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Simple Synthesis of Enantiomerically Pure Sauriols A and B

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Sauriols A and B belong to a class of diarylbutane-lignans and exhibit antifeedant activity. We succeeded in the first synthesis of sauriols A and B by using a simple and efficient asymmetric dimerization of a cinnamic acid derivative as the key step.

Key words: sauriol A; sauriol B; lignan; antifeedant

Lignans are found in many plants and exhibit various biological activities. Their diverse structures and activities have fascinated organic chemists and a large number of compounds have been synthesized up to the present.[1)] Sauriols A (**1**) and B (**2**), which belong to diarylbutane-lignan, have been isolated from emergent portions of the southeastern United States freshwater angiosperm, *Saururus cernuus* L. (Saururaceae) and exhibited crayfish antifeedant activity (Fig. 1).[2)] We report here a short-step synthesis of **1** and **2** by employing asymmetric dimerization of a cinnamic acid derivative.

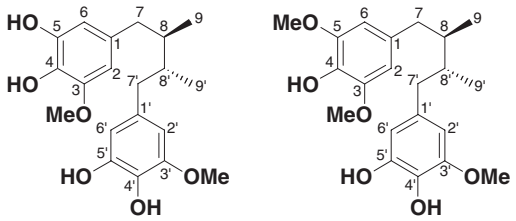

Fig. 1.

Results and Discussion

We have recently reported a novel method for asymmetric dimerization of a cinnamic acid derivative (**3** → **4**), which was much more efficient than the known enzymatic transformation,[3–5)] and synthesis of the furofuran lignans, yangambin and caruilignan A, was achieved in a small number of steps.[6)] The synthesis of sauriols A (**1**) and B (**2**) was considered to be possible by reducing the two benzylic positions and two lactone carbonyls of **4**, with subsequent partial cleavage of the methyl ethers (Scheme 1).

Dilactone **4** was converted to diol **5** by successive hydrogenolysis of the lactone ring, methyl esterification and reduction with LAH as reported previously.[6)] Recrystallization of diol **5** enabled the enantiomeric purity to be enhanced to 100% e.e. which was determined by a comparison of the ^{1}H-NMR spectrum of the corresponding bis-(*R*)-MTPA ester with that of the racemate. To deoxygenate the two primary alcohols, diol **5** was converted to dimesylate **6** and reduced with LAH to afford **7** in a good yield. Partial demethylation to **1** and **2** was accomplished by changing the reaction temperature with BBr_3. At 0 °C, two methyl ethers of each benzene ring were quickly cleaved (5 min) by excess BBr_3, and sauriol A (**1**) was obtained in a 78% yield. On the other hand, selective demethylation to sauriol B (**2**) was quite difficult, and it was found that treating **7** with excess BBr_3 overnight at −78 °C gave the best result. Although a major product was the 4,4′-*O*,*O*′-didemethylated compound (**8**, 51%), sauriol B (**2**) was obtained in a 27% yield along with a small amount of **1** (7%), all of which were easily separated by silica gel column chromatography. ^{1}H-NMR, ^{13}C-NMR and mass spectra of synthesized sauriols A (**1**) and B (**2**) agreed well with those of the natural compounds. Although values for the specific rotation were smaller than those reported for natural sauriols (sauriol A: $[\alpha]_D$ −23 (*c* 0.94, $CHCl_3$), lit.[2)] $[\alpha]_D$ −240 (*c* 0.03, $CHCl_3$); sauriol B: $[\alpha]_D$ −36 (*c* 1.1, $CHCl_3$), lit.[2)] $[\alpha]_D$ −92 (*c* 0.13, $CHCl_3$)), we think that our data are reasonable judging from the magnitude of the specific rotation of related compounds **5**–**7** (see the Experimental section). As both sauriols A (**1**) and B (**2**) are unstable and decomposed even on SiO_2, some decomposed compounds may have affected the specific rotation of the natural compounds.

