



A Short Synthesis of Sesquiterpene Ar- Himachalene from *Cedrus deodara* by Heck reaction

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Abstract: A short synthesis of ar- himachalene was carried out by palladium catalyzed Heck reaction. Heck reaction of p-iodotoluene with ethyl sorbate would yield the conjugated ester. Further hydrogenation of conjugated ester by NaOH and Raney-nickel alloy gives the saturated ester in two steps and in high overall yield. Grignard reaction of saturated ester with methyl magnesium iodide followed by Polyphosphoric acid cyclodehydration of the resultant tertiary alcohol would furnish a sesquiterpene, ar-himachalene.

Keywords: Heck reaction • p-iodotoluene • PPA • Sesquiterpene • ar- himachalene

Introduction

A large number of naturally occurring sesquiterpenes possesses a wide range of applications in drugs, pharmaceuticals, rubber, paints, perfumery, agriculture and many others (Chavan et.al., 2012). Himachalene is a structurally and biologically important class of naturally occurring sesquiterpene hydrocarbons the synthetically challenging benzo(7)annulene ring system (Silva, 2008; Srikrishna et.al, 2004). Himachalene is found as essential oil extracted from several cedar woods, which include *Cedrus deodara* Loud, *Cedrus atlantica* and *Cedrus libani* found in Himalayan and Moroccan forests (Rao et.al., 1952). The different components and essential oil of *Cedrus deodara* shows insecticidal and larvicidal activity and therefore used in pest management (Chaudhary et. al., 2011). Himachalene was also isolated as pheromonal component of *flea beetles*; *Aphthona flava* and *Phyllotreta cruciferae*, which

are typically produced by only one sex but attract both sexes (Bartlet et. al., 2001).

The structure of ar-himachalene has proved on the basis of spectral evidences and its laboratory synthesis has carried out by two different long routes first time based on spectral evidences (Joseph et.al., 1968; Pandey et. al., 1968). The third synthetic approach of ar- himachalene was reported by the use of tricyclic sesquiterpene viz. longifolene, a complex starting compound (Mehta et. al., 1974). Recently, an enantioselective synthesis of ar-himachalene was reported by chirality induction approach (Mori, 2005). The synthesized aryl and acyl derivatives of its shows antimicrobial activity (Chaudhary et. al., 2014).

In recent years, the palladium catalyzed coupling of haloarenes and haloalkenes with olefins to form new carbon-carbon bonds, Heck reaction have gained our interest in the synthesis of natural products (Hossini et. al., 2011). Heck reaction has opened the door to a



tremendous variety of elegant and highly convergent routes to structurally complex chemoselective and regioselective molecules (Heck, 1968, 1982). The synthesis of dihydro-ar-turmerone, ar-todomatuic acid and 7-methoxy-1,1-dimethyltetralin, an intermediate for the synthesis of occidol isomer- I has earlier been reported from our laboratory by applying Heck reaction (Solbannavar et. al., 2003). In continuation with these studies, we wish to report herein first time the synthesis of ar-himachalene by shortest route using Heck reaction approach.

Materials and Methods

p-Toluidine (S. D. Fine Chemicals), sorbic acid (BDH), palladium acetate (Lancaster) and potassium carbonate (S. D. Fine Chemicals) were used as received. Melting Points recorded are uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR-783 spectrophotometer. NMR spectra were recorded on Bruker AC-200 or MSL-300 (200 MHz or 300 MHz for ¹H NMR and 50 MHz or 75 MHz for ¹³C NMR) spectrometer in CDCl₃ using TMS as an internal standard and δ values are expressed in ppm. Column chromatography was performed on silica gel (60-120 mesh, Qualigens).

Procedures for Synthesis

***p*-Iodotoluene (1):** The diazotization of *p*-toluidine followed by Sandmeyer reaction with KI furnished pure *p*-iodotoluene (62 %) pale brown, mp 34-36 °C by steam distillation (Furniss et. al., 1989).

Ethyl Sorbate (2): Ethyl sorbate was prepared from sorbic acid using ethanol and conc. sulfuric acid by standard known procedure pale yellow oil, bp 195-196 °C (16).

