A Total Synthesis of Nuciferal and Nuciferol

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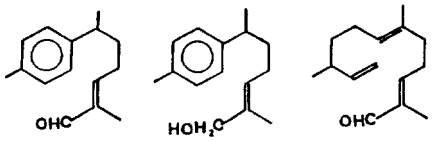
Racemic nuciferal(**1**) and nuciferol(**2**), the terpenic natural perfumeries, have been synthesized by a simple procedure. The benzylic halide **6**, 1-(1-chloroethyl)-4-methylbenzene, was prepared by converting *p*-tolualdehyde(**4**) into 1-(*p*-tolyl)-1-ethanol(**5**), followed by convertion of **5** into corresponding chloride. The Grignard reagent of **6** was reacted with the bromoacetal **7**, 2-(2-bromoethyl)-1,3-dioxolane, to give a crosscoupling product **8**, which was hydrolysed to 4-(*p*-tolyl)-pentanal (**9**). The Wittig reaction of isopropylide **10** with **9** yielded arcurcumen(**11**). The stereospecific allylic oxidation of the gem-dimethyl olefin **11** with selenium dioxide afforded a trans-aldehyde, (±)-**1**, which was reduced to corresponding alcohol, (±)-**2**.

Introduction

Nuciferal(**1**) and nuciferol(**2**) are constituents of natural volatile woold oil separated from the wood Torreya nucifera. The structure of nuciferal has been known to be an aromatic sesquiterpenic aldehyde, 2-methyl-6-(p-tolyl)-trans-2-heptenal[1], which is similar to that of sinensal(**3**)[2-4] that has been isolated from orange oil (*citrus sinensis L.*) and is an important materials for the creation of orange flavors.

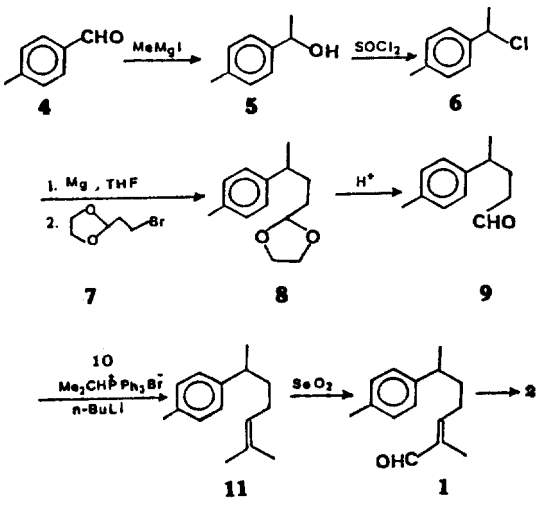


1 **2** **3**

Several synthetic procedurs for nuciferal(**1**) have been reported in the literature. Vig *et al.*[5] synthesized (±)-**1** starting from 4-(p-tolyl)-valeric acid. Buchi and Wuest[6] used p-tolylacetophenone, and Evands *et al.*[7] used 3-(p-tolyl)-2-butenoate ester as starting materials, respectively, for the synthesis of this compound. In recent communication, Yamamoto *et al.*[8] investigated a synthetic method of α,β-unsaturated aldehyde by the reaction of vinylsilanes with dichloromethyl methyl ether promoted by titanium tetrachloride, and applied this procedure to the synthesis of (±)-**1**. In this paper, the authors wish to provide a new synthetic procedure of (±)-**1** and (±)-**2** starting from p-tolualdehyde, as shown in Scheme 1.

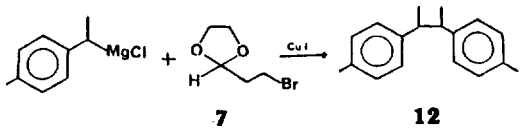
Result and Discussions

A simple synthesis of racemic nuciferal(1) was carried out using inexpensive chemicals. The benzylic chloride **6** was prepared in almost quantitative yield by reacting p-tolualdehyde (**4**) with methylmagnesium iodide to give a benzylic alcohol **5**, followed by successive conversion of **5** with thionyl chloride into corresponding chloride. The bromodioxolane **7** was prepared by condensation of acrolein with ethylene glycol in the presence of anhydrous hydrogen bromide.[6] The cross-coupling of the two halides, **6** and **7**, was investigated in several ways. The reaction of the Grignard reagent, prepared from **6**, with the bromide **7** gave rise to a cross-coupling product, the cyclic acetal **8**. It has been known that the cross-coupling of organometallic reagent with a halide is sometimes facilitated by cuprous iodide.[9-12] However, in the presence of cuprous iodide, this reaction did not give the cross-coupling product, but a self-coupling of the benzylic chloride(6) was observed, producing symmetrically substituted ethane derivative **12** in excellent yield (about 80%).



