

**A SYNTHESIS OF ($\pm$)-PINORESINOL AND ITS RELATED
COMPOUND USING POTASSIUM PERSULFATE ($K_2S_2O_8$)
OXIDATION OF BENZOYLACETATES**

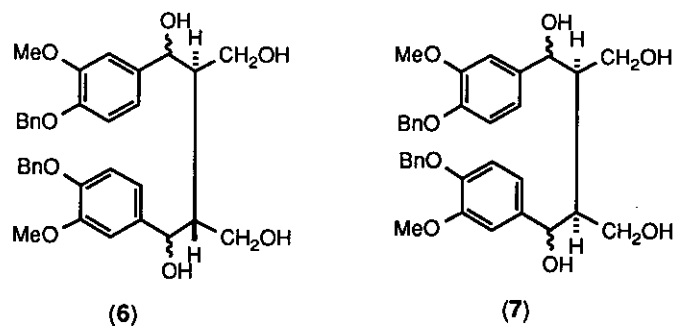
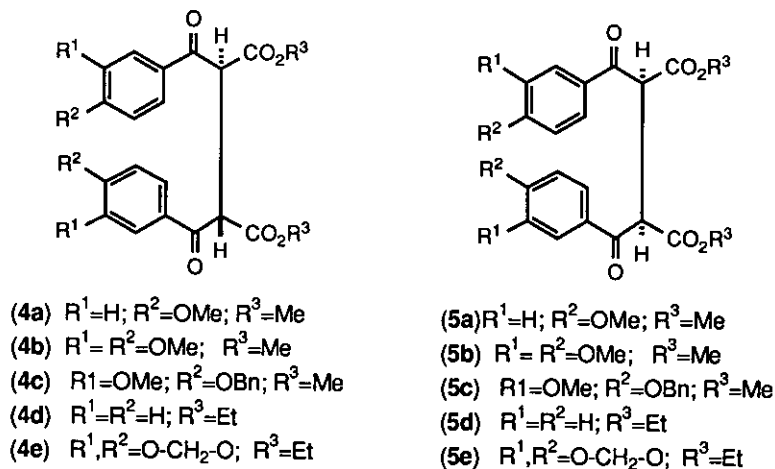
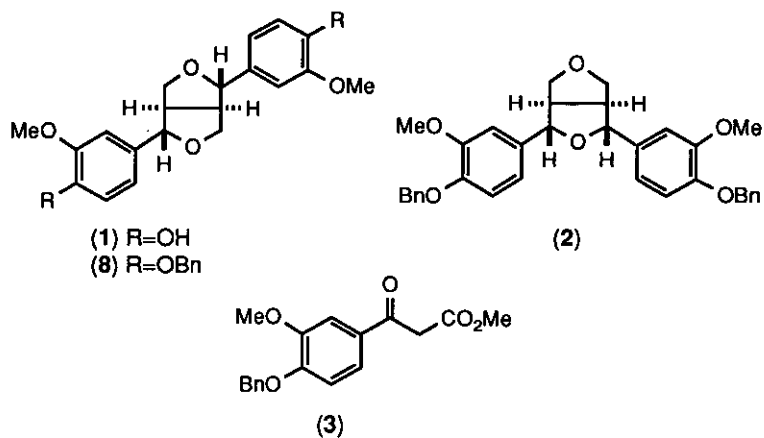
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Abstract- A synthesis of ($\pm$)-pinoresinol has been accomplished by application of the oxidative coupling reaction of benzoylacetate with potassium persulfate as a key step.

There have been several reports concerning the syntheses of the lignans and reviews summarized nicely by R. S. Ward¹ and Y. Shizuri.² As the pioneering work of these syntheses, Knorr accomplished a preparation of 2,3-dibenzoylsuccinate from benzoylacetate by an oxidative coupling using iodine.^{3,4} In continuing study of the new oxidative coupling reaction of methyl benzoylacetate with potassium persulfate ($K_2S_2O_8$),⁵ we report here a synthesis of ($\pm$)-pinoresinol (**1**) and its related compound (**2**), the former of which is one of the representative lignan having 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane structure.

