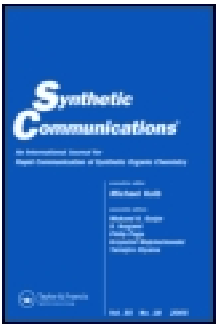

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"SOLID PHASE SYNTHESIS OF CIS-CONIFERYL ALCOHOL"

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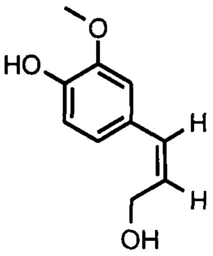
Abstract: Synthesis of cis-coniferyl alcohol (4-hydroxy-5-methoxy- cinnamyl alcohol), using support on Wang's resin is described.

Cis-coniferyl alcohol (4-hydroxy-5-methoxy-cis-cinnamyl alcohol) **1** has been obtained in a number of ways. In addition to fermentation processes[1,2] it has been isolated from the bark *Fagus silvatica L.*, as its 1-O-β-D-gluco-pyranoside, faguside.[3]



(1)

Reduction of ethyl acetoferulate **2** with LAH/-10°C gave **3** in 42.6% yield without effect on the double bond.[4] Unlike its

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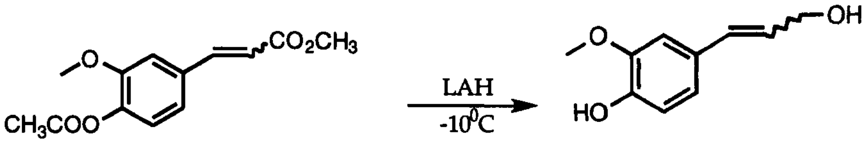
*To whom correspondence should be addressed *trans*-geometric isomer[5] (J=15.8 Hz), **1** is not a commercial product.

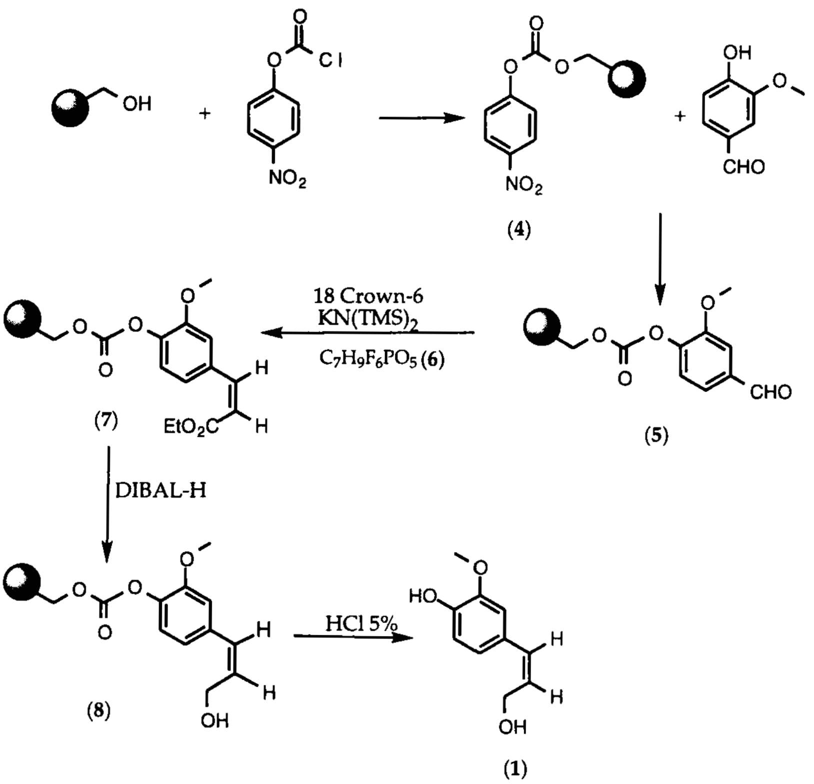


(2)

(3)

Here in we report the synthesis of **1** via solid-phase based[6,7] reaction sequence, shown in Scheme 1. Reaction of Wang's resin[8] with 4-nitrophenyl chloroformate in dichloromethane at 0°C gave the activated resin **4.** Addition of a slurry of NaH and vanillin in DMF over 24 hours to the swollen **4** gave **5**. While leaving the aldehyde of **5** free for further reaction, protection of the phenolic group of vanillin precluded later both (a) secondary reactions of the benzene ring with oxidizers and electrophiles as well as (b) alkaline-caused nucleophilic reactions of the phenoxide unit. Both reactions were quantitative.