4 **5** **6** **7** **8** **9** **11** **1**

Scheme 1



7 **12**

On the other hand, we tried the coupling reaction by exchanging the Grignard reagent of the halide **6** for that of the halide **7**. The Grignard reagent prepared from **7** was reacted with **6** in the presence and absence of the cuprous salt. Neither cross-coupling nor self-coupling products were produced. We tried also the coupling reaction by substituting the organomagnesium reagent for organolithium reagent. This reaction did not proceed well, and no coupling products were afforded.

The natural product **11**, ar-curcumene, could be obtained quantitatively by the Wittig reaction of the pentanal **9** and isopropylide **10**. The stereospecific, allylic oxidation of the gem-dimethyl olefin (**11**) could be accomplished by following the procedure of Rapoport.[13] The oxidation of **11** with selenium dioxide yielded exclussively the trans-aldehyde, racemic nuceferal (**1**), which was reduced to nuciferol (**2**).

Experimental Part

All reactions involving organometallic reagents were carried out with the usual precautions for rigorous exclusion of air and moisture. The solvents, ether and tetrahydrofuran, were purified by refluxing for several hours in the presence of sodium metal and benzophenone until the solution colored purple, followed by distillation under nitrogen. Boiling points of liquid products were unmeasured.

IR spectra were recorded with Perkin-Elmer Model 782 spectrometer, and nmr spectra were taken on Varian EM-360A and Varial XL-100 spectrometer to an internal standard of TMS.

1-(p-Tolyl)-1-ethanol (5). In a 50 m*l* three-necked round-bottomed flask fitted with a reflux condenser and a dropping funnel, 4.3 g(179 mmole) of magnesium turnings and 10 m*l* of anhydrous diethyl ether were added. While stirring under nitrogen, a solution of 21.3 g (150 mmole) of methyl iodide in 20 m*l* of anhydrous ether were added carefully through the dropping funnel during 15-20 min and stirred for five min. This Grignard reagent was transferred by cannulation under nitrogen into another three-necked round-bottomed flask fitted with a reflux condenser and a dropping funnel. A solution of 12.0 g(100 mmole) of p-tolualdehyde in 10 m*l* of anhydrous ether was slowly added to the Grignard reagent. After stirring for 20 min, a few m*l* of 2N HCl was added. The ether layer was separated and the residual aqueous layer was extracted with ether, adding the extracts to the original ether layer. The combined organic layer was washed with saturated sodium bicarbonate solution and water successively, then the organic layer was dried over anhydrous magnesium sulfate. After the solvent was removed by evaporation, the crude product was chromatographed on a silica gel column using dichloromethane as an eluant, to give a yellow liquid with the yield of 95-99%. ^{1}H-NMR($CDCl_3$); δ 1.5(d, 3H, CH_3), 2.3(s, 3H, $ArCH_3$), 2.5(s, 1H, OH), 4.8(q, tert, 1H), 7.2(s, arom, 4H). IR(neat); 3390(OH), 2990, 1520 cm^{-1}(arom. C = C).

1-(1-Chloroethyl)-4-methylbenzene(6). In a 100 m*l* three-necked round-bottomed flask fitted with a reflux condenser and a dropping funnel, 6 m*l* (82.3 mmole) of thionyl chloride was placed and cooled to 0 °C. To this flask 10g (74.1 mmole) of 1-(p-tolyl)-1-ethanol (**5**) was added carefully through the dropping funnel during 30 min, stirred overnight, and refluxed for 30 min. The reaction mixture was cooled to room temperature and water was added carefully to destroy the excess $SOCl_2$. The reaction mixture was extracted with ether, washed with saturated sodium bicarbonate solution and water, and dried over anhydrous magnesium sulfate. After ether was removed by evaporation, the reaction product was distilled under reduced pressure. A colorless liquid was obtained at 76 °C (10 mm Hg) with the yield of 90-95%. ^{1}H-NMR($CDCl_3$); δ 1.8(d, 3H, CH_3), 2.3(s, 3H, $ArCH_3$), 5.1(q, tert. 1H), 7.2(m, arom. 4H). IR(neat); 3030(Ar C-H), 2985, 1515(arom. C = C), 1440 cm^{-1}.