Oxidation of methyl 4-benzyloxy-3-methoxybenzoylacetate (**3**), prepared in a similar procedure to a preparation of the corresponding ethyl ester,⁴ with potassium persulfate in aqueous acetonitrile gave an 1:1 mixture of the *dl*- and *meso*-diketodiester (**4c** and **5c**)⁵ in 58% yield. These two esters were separated in pure forms by fractional recrystallization from ethanol. The structures of these diketodiesters (**4c** and **5c**) were elucidated by comparison of their ¹H-nmr spectra with those of the *dl*- (**4b**) and *meso*-4-methoxyphenyl-diketodiester (**5b**), respectively, the structures of which had been confirmed by the ¹H-nmr experiments using addition of the chiral shift reagent.⁵ Based on the experiment, it has been possible to discriminate the structures of *dl*- and *meso*-diketodiesters using the chemical shift difference of the signals of a methine and methyl protons of the ester group between two isomers. Thus, the chemical shift differences are summarized in Table including the values



reported by Pelter and Ward and their co-workers (compounds **4d,e** and **5d,e**).⁴ Though we have had no plausible explanation for this observation, these chemical shift differences might be due to that the *dl*-isomers and the *meso*-isomers are taking a similar conformation, respectively, and the subtle difference of environment where these protons are placed in stable conformation.

As indicated in Table, the signal of the methine protons on the carbon bearing the methoxycarbonyl group in *dl*-diketodiester (**4c**) was observed in the higher field (δ , 5.50) than that (δ , 5.53) of *meso*-compound (**5c**) and the methyl signal of the ester groups of **4c** was observed in lower field (δ , 3.68) than that (δ , 3.51) of **5c**.

Table

Comparison of the Chemical Shifts of the Methine Protons on the Carbon Bearing an Ester Group and Methyl and Methylene Protons of the Ester Group

Compounds	4a	5a	4b	5b	4c	5c	4d*	5d*	4e*	5e*
H α	5.52	5.56	5.54	5.57	5.50	5.53	5.48	5.54	5.39	5.45
Δ (4-5)	-0.04		-0.03		-0.03		-0.06		-0.06	
CO ₂ CH ₃	3.68	3.51	3.71	3.54	3.68	3.51				
Δ (4-5)	+0.17		+0.17		+0.17					
CO ₂ CH ₂ CH ₃							4.06	3.88	4.11	3.96
Δ (4-5)							+0.18		+0.15	

* From Reported Values by A. Pelter et al.¹

Reduction of *dl*- and *meso*-diketodiester (**4c** and **5c**) with diisobutylaluminum hydride in toluene gave a mixture of diastereoisomers of the tetraols (**6** and **7**), respectively. Treatment of the mixture thus obtained from **4c** with hydrogen chloride in methanol gave ($\pm$)-bis-*O*-benzylpinosresinol (**8**) in 40% overall yield from **4c**, while treatment of **6** with methanesulfonyl chloride (MsCl) in pyridine gave a intractable mixture from which no isolable product was obtained. The same treatment of the mixture of **7** obtained from **5c** with MsCl in pyridine gave the 2,4-diphenyl derivative (**2**) in 16% isolated yield from **5c**. When the tetraol (**6**) was transformed to the *cis*-3,7-dioxabicyclo[3.3.0]octane, the ether formation has to take place between primary and secondary hydroxyl groups. On the other hand, the ring formation has to take place between two primary alcohols in case of the tetraol (**7**). When **7** was

treated with methanesulfonyl chloride in pyridine, one of the primary alcohols would be mesylated at first and cyclized with another less hindered primary hydroxyl group followed by cyclization between two secondary hydroxyl groups, constructing *cis*-dioxabicyclo[3.3.0]octane. In case of the tetraol (6), when the same type of reaction took place between two primary alcohols, the second cyclization had to take place to form the *trans*-3,7-dioxabicyclo[3.3.0]octane to be difficult. On the other hand, when the tetraol (6) was treated with hydrogen chloride, a benzyl cation would be produced and subjected to cyclization with a primary alcohol. Thus, in the case of 6, primary and secondary alcohols combination makes possible to form the *cis* fused dioxabicyclo[3.3.0]octane.

Hydrogenation of the 2,6-derivative (8) gave the phenolic product, spectroscopic properties of which were identical with those of pinoresinol (1) reported in literature,⁴ indicating the accomplishment of the synthesis of (±)-pinoresinol and providing a new method for the synthesis of lignans having the same symmetrical substituent pattern on the benzene ring.

EXPERIMENTAL

All the melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded on Shimadzu IR-408 spectrophotometer. ¹H-Nmr spectra and ¹³C-nmr were recorded JEOL PMX-60, JEOL-FX90Q, and JNM-GX 400 NMR spectrometers with tetramethylsilane as an internal standard and chemical shifts are given in δ (ppm). Nominal (ms) and high resolution mass spectra (hr-ms) were recorded with a JEOL-DX303 instrument. Column chromatography was performed with Kieselgel 60 (70-230 mesh). Thin layer chromatography (tlc) and preparative thin layer chromatography (preparative TLC) were carried out on Kieselgel 60F254 (Merck) with appropriate solvents.

