 MeOH were successively added $AgNO_3$ (102 mg, 0.6 mmol) in 1.5 ml of H_2O and KOH (67 mg, 1.2 mmol) in 1 ml of H_2O. After stirring for 0.5 h at 0 °C, the mixture was acidified with concentrated HCl and heated at 50 °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/Et_2O=1:2 to Et_2O only) to give 56 mg (91%) of **1a** as a colorless oil.

1a: R_f 0.26 (Et_2O); $[\alpha]_D^{21}$ +59.8° (*c* 1.04, $CHCl_3$); IR (neat) 3500, 1769, and 1191 cm^{-1}; ^1H NMR δ=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}C NMR δ=23.92, 28.55, 39.89, 74.26, 81.21, 126.61, 128.53(×2), 129.26(×2), 137.19, 177.43. Found: *m/z* 206.0932. Calcd for $C_{12}H_{14}O_3$: M, 206.0943.

1c, enantiomer of **1a**: $[\alpha]_D^{21}$ −60.0° (*c* 0.5, $CHCl_3$).

Preparation of 1b from 1a. To an ice-cooled mixture of alcohol **1a** (65 mg, 0.32 mmol), Et_3N (88 µl, 0.63 mmol) and a catalytic amount of 4-(dimethylamino)pyridine in 3.0 ml of dry CH_2Cl_2 was added methanesulfonyl chloride (30 µl, 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), CsOAc (200 mg, 1.0 mmol) and 18-crown-6 (100 mg, 0.38 mmol) was refluxed in dry C_6H_6 (9 ml) for 12 h. After dilution with Et_2O, the organic layer was treated conventionally and the crude product was purified by column chromatography (flash silica gel; hexane/Et_2O=1:2) to give 56 mg (71%) of acetate **6** as colorless needles (recrystallized from Et_2O-hexane).

6: Mp 75.0—76.0 °C; R_f 0.40 (Et_2O); $[\alpha]_D^{19}$ +43.1° (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 1779, 1744, 1236, and 1044 cm^{-1}; ^1H NMR δ=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 $C_{14}H_{16}O_4$: C, 67.73; H, 6.50.

Enantiomer of **6**: Mp 74.5—75.0 °C; $[\alpha]_D^{19}$ −41.8° (*c* 1.3, $CHCl_3$).

Preparation of 1b from 6. To a solution of acetate **6** (80 mg, 0.32 mmol) in 5 ml of absolute MeOH was added 0.4 M NaOMe/MeOH (1 ml, 0.4 mmol) at 0 °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 HCl and heated at 50 °C for 0.5 h. After removing most of the organic solvent, the residue was extracted with AcOEt. The usual workup gave a crude product which was purified by column chromatography (flash silica gel, hexane/Et_2O=1:4) to afford 64 mg (97%) of **1b** as colorless needles (recrystallized from Et_2O-hexane).

1b: Mp 60.0—61.0 °C (lit,[2] 59—60 °C); R_f 0.30 (Et_2O); $[\alpha]_D^{20}$ +34.0° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 3434, 1775, and 1187 cm^{-1}; ^1H NMR δ=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}C NMR δ=21.60, 28.49, 39.01, 72.52, 81.85, 126.64, 128.53(×2), 129.14(×2), 136.94, 177.37. Found: C, 69.89; H, 6.86. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84.

1d, enantiomer of **1b**: Mp 58.0—60.5 °C; $[\alpha]_D^{20}$ −34.2° (*c* 1.20, $CHCl_3$).

The authors are grateful to Dr. Ayumi Ohsaki of Kinki University for the measurements of high-resolution mass spectra. We also thank Central Glass Co., Ltd., for partial support of this work.

References

1) a) H. Kotsuki, I. Kadota, and M. Ochi, *Tetrahedron Lett.*, **30**, 1281 (1989). b) H. Kotsuki, I. Kadota, and M. Ochi, *ibid.*, **30**, 3999 (1989). c) H. Kotsuki, Y. Ushio, I. Kadota, and M. Ochi, *J. Org. Chem.*, **54**, 5153 (1989). d) H. Kotsuki, I. Kadota, and M. Ochi, *ibid.*, **55**, 4417 (1990). e) H. Kotsuki, I. Kadota, and M. Ochi, *Tetrahedron Lett.*, **31**, 4609 (1990). f) H. Kotsuki, in "Research Trends-Organic Chemistry," Council of Scientific Research Integration, Trivandrum, India; in press.

2) A. E. Wright, M. Schäfer, S. Midland, D. E. Munnecke, and J. J. Sims, *Tetrahedron Lett.*, **30**, 5699 (1989).

3) As the target molecules we chose lactones **1** which were isolated as artifacts of 4,5-dihydroxy-6-phenylhexanoic acid. See Ref. 2.

4) For the convenience, the numbering of these compounds is based on their parent molecule of 4,5-dihydroxy-6-phenylhexanoic acid.

5) Y. Torisawa, H. Okabe, and S. Ikegami, *Chem. Lett.*, **1984**, 1555.

6) "Stereochemistry and Biological Activity of Drugs," ed by E. J. Ariens, W. Soudijn, and P. B. M. W. M. Timmermans, Blackwell Scientific Publications, Oxford (1983).

7) For the procedure of bioassay, see Ref. 2.

8) "Yukikagaku Jikken no Tebiki," ed by T. Goto, T. Shiba, and T. Matsuura, Kagakudojin, Kyoto (1988), Vol. 1.