Using the Wadsworth-Horner-Emmons (WHE) variation of the Wittig reaction, modified to give primarily the *cis*-stereoisomer[9], addition of **5** to a cold solution (-78°C) of the anion resulting from addition of bis(2,2,2,-trifluoroethyl) methoxycarbonylmethyl phosphonate **6** to potassium bis(trimethylsilyl) amide in THF (catalytic amount of 18-crown-6) gave a quantitative yield of the labeled resin **7**. Earlier, when this reaction was carried out without vanillin bound to a resin, the yield of unsaturated esters was 95%, Scheme 1:



containing 5% of the trans-coniferyl alcohol (based on ^{1}H-NMR), similar to results observed by others under solution conditions.[9]

The absence of the trans isomer in our work may be due to the "template effect", arising from the topological surface of the solid phase.[10]

Finally, reduction of **7** with DIBAL-H at –78°C gave **8**, and **1** was freed from the resin by treatment with 5% HCl in place of the usual trifluoroacetic acid, giving **1** in 98% overall yield.

Other protective groups, including the MOM and TBDMS groups were explored; however, the use of Wang's resin was the most efficient and fastest, as it was not necessary to make extensive purification at each step.

Experimental: Melting points were obtained on an Electrothermal 88629 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR 1600 spectrophotometer. Nuclear magnetic resonance ^1H spectra and ^{13}C spectra (50.289 Hz in $CDCl_3$) were recorded on a Varian Gemini 200 Spectrometer with TMS as internal standard. Elemental analysis for carbon and hydrogen were performed by Galbraith Laboratories, Incorporated (Knoxville, TN). Mass spectra were obtained on a Hewlett-Packard 5989 by EI at 70 eV by direct insertion.

Actived Wang's-resin (**4**): Wang's resin (1.0 g, 0.65 mmol), and pyridine (0.68 mL, 8.68 mmol), were suspended in dichloromethane (10 mL), under constant agitation for 1/2 hour at 0°C. A solution of 4-nitrophenyl chloroformate (1.62 g, 7.90 mmol) in dichloromethane (10mL) was slowly added to the mixture. The mixture was filtered and the residue was washed with dichloromethane (3x20mL). The resin **4** was recovered in 100% yield. IR(KBr): 3025, 2922, 1764, 1526, 1212 cm^{-1}.

(**5**): Activated Wang's-Resin **4** (1.0 g, 0.59 mmol) was allowed to swell in DMF (10 mL) for 15 minutes, under constant stirring in an argon atmosphere. A suspension of NaH (0.10 g, 4.50 mmol) in DMF (10 mL) along with vanillin (0.50 g, 3.29 mmol) was added in small portions over 10 minutes, followed by constant stirring over 24 hours at RT. The suspension was filtered and washed with DMF (3x20 mL), methanol (3x20 mL) and dichloromethane (3x20 mL). Solid **5** was recovered in 100 % yield after drying under high vacuum. IR(KBr): 3015, 2923, 1764, 1697, 1503, 1230, 1020 cm^{-1}.

(**7**): To a solution of 18-crown-6 (0.98 g, 3.69 mmol) dissolved in anhydrous THF (10mL), was added potassium potassium *bis*-trimethylsilylamide (0.17 g, 0.85 mmol) in small portions over

10 minutes with constant stirring and cooling at –78°C. Maintaining the low temperature and stirring, a solution of *bis* - (2,2,2-trifluoroethyl) methoxycarbonylmethylphosphonate (**6**) (0.28 g, 0.87 mmol) in THF (10 mL), was added over 15 minutes followed by a suspension of **5** (0.30 g, 0.174 mmol) in THF (10 mL), then allowing the mixture to stir for 2 hours more. Saturated aqueous ammonium chloride was added and the mixture was filtered and washed with water (50 mL), DMF (3x20 mL), methanol (3x20 mL) and dichloromethane (3x20 mL). The resin obtained was dried under high vacuum for 18 hours, resulting in a quantitative yield of **7**. IR(KBr): 3025, 2923, 1764, 1723, 1512, 1235, 1030 cm^{-1}.