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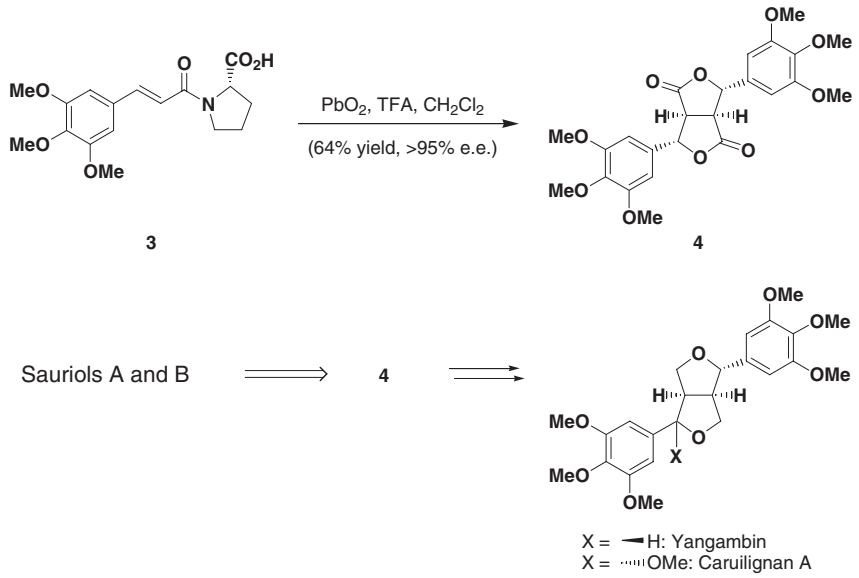
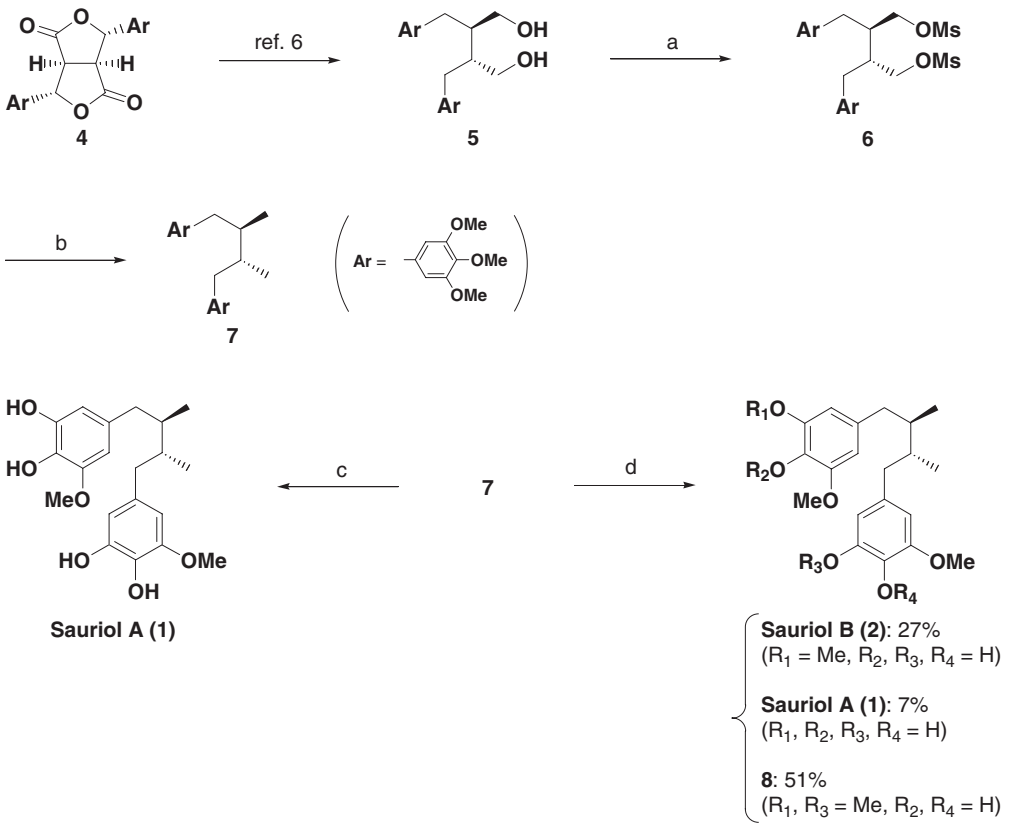


Scheme 1.



Scheme 2. Reagents and conditions: a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 94%; b) LAH, THF, reflux, 2 h, 92%; c) BBr_3 (9 eq.), CH_2Cl_2, 0 °C, 5 min, 78%; d) BBr_3 (9 eq.), CH_2Cl_2, −78 °C, overnight.

In conclusion, we accomplished the first synthesis of sauriols A (**1**) and B (**2**) in a small number of steps. The yields of **1** and **2** starting from dilactone **4** were 50% in 6 steps and 17% in 6 steps, respectively. The usefulness of our asymmetric dimerization of **3** for synthesizing diarylbutane-lignans as well as furofuran lignans could be shown through this synthesis.

Experimental

Optical rotation values were recorded with a Jasco DIP-1000 polarimeter. IR spectra were measured with a Jasco FT/IR-230 spectrophotometer. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) data were recorded with a Jeol JNM AL300 instrument. Chemical shifts (δ) are referenced to the residual solvent peak as the internal standard ($CDCl_3$: $\delta_H = 7.26$, $\delta_C = 77.0$). Mass spectra were recorded with a Jeol JMS-700T instrument. Column chromatography was performed with Merck silica gel 60 (0.060–0.200 mm). Melting point values are uncorrected.

