Facile Synthesis of (±)-Parahigginone Methyl Ether and (±)-Curcuphenol

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Using Grinard coupling as a key step, a facile synthetic approach to (±)-parahigginone methyl ether **1** and (±)-curcuphenol **2** has been achieved by five steps with 42.3% and 58.6% overall yield, respectively.

Keywords: Synthesis; Parahigginone; Curcuphenol.

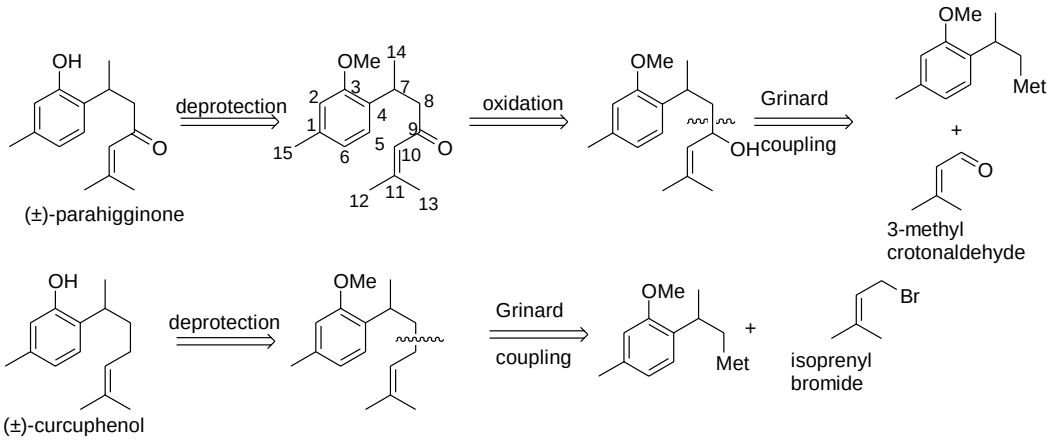
INTRODUCTION

A variety of phenolic sesquiterpenes of the bisabolane family (Scheme I) have been isolated from many different natural resources.[1] They are the olfactorally active components of a large number of essential oils and show a wide range of biological activities. These compounds are attractive synthetic targets especially to verify the usefulness of newly developed synthetic methodology.

(+)-Parahigginone was firstly separated as an aromatic bisabolane sesquiterpene by Imai from the spice turmeric[2] in 1990, and was detected again by Shen and coworkers from the Taiwan marine sponges *Parahigginsia ps* in 1999, and it shows modest antitumor activity.[3] Sharma depicted a route to parahigginone **1** in racemic form.[4] Using the BINOL as the chiral ligand, Tanaka reported a synthetic approach to (+)-parahigginone.[5]

(+)-Curcuphenol bearing the same skeleton was isolated from the marine organisms in both deep and shallow water collection of the sponge *Didiscus flavis*.[6] (+)-Curcuphenol shows antifungal biological activities. (-)-Curcuphenol, a cytotoxic bisabolane sesquiterpene, was firstly discovered in a metabolite of the gorgonian soft coral *Pseudopterogorgia rigida*[7] and possesses antibacterial activity against *Staphylococcus aureus*.[3] Due to their interesting biological activities, a number of synthetic approaches have been reported.[8] Ono described a methodology in synthesis of a series of such sesquiterpenes by enantioselective hydrolysis resolution of (±)-4-aryl-5-hydroxy-(2*E*)-pentenoate by immobilized lipase.[8b,8c,8d] Based on the baker yeast's enantioselective reduction ability on some special structures, Fuganti constructed the key benzyl chiral carbon successfully.[8h,8j] Ho and coworkers exploited an oxidative cleavage of bicyclic benzocycloheptane derivatives pathway to synthesize (±)-curcuphenol methyl ether;[8e] and very recently Sugahara and coworkers synthesized (+)-curcuphenol by using a concurrent retro-Diels-Alder reaction and Claisen rearrangement.[8f] (±)-Curcuphenol methyl ether was also used as a key intermediate to synthesize (±)-α-Cedrene[8k] by Wender owing to its characteristic structure.