Cis-Coniferyl Alcohol (4-Hydroxy-5-methoxy-cis-cinnamyl alcohol) (**1**) (via **7**): To the resin **7** (0.3 g, 0.168 mmol) swollen in 30 mL anhydrous diethyl ether for 20 minutes and then cooled to -78°C, and DIBAL-H (0.468 mL, 2.63 mmol) was added thorough a syringe. After the mixture was maintained a –78°C for 2.5 hours under stirring, the temperature was raised to 0°C and a solution of 10% HCl (80 mL) was added dropwise. The suspension was filtered under reduced pressure and the resin was washed with H_2O (3x20 mL), ethyl ether (3x20mL) and the filtrate was extracted with dichloromethane (2x25 mL). The organic phase was washed with water (2x30 mL) and dried over anhydrous sodium sulfate and removal of solvent under reduced pressure gave a crystalline white solid (29 mg, 98% yield). Mp. 72-74°C. IR(KBr): 3126, 1510, 1267, 1169 cm^{-1}. ^{1}H RMN(200 MHz/$CDCl_3$): δ 7.03(d, 1H, J=7.9 Hz, Ar-H), 6.82(m, 2H, Ar-CH), 6.64(d, 1H, J=11.7 Hz, Ar-CH-CH), 5.95-5.83(dt, 1H, J_1=11.7 J_2=6.4 Hz, CH-CH_2), 5.75 (sa, 1H, OH), 4.57-4.53(dd, 2H, J_1=6.5, J_2=1.6 Hz, CH-CH_2) 4.01(s, 3H, OCH_3) ppm. ^{13}C RMN: δ 131, 129, 122, 114, 111, 59, 55 ppm. EM (m/e): 180 (M$^+$,59), 137 (100), 124 (45), 91 (24).

Anal. calcd. for $C_{10}H_{12}O_3$; C, 66.65; H, 6.71. Found: C, 66.90; H, 6.73.

Cis-Coniferyl Alcohol (4-Hydroxy-5-methoxy-cis-cinnamyl alcohol) (**1**) (via solution reaction): Methyl 4-*tert*-butyldimethylsilyl-oxy-3-methoxy-cinnamoate (1.5 g, 5.95

mmol) was disolved in anhydrous ethyl ether (30 mL). After 20 minutes, the suspension was cooled to -78°C and DIBAL-H (2.34 mL, 13.15 mmol) was added thorough a syringe, maintaining the mixture to this temperature and with constant stirring for 2.5 hours. After the mixture was led to rise 0°C and added drop to drop of a solution of HCl (10%, 80 mL). The solution was extracted with anhydrous ethyl ether (8 X 50 mL). The organic phase was dried with anhydrous sodium sulfate. Excess solvent was eliminated at reduced pressure. The residue obtained was a white solid (0.54g 50.46% yield).

Mp. 72-74°C. IR(KBr): 3418, 3126, 2944, 1600, 1510, 1267, 1169 cm^{-1}. ^{1}H RMN[major isomer cis (95%)](200 MHz/CDCl$_3$): δ 7.03(d, 1H, J=7.9 Hz, Ar-H), 6.82(m, 2H, Ar-CH), 6.64(d, 1H, J=11.7 Hz, Ar-CH-CH), 5.95-5.83(dt, 1H, J_1=11.7 J_2=6.4 Hz, CH-CH$_2$), 5.75 (sa, 1H, OH), 4.57-4.53(dd, 2H, J_1=6.5, J_2=1.6 Hz, CH-CH$_2$) 4.01(s, 3H, OCH$_3$) ppm. Mp. 75-76°C. Minor isomer trans (5%): δ 6.94-6.82(sb, 1H, Ar-OH), 6.92(s, 1H, Ar-H), 6.84(m, 2H, Ar-H), 6.52(dt, 1H, J_1=15.8 Hz, J_2=1.4 Hz Ar-CH-CH), 6.20(dt, 1H, J_1=15.8 Hz J_2=5.7 Hz, Ar-CH-CH), 4.27(dd, 2H, J_1=5.7 Hz, J=$_2$1.4 Hz, CH$_2$-O), 3.89(s, 3H, OCH$_3$) ppm. ^{13}C RMN: δ 146, 131, 126, 120, 115, 109, 63, 56 ppm. EM (m/e): 180 (M$^+$,59), 137 (100), 124 (45), 91 (24).

Anal. calcd. for $C_{10}H_{12}O_3$; C, 66.65; H, 6.71. Found: C, 66.90; H, 6.73.

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