(R)-MTPA ester of racemic ***5***. To a solution of racemic **5** (1 mg) in pyridine (2 drops) was added (*S*)-MTPACl (1 drop). After stirring overnight, the reaction mixture was diluted with ethyl acetate, and successively washed with a diluted HCl solution, saturated $NaHCO_3$ solution, water and brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated *in vacuo*. ^{1}H-NMR δ ($CDCl_3$) ppm: 1.97–2.79 (6H, m), 3.50 (6H, s), 3.72 (12/2H, s), 3.74 (12/2H, s), 3.81 (6/2H, s), 3.82 (6/2H, s), 4.01 (2/2H, dd, $J = 5.7$, 11.4 Hz), 4.16 (2/2H, dd, $J = 4.8$, 11.4 Hz), 4.37 (2/2H, dd, $J = 4.5$, 11.4 Hz), 4.49 (2/2H, dd, $J = 4.8$, 11.4 Hz), 6.16 (4/2H, s), 6.21 (4/2H, s), 7.35–7.48 (10H, m).

(R)-MTPA ester of ***5***. To a solution of recrystallized **5** (1 mg) in pyridine (2 drops) was added (*S*)-MTPACl (1 drop). After stirring for 2 days, the reaction mixture was diluted with ethyl acetate, and successively washed with a diluted HCl solution, saturated $NaHCO_3$ solution, water and brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated *in vacuo*. ^{1}H-NMR δ ($CDCl_3$) ppm: 2.01–2.13 (2H, m), 2.42–2.62 (4H, m), 3.50 (6H, s), 3.74 (12H, s), 3.81 (6H, s), 4.01 (2H, dd, $J = 5.7$, 11.4 Hz), 4.49 (2H, dd, $J = 4.8$, 11.4 Hz), 6.16 (4H, s), 7.35–7.48 (10H, m). Other peaks corresponding to the diastereomer were not observed.

*(2R,3R)-2,3-Bis(methanesulfonyloxymethyl)-1,4-bis(3,4,5-trimethoxyphenyl)butane (****6****).* To a solution of **5**[6] (58.9 mg, 0.131 mmol) and triethylamine (50 µl, 0.359 mmol) in CH_2Cl_2 (2 ml) was added MsCl (40 µl, 0.524 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was poured into water and extracted with $CHCl_3$. The organic layer was dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (1:3) gave **6** (74.8 mg, 94%). Recrystallization from CH_2Cl_2/hexane gave colorless crystals.

Mp 162–165 °C. $[\alpha]^{25}_D$ −15 (*c* 0.85, $CHCl_3$). IR ν_{max} (KBr) cm^{-1}: 2937, 2828, 1591, 1508, 1466, 1425, 1350, 1241, 1172, 1129, 959. ^{1}H-NMR δ ($CDCl_3$) ppm: 2.27–2.33 (2H, m, 2-H and 3-H), 2.59 (2H, dd, $J = 9.0$, 13.8 Hz, 1-H_a and 4-H_a), 2.85 (2H, dd, $J = 5.7$, 13.8 Hz, 1-H_b and 4-H_b), 3.01 (6H, s, SO_2CH_3), 3.83 (18H, s, OCH_3), 4.21 (2H, dd, $J = 4.2$, 9.9 Hz, CH_aOMs), 4.32 (2H, dd, $J = 5.7$, 9.9 Hz, CH_bOMs), 6.38 (4H, s, ArH). ^{13}C-NMR δ ($CDCl_3$) ppm: 34.5, 37.4, 40.1, 56.1, 60.8, 69.1, 105.9, 134.2, 136.7, 153.4. *Anal.* Calcd. for $C_{26}H_{38}O_{12}S_2$: C, 51.47; H, 6.31. Found: C, 51.34; H, 6.34.

*(2R,3R)-2,3-Dimethyl-1,4-bis(3,4,5-trimethoxyphenyl)butane (****7****).* To a solution of **6** (74.8 mg, 0.123 mmol) in THF (6 ml) was added LAH (20 mg, 0.527 mmol) at 0 °C, and the mixture was refluxed for 2 h. After cooling to 0 °C, water and 3 N HCl were added, and the reaction mixture was extracted with $CHCl_3$. The organic layer was dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (3:1) gave **7** (47.5 mg, 92%). Recrystallization from MeOH gave colorless needles.