Scheme I



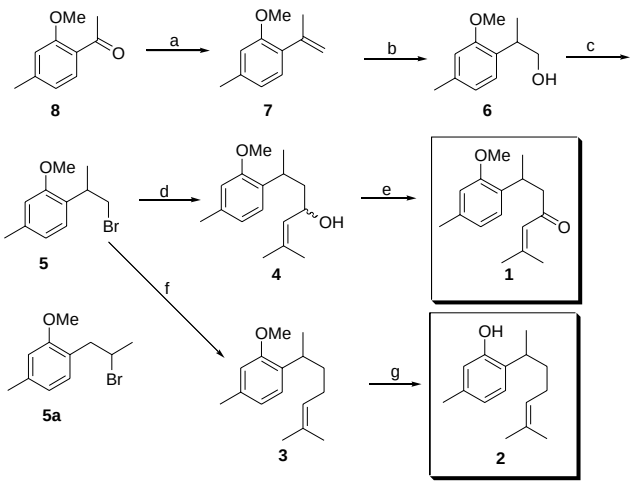
As an extension of our continuous effort to synthesize these kinds of naturally occurring products,[9] herein, we report a facile synthesis of (±)-parahigginone methyl ether **1** and (±)-curcuphenol **2** through five chemical operations using cheap starting materials.

Our retro-synthetic plan is outlined in Scheme I. The hydroxyl group should be protected firstly, and the two molecules can be disconnected between C-9 and C-10. Leading by this strategy, parahigginone can be divided into two parts: 3-methyl crotonaldehyde and a metalized alkyl bromide. Curcuphenol methyl ether can be divided into prenyl bromide and metalized alkyl bromide moiety.

RESULTS AND DISCUSSION

As shown in Scheme II, 2-methoxy-4-methyl acetophenone **8** was used as starting material, which was treated with methyl magnesium iodide to give a tertiary alcohol. This alcohol was dehydrated in the presence of *p*-toluic acid in benzene to give styrene derivative **7**. It should be noted that the dehydration reaction should be performed under an argon atmosphere in low concentration, otherwise the dimer of styrene would be produced whose mass spectrum displayed a double M^+ (324). The mechanism of polymerization was studied in progress.

Scheme II



Reagents and Conditions: (a) i, 1.5 eq MeMgI, -20 °C; ii, *p*-TosOH, Benzene, reflux, 93%; (b) BH_3·THF, 0 °C, then aqueous NaOH, 30% H_2O_2, reflux, 97%; (c) PPh_3, CBr_4, CH_2Cl_2, 95%; (d) Mg powder, 3-methyl-crotonaldehyde, -20 °C, 52%; (e) MnO_2, CCl_4, reflux, 95%; (f) Mg powder, CuI, then prenyl bromide, 76%; (g) EtSNa, DMF, 130 °C, 95%.

Compound **7** after hydroboration oxidization reaction 2-arylpropane-1-ol **6** can be furnished in 97% yield. This alcohol can be easily converted into bromide **5** through carbon tetrabromide and triphenyl phospine in methylene chloride. But when PBr_3 was used as an alternative method, the rearranged product **5a** was found in nearly quantitative amounts. The mechanism of rearrangement has been discussed by Hauser.[10]

With this key intermediate in hand, compound **5** was treated with Mg powder to afford corresponding Grinard reagent. It should be noted that the addition of some methyl iodide is very helpful in preparing the Grinard reagent. 3-Methyl-crotonaldehyde reacted with this Grinard reagent at -20 °C to afford the intermediate **4** which included a pair of diastereomers. Both were oxidized with MnO_2 in carbon tetrachloride to afford parahigginone methyl ether **1** in 95%.

On the other hand, prenyl bromide can be coupled with the Grinard reagent prepared from **5** in the presence of CuI in THF at -20 °C to give curcuphenol methyl ether **3**, which was subjected to demethylation to afford (±)-curcuphenol **2** by EtSNa at 130 °C.