Methyl 4-benzyloxy-3-methoxybenzoylacetate (3) A solution of 4-benzyloxy-3-methoxybenzoyl chloride (prepared from 4-benzyloxy-3-methoxybenzoic acid (725 mg, 2.8 mmol) with thionyl chloride in the usual manner) in ether (20 ml) was added to a suspended solution of the sodium salt of methyl acetoacetate (prepared from methyl acetoacetate (350 mg, 3.0 mmol) and sodium hydride (145 mg as coated in mineral oil, in 60%, 3.6 mmol) under reflux for 1 h in ether (15 ml)). The whole was refluxed overnight and concentrated to leave a residue, which was dissolved in cold water. The aqueous solution was acidified with 8%

hydrochloric acid and extracted with ether. The ethereal solution was washed with water, dried over MgSO_4 , and concentrated to give a residue. A solution of the residue and sodium acetate (12.0 g, 0.15 mmol) in ethanol (5 ml) was heated under reflux for 6 h and concentrated to give a residue which was taken up in chloroform. The chloroform solution was washed with water, dried over MgSO_4 , and concentrated to leave a residue which was chromatographed on silica gel in chloroform. Elution with the same solvent gave methyl 4-benzyloxy-3-methoxybenzoylacetate (**3**) (500 mg, 57%). mp 66–68°C. Ir cm^{-1} (Nujol): 1728, 1670, 1584. $^1\text{H-Nmr}$: 3.73 (3H, s), 3.94 (5H, s), 5.23 (2H, s), 6.90 (1H, d, $J=8.1$ Hz), 7.22–7.58 (8H, m). Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{O}_5$: C, 68.78; H, 5.77. Found: C, 68.70; H, 5.77.

Oxidative coupling of methyl 4-benzyloxy-3-methoxybenzoylacetate (3) with potassium peroxodisulfate ($\text{K}_2\text{S}_2\text{O}_8$) A mixture of the keto ester (**3**) (314 mg, 1.0 mmol) in acetonitrile (10 ml) and an aqueous solution of $\text{K}_2\text{S}_2\text{O}_8$ (540 mg, 2.0 mmol) and CuSO_4 (32 mg, 0.2 mmol) in water (10 ml) was refluxed in an argon atmosphere (removal of air was essential) for 7 h and concentrated under reduced pressure to leave a residue which was thoroughly extracted with chloroform. The chloroform solution was washed with 2% aqueous sodium hydrogen carbonate and water, and dried over MgSO_4 . Removal of the solvent gave a residue (284 mg) which was chromatographed on silica gel in ether-hexane (1:1). Elution with the same solvent gave a mixture of *dl*- and *meso*-diketodiester (175 mg, 58%), which was subjected to fractional recrystallization with ethanol. The slightly soluble *meso*-compound (**5c**) (32% as an isolated yield) was obtained as colorless fine needles, mp 190–191°C. Ir cm^{-1} (CHCl_3): 1735, 1665. $^1\text{H-Nmr}$ (CDCl_3): 3.51 (6H, s), 3.95 (6H, s), 5.25 (4H, s), 5.53 (2H, s), 6.97 (2H, d, $J=9.0$ Hz), 7.63 (2H, d, $J=1.8$ Hz), 7.83 (2H, dd, $J=9.0, 1.8$ Hz). Anal. Calcd for $\text{C}_{36}\text{H}_{34}\text{O}_{10}$: C, 69.00; H, 5.47. Found: C, 68.67, H, 5.56. The easily soluble *dl*-compound (**4c**) (18% as an isolated yield): mp 122–124°C. Ir cm^{-1} (CHCl_3): 1735, 1670. $^1\text{H-Nmr}$ (CDCl_3): 3.68 (6H, s), 3.89 (6H, s), 5.23 (4H, s), 5.50 (2H, s), 6.94 (2H, d, $J=9.0$ Hz), 7.53 (2H, d, $J=1.8$ Hz), 7.81 (2H, dd, $J=9.0, 1.8$ Hz). Anal. Calcd for $\text{C}_{36}\text{H}_{34}\text{O}_{10}$: C, 69.00, H, 5.47. Found: C, 68.71; H, 5.47

