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Note

Facile Synthesis of Hydroxystilbenes and Determination of Their Double Bond Configuration

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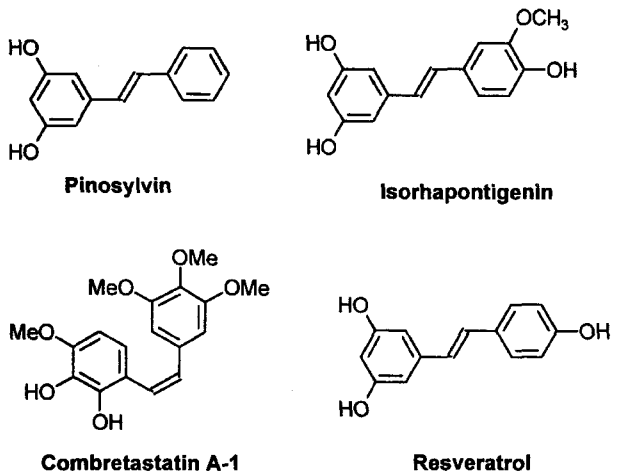
Hydroxystilbenes such as pinosylvin, isorhapontigenin, ombretastatins A-1, and resveratrol have been isolated om wood, bark, leaves of plant, and grapevine. (Scheme 1) he hydroxystilbenes and their methyl ethers have shown to ave various biological activities such as nematocidal, anti-ngal, and tubulin inhibitory activity.[1-3] In the course of ur screening program of plant materials for Leukotriene D_4 LTD_4) antagonist, we found that resveratrol showed strong TD_4 antagonist activity.

We wished to obtain differently substituted hydroxystilbenes s resveratrol analogues. In particular we required a facile ynthetic method which we could later apply to the synthesis f a number of other naturally occurring hydroxystilbenes r their methyl ethers.

Among the many general methods studied,[4] Wittig reaction is ominantly used to produce both *cis* and *trans* isomers of tilbene, which might show different biological activities. lowever, extremely strong basic conditions (BuLi or NaH) nd well-dried solvent system are usually required to enerate ylides from phosphonium halides. Avoiding the astidious conditions, the Wittig reaction conducted in a two-phase solvent system, for example concentrated aqueous NaOH and CH_2Cl_2, were reported.[5] The two-phase solvent system could be the best application for our polyhydroxystilbene synthesis because aldehyde bearing hydroxyl groups is one part of starting materials. Phosphonium halide salt was prepared according to general procedures appeared in literature.[2] (Scheme 2) *p*-Anisaldehyde (**1**) was reduced to an alcohol with $NaBH_4$. Under mild PPh3/CCl_4 conditions, resulting alcohol was converted to corresponding benzylhalide. After evaporation of solvent, the desired halide was separated from by-product triphenylphosphine oxide ($Ph_3P=O$) by dissolving into ether where $Ph_3P=O$ was precipitated. Without purification, the halide was treated with PPh_3 in toluene under refluxing, affording phosphosnium salt product (**2**) precipitated out from the solvent. The desired phosphonium halide salt was filtered off to give pure enough solid for next reaction (87% for three steps). No purification was required during three step reaction. For a typical Wittig reaction performed in two-phase solvent system, 1 equivalent of 2-hydroxybenzaldehyde (**3**) and 1.2 equivalent of 4-methoxy benzyltriphenylphosphonium chloride (**2**) was dissolved in CH_2Cl_2 to give a clear solution. To the solution, was slowly added 50% aqueous NaOH solution (equal amount of CH_2Cl_2). The resulting heterogeneous solution was stirred for 2 days at room temperature to give one major product which turned out trans isomer after considerable NMR experiment. The same reaction was conducted on 2-hydroxybenzaldehyde (**3**) with commercially available phosphonium salt **5**, furnishing also one major isomer **7**. In the case of reaction between benzaldehyde (**4**) and phosphonium salt **2**, both *trans* (**8**) and *cis* (**9**) isomers were obtained as 2:3 ratio. The reverse case, reaction between *p*-anisaldehyde (**1**) and phosphonium salt **5**, gave also *trans* (**8**):*cis* (**9**)=3:5 ratio. The hydroxystilbene (**6-9**) obtained from the Wittig reaction showed that double bond hydrogens were complicated with aromatic protons, which made determination of double



Scheme 1. Naturally occurring hydroxystilbenes.

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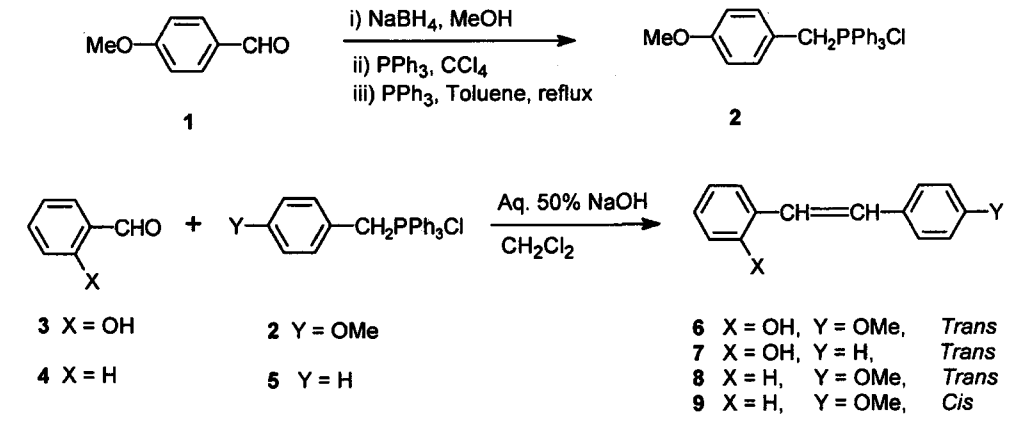