Mp 116–118 °C. $[\alpha]^{22}_D$ −33 (*c* 0.5, $CHCl_3$). IR ν_{max} (KBr) cm^{-1}: 2930, 1585, 1509, 1467, 1421, 1325, 1240, 1134, 997. ^{1}H-NMR δ ($CDCl_3$) ppm: 0.86 (6H, d, $J =$ 6.6 Hz, 2-CH_3 and 3-CH_3), 1.77 (2H, m, 2-H and 3-H), 2.42 (2H, dd, $J = 7.5$, 13.5 Hz, 1-H_a and 4-H_a), 2.54 (2H, dd, $J = 7.5$, 13.5 Hz, 1-H_b and 4-H_b), 3.80 (12H, s, OCH_3), 3.82 (6H, s, OCH_3), 6.28 (4H, s, ArH). ^{13}C-NMR δ ($CDCl_3$) ppm: 13.8, 37.2, 41.7, 56.0, 60.8, 105.7, 135.9, 137.3, 152.9. *Anal.* Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.36; H, 8.23.

*Sauriol A (****1****).* To a solution of **7** (47.5 mg, 0.113 mmol) in CH_2Cl_2 (3 ml) was added BBr_3 (1.0 M in CH_2Cl_2, 1.0 ml, 1.0 mmol) at 0 °C. After stirring for 5 min, the reaction mixture was poured into water and extracted with $CHCl_3$. The organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (2:1) gave **1** (32.1 mg, 78%) as an amorphous solid.

$[\alpha]^{22}_D$ −23 (*c* 0.94, $CHCl_3$), lit. $[\alpha]_D$ −240 (*c* 0.03, $CHCl_3$). IR ν_{max} ($CHCl_3$) cm^{-1}: 3556, 3022, 2962, 1618, 1518, 1466, 1304, 1238, 1201, 1097. ^{1}H-NMR δ ($CDCl_3$) ppm: 0.81 (6H, d, $J = 6.6$ Hz, 9-H and 9′-H), 1.74 (2H, m, 8-H and 8′-H), 2.35 (2H, dd, $J = 7.5$, 13.5 Hz, 7-H_a and 7′-H_a), 2.49 (2H, dd, $J = 7.2$, 13.5 Hz, 7-H_b and 7′-H_b), 3.81 (6H, s, OCH_3), 5.25 (2H, *br* s, ArOH), 5.29 (2H, *br* s, ArOH), 6.17 (2H, d, $J = 1.5$ Hz, ArH), 6.35 (2H, d, $J = 1.5$ Hz, ArH). ^{13}C-NMR δ ($CDCl_3$) ppm: 13.8, 37.1, 41.2, 56.0, 103.8, 109.2, 130.3, 133.5, 143.4, 146.7. FAB-HRMS *m/z*: calcd. for $C_{20}H_{27}O_6$ $[M + H]^+$, 363.1808; found, 163.1840.

*Sauriol B (****2****).* To a solution of **7** (30.0 mg, 0.072 mmol) in CH_2Cl_2 (1.5 ml) was added BBr_3 (1.0 M in CH_2Cl_2, 0.65 ml, 0.65 mmol) at −78 °C. After stirring overnight, the reaction mixture was poured into water and extracted with $CHCl_3$. The organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel.

Elution with MeOH/$CHCl_3$ (100:1) gave **2** (7.4 mg, 27%) as an amorphous solid, **1** (2.0 mg, 7%) and **8** (14.4 mg, 51%).

$[\alpha]^{27}_D$ −36 (*c* 1.1, $CHCl_3$), lit. $[\alpha]_D$ −92 (*c* 0.13, $CHCl_3$). IR ν_{max} ($CHCl_3$) cm^{-1}: 3548, 2962, 1618, 1516, 1464, 1304, 1213, 1117. ^{1}H-NMR δ ($CDCl_3$) ppm: 0.83 (6H, d, $J = 6.6$ Hz, 9-H and 9′-H), 1.65–1.77 (2H, m, 8-H and 8′-H), 2.34–2.52 (4H, m, 7-H and 7′-H), 3.79 (3H, s, OCH_3), 3.83 (6H, s, OCH_3), 5.22 (2H, *br* s, ArOH), 5.35 (1H, s, ArOH), 6.14 (1H, d, $J = 1.8$ Hz, ArH), 6.28 (2H, s, ArH), 6.35 (1H, d, $J = 1.8$ Hz, ArH). ^{13}C-NMR δ ($CDCl_3$) ppm: 13.9, 37.2, 41.3, 41.5, 56.0, 56.2, 103.7, 105.5, 109.2, 130.2, 132.5, 132.7, 133.5, 143.4, 146.6, 146.7. FAB-HRMS *m/z*: calcd. for $C_{21}H_{29}O_6$ $[M + H]^+$, 377.1964; found, 377.1951.

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