2-(2-Bromoethyl)-1,3-dioxolane(7). In a 250 m*l* three-necked round-bottomed flask fitted with a dropping funnel, 40 g(645 mmole) of ethylene glycol was placed. While stirring the ethylene glycol at 0 °C, anhydrous HBr gas was bubbled. After saturation of the gas, 12.2 g(218 mmole) of acrolein was added through the dropping funnel at 5-10 °C. After stirring for 1 hr at room temperature the mixture was extracted with petroleum ether. The organic layer was washed with saturated sodium bicarbonate solution and water, and dried over anhydrous magnesium sulfate. After the solvents were removed by evaporation, the crude product was distilled under reduced pressure. A colorless liquid was obtained at 74-77 °C (10 mmHg) in 55% yield. ^{1}H-NMR($CDCl_3$); δ 2.2(d of t, J = 4.5 and 7Hz, 2H, -CH_2CH_2Br), 3.5(t, 2H, -CH_2Br), 3.9(broad s, 4H, -OCH_2CH_2O-), 5.1(t, tert. 1H). IR(neat); 2960, 2880, 1400 cm^{-1}.

The cyclic acetal(8). In a 100 m*l* three-necked round-bottomed flask fitted with a reflux condenser and a dropping funnel, was placed 50 m*l* of freshly dried THF and 0.48 g(19.7 mmole) of magnesium turnings under nitrogen. To this flask, was added dropwise with stirring a solution of 2.32 g(15 mmole) of 1-(1-chloroethyl)-4-methyl-benzene (**6**) in 10 m*l* of dry THF at room temperature. After the addition, the mixture was refluxed overnight to form a Grignard reagent, which was cooled before use. In a 250 m*l* three-necked round-bottomed flask, was placed a solution of 1.8 g(9.9 mmole) of 2-(2-bromoethyl)-1,3-dioxolane (**7**) in 50 m*l* of THF. To this solution was added dropwise with stirring, by cannulation at room temperature, the Grignard reagent prepared above. The mixture was stirred for 6 hr, and refluxed for 1-2 hr. After cooled, the reaction mixture was quenched with 25 m*l* of water and 2 m*l* of 6N HCl. The solvent (THF) was removed in a rotary evaporator. The mixture was extracted with ether, washed with aqueous sodium bicarbonate and water successively, and dried over anhydrous magnesium sulfate. After the solvent was removed by evaporation, the crude product was chromatographed on a silica gel column, using cyclohexane/dichloromethane (3:1, v/v). A colorless liquid was obtained in 53-70% yield. ^{1}H-NMR($CDCl_3$); δ 1.2(d, 3H, CH_3), 1.7(m, 4H, -CH_2CH_2-), 2.3(s, 3H, $ArCH_3$), 2.8(m, tert. 1H), 3.9(m, 4H, -CH_2CH_2O-), 4.8(m, 1H, -OCHO-), 7.1(s, arom. 4H). IR(neat); 2960, 2880, 1515(arom. C = C), 1145, 1125 cm^{-1}. MS(m/e); 220(M^+).

4-(p-Tolyl)-pentanal(9). In a 50 m*l* one-necked round-bottomed flask, was placed a solution of the 0.48 g(2.3 mmole) of the acetal (**8**) in 10 m*l* THF and 10 m*l* of 0.5 N HCl. The reaction mixture was refluxed for 45 min and cooled to room temperature. The solvent was removed by evaporation and the reaction mixture was extracted with ether. The organic layer was washed with aqueous sodium bicarbonate and water, and dried over anhydrous magnesium sulfate. After the solvent was removed by evaporation, the re-

action product was chromatographed on a silica gel column, using cyclohexane/dichloromethane (1:1, v/v) to give a yellow liquid with the yield of 70-85%. ^{1}H-NMR($CDCl_3$); δ 1.2 (d, 3H, CH_3), 1.8-2.2(m, 4H, $-CH_2CH_2-$), 2.3(s, 3H, $ArCH_3$), 2.8(m, tert. 1H), 7.1(s, arom. 4H), 9.7(t, 1H, CHO). IR(neat); 3030, 2950, 2720(CHO), 1720(C = O), 1515 cm^{-1} (arom. C = C).

Isopropyltriphenylphosphonium bromide(10). In a 50 m*l* two-necked round-bottomed flask, 7.9 g(30 mmole) of triphenylphosphine and 18.5 g(150 mmole) of isopropyl bromide was added. The reaction mixture was refluxed for 2-3 days. The reaction product was recrystalized from EtOH-Et_2O, followed by washing with ether. The salt was dried in an oven for 2 days and stored in an oven. The yield was 41-50%. ^{1}H-NMR($CDCl_3$); 1.4(d, of d, 6H, $2CH_3$), 5.4(m, tert. 1H), 8.0(m, arom. 15H). IR(KBr); 3030, 2950, 2860, 1580 (arom. C = C), 1390 and 1370 cm^{-1} (isopropyl).