In summary, we have developed a novel route to construct bisabolane skeleton with Grinard coupling as the key step reaction. In our approach, the bisabolane sesquiterpenes which have a C-9 oxidative state can be obtained easily. Spectroscopic data of synthetic **1** and **2** agree with those reported before.[3,8d]

EXPERIMENTAL SECTION

General Methods

The ^{1}H-NMR and ^{13}C-NMR data were recorded in $CDCl_3$ solution with a Bruker AC 200 MHz or Virian BB 300 MHz spectrometer, if not noted otherwise. The chemical shifts are referenced on TMS in *ppm* on the 'δ' scale. Mass spectra were recorded on a HP-5988 mass spectrometer (EI). Standard flash chromatography was employed to purify the crude reaction mixture using 200-300 mesh silica gel under a positive nitrogen pressure.

2-(2-Methoxy-4-methylphenyl)propene (7)

To a suspension of magnesium (1.0 g, 45.6 mmol) in absolute ether (70 mL) was added methyl iodide (2.8 mL, 45.6 mmol) in ether (30 mL) dropwise over a half hour; then the mixture was refluxed for 1 hour. Then the mixture was cooled with an ice-salt bath and then 2-methoxy-4-methyl acetophenone **8** (5 g, 30 mmol) in ether (20 mL) was added

dropwise over 1 hour. The system was quenched with saturated ammonium chloride and extracted with ether (3 × 100 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation *in vacuo* the crude product (tertiary alcohol) was obtained. This compound was not purified further for the next reaction directly. The crude product was dissolved in benzene (150 mL) and a catalytic *p*-toluic acid was added and then equipped with a Dean-Stark trap. This solution was refluxed for 3 hours, and then another 100 mL benzene was added to dilute the system. The mixture was washed with saturated sodium hydrogen carbonate and brine and then dried over Na_2SO_4. After evaporation, the residue was purified through column chromatography to give **7** (4.5 g, 93%) as colorless oil. ^{1}H-NMR: 2.15 (3H, s), 2.39 (3H, s), 3.86 (3H, s), 5.09 (1H, br s), 5.16 (1H, br s), 6.74 (1H, s), 6.77 (1H, d, *J* = 8.0 Hz), 7.13 (1H, d, *J* = 8.0 Hz), MS (EI): 162 (M^+, 42) 147 (86), 119 (100), 91 (37).

2-(2-Methoxy-4-methylphenyl)propane-1-ol (6)

To a solution of styrene derivative **7** (3.0 g, 18.5 mmol) in THF (15 mL) was added in borane THF (1 M, 19 mL) dropwise at 0 °C. After 2 hours, 30% NaOH solution (12 mL) and 30% H_2O_2 (12 mL) was added to the reaction system. The mixture was refluxed for 2 hours and then saturated by the addition of solid sodium chloride. The reaction mixture was extracted with ethyl acetate and ether (v/v: 1:3, 3 × 100 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation, the residue was purified through column chromatography to give **6** (3.2 g, 97%) as colorless oil. ^{1}H-NMR: 1.26 (3H, d, *J* = 7.0 Hz), 1.64 (1H, br s), 2.35 (3H, s), 3.35-3.45 (1H, m), 3.61-3.73 (2H, m), 3.90 (3H, s), 6.71 (1H, s), 6.77 (1H, d, *J* = 7.6 Hz), 7.08 (1H, d, *J* = 7.6 Hz). MS (EI): 180 (M^+, 14), 149 (100), 134 (6), 119 (15).