2,6-Bis-(4-benzyloxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]-octane (8) (($\pm$)-Pinoresinol dibenzyl ether) A 1.5 M solution of diisobutylaluminum hydride in toluene (1 ml) was added to a solution of the *dl*-compound (**4c**) (100 mg, 0.16 mmol) in toluene (10 ml) at room temperature. The whole was stirred at the same temperature overnight,

diluted with saline, stirred for 1.5 h and filtered. The filtrate was extracted with methylene chloride. The extract was washed with water, dried over MgSO_4 , and concentrated to dryness to leave an oil (70 mg, 76%) (no carbonyl band on its ir-spectrum), which was subjected to the forthcoming reaction without further purification. A solution of the foregoing oily residue in 0.5 M methanolic hydrogen chloride (5.5 ml) was stirred at 0°C overnight and diluted with ethyl acetate. The solution was washed with saline and water, dried over MgSO_4 , and concentrated to leave an oily residue which was subjected to preparative thin layer chromatography on silica gel plate with hexane-ethyl acetate (1:1). The product collected from the major zone was recrystallized from hexane-ether-ethanol to give ($\pm$)-pinoresinol dibenzyl ether (**8**) (35 mg, 53%). mp $108-112^\circ\text{C}$. Ir cm^{-1} (CHCl_3): 1600. $^1\text{H-Nmr}$ (CDCl_3): 3.09 (2H, m), 3.87 (2H, dd, $J=9.2, 3.7$ Hz), 3.90 (6H, s), 4.24 (2H, dd, $J=8.8, 3.7$ Hz), 4.74 (2H, 2H, d, $J=4.0$ Hz), 5.14 (4H, s), 6.78-6.93 (6H, m), 7.27-7.43 (10H, m). Hr-ms: Calcd for $\text{C}_{34}\text{H}_{34}\text{O}_6$; 538.2355. Found; 538.2359.

($\pm$)-Pinoresinol (1**)** A mixture of the dibenzyl ether (**8**) (10 mg, 0.02 mmol) and 10% Pd-C (3 mg) in ethanol (1.5 ml) was hydrogenated at room temperature for 2 h. After removal of the catalyst by filtration, the filtrate was concentrated to give ($\pm$)-pinoresinol (4.0 mg, 60%) as an oil. Ir cm^{-1} (CHCl_3): 3550, 1615. $^1\text{H-Nmr}$ (CDCl_3): 3.10 (2H, m), 3.88 (2H, dd, $J=9.2, 3.7$ Hz), 3.91 (6H, s), 4.24 (2H, m), 4.73 (2H, d, $J=4.4$ Hz), 5.57 (4H, s), 6.81-7.29 (6H, m). $^{13}\text{C-Nmr}$ (CDCl_3): 54.2, 56.0, 71.7, 85.9, 109.0, 114.3, 119.0, 133.0, 145.3, 146.7. Hr-ms: Calcd for $\text{C}_{20}\text{H}_{22}\text{O}_6$; 358.1416. Found; 358.1405.

2,4-Bis-(4-benzyloxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]-octane (2**)** The *meso*-compound (**5c**) (100 mg, 0.16 mmol) was treated with diisobutylaluminum hydride in the same manner as mentioned above to give the tetraol (**7**) (80 mg, 87%). A solution of the tetraol and methanesulfonyl chloride (10 mg, 0.08 mmol) in pyridine (2.0 ml) was stirred at room temperature overnight and methanesulfonyl chloride (10 mg, 0.08 mmol) was added to the solution additionally. The whole was stirred overnight and diluted with water and extracted with ethyl acetate. The organic extract was washed with 2% hydrochloric acid, water, and saline, and dried over MgSO_4 . Removal of the solvent gave a residue, which was submitted to a preparative thin layer chromatography in hexane-ethyl acetate (1:1) to give 2,4-bis-(4-benzyloxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]-octane (**2**) (14 mg after recrystallization from ethanol) as colorless needles, mp $131-133^\circ\text{C}$. Ir cm^{-1} (CHCl_3): 1600. $^1\text{H-Nmr}$ (CDCl_3): 2.94 (2H, m), 3.58 (2H, dd, $J=9.0, 5.0$ Hz), 3.90 (6H, s), 4.01

(2H, d, $J=9.0$, 3.7 Hz), 4.52 (2H, d, $J=7.6$ Hz), 5.14 (4H, s), 6.87-7.54 (16H, m). Hr-ms: Calcd. for $C_{34}H_{34}O_6$; 538.2355. Found; 538.2359.

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