ar-Curcumene: 2-methyl-6-(p-tolyl)-2-heptene(11). In a 50 m*l* three-necked round-bottomed flask fitted with a dropping funnel, 1.02 g(2.6 mmole) of the Wittig salt (**10**) and 10 m*l* of anhydrous THF were added. While stirring the mixture under nitrogen, 3.54 m*l*(2.66 mmole) of n-butyllithium(0.75N in hexane) was added at 0 °C. After stirring for 1 hr, a solution of 155.6 mg(0.88 mmole) of 4-(p-tolyl)-pentanal (**9**) in 10 m*l* of anhydrous THF was added through the dropping funnel during 5-10 min and stirred for 2 hr. To this mixture water was added, the solvent(THF) was removed by evaporation and the mixture was extracted with ether. The organic layer was washed with sodium bicarbonate solution and water, and dried over anhydrous magnesium sulfate. After the solvent was removed by evaporation, the resultant semisolid residue was triturated with petroleum ether, and the insoluble solid triphenylphosphine oxide was removed by filtration. After the solvent of the filtrate was removed by evaporation, the crude product was chromatographed on a silica gel column using n-hexane as an eluant, to give a colorless liquid product. The yield was 95-99%. ^{1}H-NMR($CDCl_3$); δ 1.2(d, 3H, CH_3), 1.5-2.0(m, 10H), 2.3(s, 3H, $ArCH_3$), 2.7(m, tert. 1H), 5.2(m, 1H, vinyl), 7.2(s, arom. 4H). IR(neat); 3040-3000, 2940, 1515(arom. C = C), 1450, 1375, 810 cm^{-1}.

Nuciferal: 2-methyl-6-(p-tolyl)-trans-2-heptenal(1). A mixture of 100 mg(0.495 mmole) of ar-curcumene and 100.2 mg(0.99 mmole) of selenium dioxide in 15 m*l* of 95% ethanol was refluxed for 10 hr. The ethanol was removed by evaporation and the reaction mixture was extracted with ether. The organic layer was washed with saturated sodium bicarbonate solution and water, and dried over anhydrous magnesium sulfate. After the solvents were removed by evaporation, the crude product was chromatographed on a silica gel column, using cyclohexane/dichloromethane(1:1, v/v), to give a yellow liquid with the yield of 55-60%. ^{1}H-NMR ($CDCl_3$); δ 1.2(d, 3H, CH_3, J = 7Hz), 1.7(s, 3H, CH_3), 1.5-2.2 (m, 4H), 2.3(s, 3H, $ArCH_3$), 2.8(m, tert. 1H), 6.4(t, 1H, vinyl, J = 7Hz), 7.1(s, arom. 4H), 9.3(s, 1H, CHO). IR(neat); 3030, 2940, 2850, 2820 and 2710(CHO), 1690(C = O), 1645(C = C), 1515(arom. C = C), 1450, 1380, 820 cm^{-1}. MS(m/e); 216 (M^+).

Nuciferol: 2-methyl-6-(p-tolyl)-trans-2-hepten-1-ol (2). In a 50 m*l* two necked round-bottomed flask fitted with a dropping funnel, was placed under nitrogen 20 m*l* of anhydrous ethyl ether and 0.04 g(1.06 mmole) of $LiAlH_4$ to form a suspension. The flask was cooled to −5 °C in an ice-salt mixture. To this suspension, was added dropwise with stirring a solution of 100 mg (0.46 mmole) of nuciferal (**1**) in 10 m*l* ether during 5 min. After the addition, the mixture was stirred for 1 hr at 0 °C. To this reaction mixture, was added carefully a small amount of ethyl acetate to destroy the excess $LiAlH_4$, followed by the addition of 30 m*l* water. The mixture was poured with stirring to about 20 m*l* of 10% HCl, extracted with ether, washed with aqueous sodium bicarbonate and water again successively, and dried over anhydrous magnesium sulfate. After the solvents were removed by evaporation, the crude product was chromatographed on a silica gel column using cyclohexane/dichloromethane(1:1, v/v), to give a yellow liquid product of (±)-nuciferol. The yield was 65-73%. ^{1}H-NMR($CDCl_3$); δ 1.2(d, 3H, CH_3), 1.65(s, 3H, CH_3), 1.8-2.1(m, 4H), 2.3(s, 3H, $ArCH_3$), 2.8(m, tert. 1H), 4.0(s, 2H, CH_2OH), 5.4(t, 1H, vinyl), 7.2(s, arom. 4H). IR (neat); 3310(OH), 3010, 2900, 1510(arom. C = C), 1450 cm^{-1}. MS(m/e); 218(M^+).

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