1-Bromo-2-(2-methoxy-4-methylphenyl)propane (5)

To a solution of 2-(2-methoxy-4-methyl-phenyl)propyl-1-ol **6** (1.8 g, 10 mmol) in anhydrous methylene chloride (15 mL) was added triphenyl phospine (3.14 g, 12 mmol) and carbon tetrabromide (4.1 g, 12 mmol) portionwise at 0 °C. The solution was stirred for 5 hours and methanol (2 mL) was added to quench the reaction. An additional 100 mL of methylene chloride was introduced to above mixture and then washed with sodium hydrogen carbonate and brine. After evaporation, the residue was purified through column chromatography to give **5** (3.24 g, 95%) as colorless oil. ^{1}H-NMR: 1.43 (3H, d, *J* = 7.2 Hz), 2.40 (3H, s), 3.47-3.65 (2H, m), 3.61-3.78 (1H, m), 3.88 (3H, s), 6.76 (1H, s), 6.86 (1H, d, *J* = 7.6 Hz), 7.11 (1H, d, *J* = 7.6 Hz). MS (EI): 242 (M^+, 5), 163 (21), 149 (100), 135 (44).

2-Bromo-1-(2-methoxy-4-methylphenyl)propane (5a)

To a solution of 2-(2-methoxy-4-methyl-phenyl)propyl-1-ol **6** (243 mg, 1 mmol) in anhydrous CH_2Cl_2 (5 mL), PBr_3 (91 mg, 0.33 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise. After 5 minutes, CH_2Cl_2 (20 mL) was added to the solution and the organic layer was washed by saturated $NaHCO_3$ and brine. After evaporation **5a** was given quantitatively as colorless oil. ^{1}H-NMR: 1.70 (3H, d, *J* = 6.6 Hz), 2.37 (3H, s), 3.08 (1H, dd, *J* = 7.2 Hz, *J* = 13.5 Hz), 3.22 (1H, dd, *J* = 7.2 Hz, *J* = 13.5 Hz), 3.83 (3H, s), 4.42-4.49 (1H, m), 6.70 (1H, br s), 6.75 (1H, d, *J* = 7.8 Hz), 7.05 (1H, d, *J* = 7.8 Hz). MS (EI): 242 (M^+, 18), 163 (21), 149 (15), 135 (100), 105 (43).

2-Methyl-6-(2-methoxy-4-methylphenyl)-hept-2-ene-3-ol (4)

To a suspension of magnesium powder (70 mg, 2.9 mmol) in absolute ether, 0.05 mL methyl iodide was added to start the reaction, and then bromide **5** (486 mg, 2 mmol) in ether (10 mL) was introduced slowly. After addition the reaction mixture was stirred for 3 hours at room temperature then was cooled with an ice-salt bath to -20 °C. 3-Methyl-crotonaldehyde (0.3 mL, 3.1 mmol) was added to the corresponding Grinard reagent over 30 minutes. The ice-salt bath was removed and the mixture was refluxed for 3 hours. Saturated ammonium chloride was added through a syringe to quench the reaction. The reaction mixture was extracted with ether (3 × 20 mL) and then washed with brine and dried over Na_2SO_4. After evaporation the residue was purified through column chromatography to give **4** (258 mg, 52%) as colorless oil. ^{1}H-NMR: 1.20 (3H, d, *J* = 7.2 Hz), 1.47 (3H, s), 1.51-1.59 (1H, m), 1.74 (3H, s), 1.75-1.83 (1H, m), 2.34 (3H, s), 3.30-3.35 (1H, m), 3.80 (3H, s), 3.98-4.05 (1H, m), 5.16 (1H, d, *J* = 8 Hz), 6.70 (1H, s), 6.78 (1H, d, *J* = 7.5 Hz), 7.01 (1H, d, *J* = 7.5 Hz). MS (EI): 248 (M^+, 3), 230 (1), 215, (1), 187, (1), 163 (5), 149 (100), 153 (14), 105 (8). HRMS: Required $C_{16}H_{24}O_2$ 248.1776, found 248.2010.