Scheme 2. Synthesis of phosphonium salt and hydroxystilbenes.

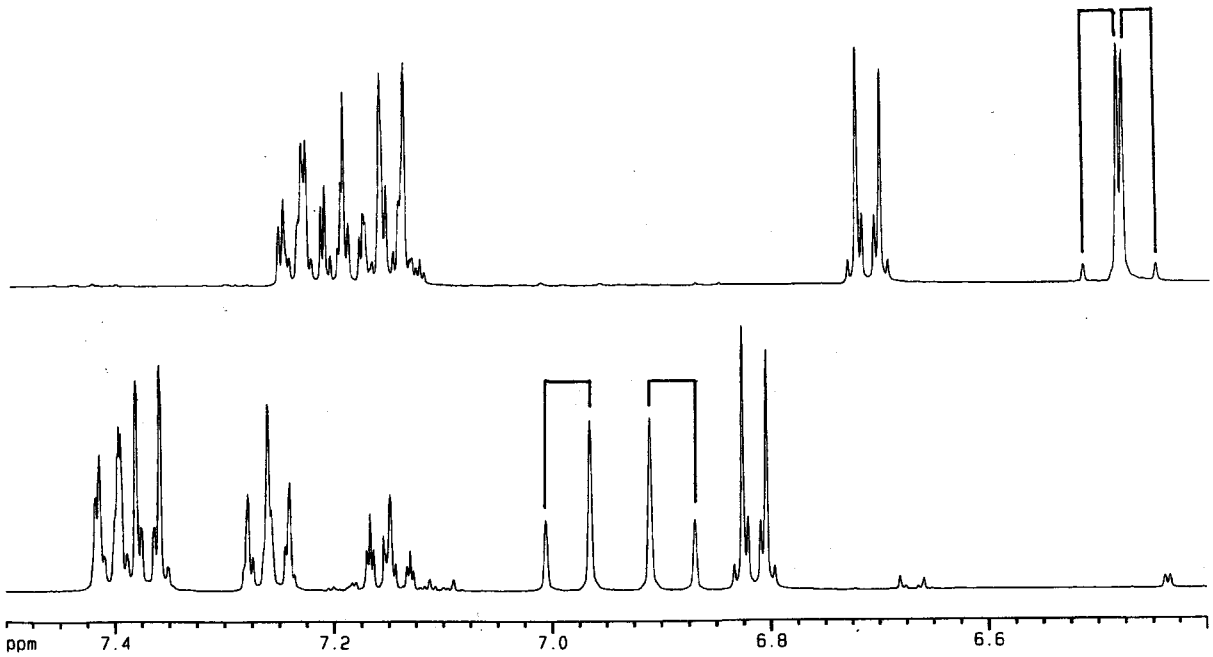

Fig. 1. A comparison of ^{1}H-NMR spectra of 8 (bottom) and 9 (top).

bond configuration difficult.

In order to determine the configuration, NMR experiments were carried out on the Bruker DPX400 (9.4 T) spectrometer. For the complete assignments, ^{1}H- and ^{13}C-NMR, DEPT, HMQC, HMBC, and COSY data were collected. Two peaks at 7.23 ppm (1H, d, J=16.5 Hz) and 7.48 ppm (1H, d, J=16.5 Hz) of ^{1}H-NMR of **7** were assigned as two methine protons of the double bond. The same coupling constant was observed in two peaks at 6.99 ppm (1H, d, J=16.5 Hz) and 7.15 ppm (1H, d, J=16.5 Hz) of **6**, and two peaks at 6.88 ppm (1H, d, J=16.5 Hz) and 6.99 ppm (1H, d, J=16.5 Hz) of **8**. However, two peaks at 6.47 ppm (1H, d, J=12.3 Hz) and 6.50 ppm (1H, d, J=12.3 Hz) of **9** showed different coupling constant. By Karplus curve in olefinic systems, the coupling constant of *trans* configuration ($^3J_{180°}$) is always larger than that of *cis* configuration ($^3J_{0°}$).[6] In other words, Jgauche is less than J_{trans}. Therefore, configuration of **6**, **7**, and **8** should be determined to be *trans*, while the configuration of **9**, *cis*. Fortunately, since compounds **8** and **9** are the same except their configuration the comparison of their ^{1}H-NMR spectra shown in Fig. helps us to make clear.

Acknowledgement

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Hydroxystilbenes 유도체의 합성 및 configuration의 결정

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