(±)-Parahigginone methyl ether (1)

To a solution of 2-methyl-6-(2-methoxy-4-methylphenyl)-hept-2-ene-3-ol **4** (100 mg, 0.4 mmol) in carbon tetrachloride (5 mL) was added activated manganese oxide (1 g). The reaction mixture was refluxed for 3 hours. Then the manganese oxide was filtered; the filtrated was evaporated and the residue was purified by column chromatography to give parahigginone methyl ether **1** (92 mg, 95%) as colorless

oil. IR (film): 2925, 1625, 1560, 1067. ^{1}H-NMR: 1.20 (3H, d, J = 7.2 Hz), 2.12 (3H, s), 2.32 (3H, s), 2.36 (3H, s), 2.50-2.62 (1H, m), 2.67-2.78 (1H, m), 3.62-3.72 (1H, m), 3.81 (3H, s), 6.08 (1H, s), 6.68 (1H, s), 6.78 (1H, d, J = 7.5 Hz), 7.02 (1H, d, J = 7.5 Hz). ^{13}C-NMR: 20.11, 20.43, 20.65, 27.64, 29.04, 51.48, 55.25, 111.51, 121.07, 124.07, 126.68, 131.66, 136.80, 154.54, 156.68, 200.59. MS (EI): 246 (M^+, 8), 231 (4), 163 (12), 149 (100) and 83 (81). HRMS: required $C_{16}H_{23}O_2$ 147.1693, found 247.1689.

(±)-Curcuphenol methyl ether (3)

To a suspension of CuI (38 mg, 0.2 mmol) in THF (8 mL), the Grinard reagent prepared from **5** (486 mg, 2 mmol) was added, and then prenyl bromide (300 mg, 2 mmol) in THF (2 mL) was added dropwise at -20 °C. After 24 hours the mixture was poured into 5 mL water and extracted with ether (3 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation, the residue was purified through column chromatography to give **3** (353 mg, 76%) as colorless oil. ^{1}H-NMR: 1.19 (3H, d, J = 7.0 Hz), 1.48-1.65 (2H, m), 1.55 (3H, s), 1.69 (3H, s), 1.88-2.07 (2H, m), 2.35 (3H, s), 3.15 (1H, sex, J = 7.0 Hz), 3.82 (3H, s), 5.13 (1H, br s, J = 7.0 Hz), 6.69 (1H, s), 6.75 (1H, d, J = 7.8 Hz), 7.06 (1H, d, J = 7.8 Hz). ^{13}C-NMR: 17.6, 21.1, 21.4, 25.7, 26.3, 31.4, 37.2, 55.3, 111.5, 121.1, 124.9, 126.6, 132.9, 136.2, 156.9. MS (EI): 232 (M^+, 20), 217 (3), 189 (6), 175 (5), 162 (13), 149 (100). HRMS: required $C_{16}H_{25}O$ 233.1906, found 233.1990.

(±)-Curcuphenol (2)

To DMF (3 mL) was added ethanethiol (147 mg, 2.36 mmol) and NaH in 60% mineral oil (94 mg, 2.36 mmol), after hydrogen evolved ceased (about 30 minutes) then compound **3** (110 mg, 0.47 mmol) in DMF (1 mL) was added. The mixture was warmed to 130 °C and stirred for 4 hours. The reaction was quenched by saturated ammonium chloride and extracted with ether (3 × 20 mL); the combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation the residue was purified through column chromatography to give **1** (98 mg, 95%) as colorless oil. IR: 3537, 2965, 2935, 2866, 1664, 1617, 1421, 808. ^{1}H-NMR: 1.22 (3H, d, J = 7.0 Hz), 1.54 (3H, s), 1.55-1.69 (2H, m), 1.68 (3H, s), 1.89-1.97 (2H, m), 2.27 (3H, s), 2.96 (1H, sextet, J = 7.0 Hz), 4.67 (1H, s, OH), 5.13 (1H, br t, J = 7.0 Hz), 6.59 (1H, brs), 6.72 (1H, d, J = 8.0 Hz), 7.03 (1H, d, J = 8.0 Hz). ^{13}C-NMR: 17.7, 20.8, 21.1, 25.7, 26.1, 31.4, 37.3, 116.2, 121.7, 124.6, 126.8, 130.0, 132.0, 136.5, 152.8. MS (EI): 218 (M^+, 4), 203 (3), 161 (8), 148 (33), 135 (100). HRMS: required $C_{15}H_{23}O$, 219.1751, found 219.1743.

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