Ethyl 5-(4'-methylphenyl)sorbate (3): A mixture of *p*-iodotoluene 0.9 g (4 mmol), K₂CO₃ 0.55 g (4 mmol) ethyl sorbate 0.6 mL (4.5 mmol), palladium acetate 0.009 g (0.04 mmol), triphenylphosphine 0.021 g (0.04 mmol) and DMF (5 mL) was heated with stirring at 100 °C on an oil bath till completion of reaction (TLC, 20 hr.). The progress of reaction was monitored by TLC. The reaction mixture was then cooled, acidified with ice-cold dilute HCl (10

mL) and extracted with ether. (3 x10 mL) The ether extract was washed with water and dried over anhydrous sodium sulfate. Removal of ether gave crude ester, which was purified by column chromatography to yield pure ethyl 5-(4'-methylphenyl) sorbate, 0.650 g (68 %).

IR spectrum, ν , cm⁻¹: 1721 s (COOR), 1655- 1514 (C=C).

¹H NMR, δ , ppm: 1.3 m (3H, -CH₂-CH₃), 2.3 s (3H, Ar-CH₃), 4.2 m (2H, -CH₂-CH₃), 5.1 and 6.0 two d (1H, J 16 Hz, CH-COOEt), 6.3 and 6.6 two d (1H, J 8 Hz, CH-CH-CH-COOEt), 7.2 m (4H, Ar-Hs), 7.38 dd (1H, J 16 Hz and 8 Hz, CH-CH-COOEt).

5-(4'-Methylphenyl)hexanoic acid (4): Ethyl 5-(4'-methylphenyl)sorbate 0.4 g (2 mmol) was dissolved in 10 % aqueous NaOH solution (15 mL) and Raney- nickel alloy 4.00 g was added in portions with stirring at 95 °C during 4 hr. The reaction mixture was stirred at 95 °C for additional 2 hr. The catalyst was filtered off, washed with boiling water and the alkaline filtrate was acidified with excess of HCl (1:1) and then extracted with ether. From the ether extract, saturated acid, 5-(4'-methylphenyl)hexanoic acid was quenched using aqueous sodium bicarbonate. Acidification of the bicarbonate layer followed by reextraction of the resultant acid in ether furnished almost pure acid 5-(4'-methylphenyl)hexanoic acid, 0.310 g (77.50 %).

Methyl 5-(4'-methylphenyl)hexanoate (5): 5-(4'-Methylphenyl)hexanoic acid, 0.31 g (1.4 mmol) was dissolved in methanol (5 mL) and was added conc. H₂SO₄ (2-3 drops). The solution was refluxed for 8 hours on water bath. The routine work-up of the reaction mixture furnished methyl 5-(4'-methylphenyl)hexanoate, 0.280 g (85 %). This ester was purified by column chromatography over silica gel to yield pure ester, 0.220 g (66%).

IR spectrum, ν , cm⁻¹: 1732 s (COOR), 1601 s (C=C).

¹H NMR, δ , ppm: 1.4 d (3H, -CH-CH₃), 2.3 s (3H, Ar-CH₃), 2.7 m (1H, (CH₃)₂-CH), 3.5 m (2H, -OCH₂-CH₃), 3.6 s (3H, Ar-OCH₃), 3.9 m (4H, α -CH₂ and γ -CH₂), 7.1 s (4H, Ar-Hs).



6-(4'-Methylphenyl)-2-methylheptan-2-ol (6): To a magnetically stirred solution of Grignard reagent (prepared from 0.050 g of magnesium and 0.4 mL of methyl iodide in (10 mL) of dry ether) was added the solution of methyl 5-(4'-methylphenyl)hexanoate, 0.220 g (1 mmol) in dry ether (10 mL) during 1 hour. The reaction mixture was stirred at room temperature for 1 hour and then refluxed on water bath for an additional hour. After cooling, the reaction mixture was decomposed by pouring it into saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ether. The combined ether extract was repeatedly washed with water, dried over anhydrous sodium sulfate and ether was removed to give the alcohol, 6-(4'-methylphenyl)-2-methylheptan-2-ol, 0.190 g (73 %).

Ar-Himachalene (7): To a well stirred solution of polyphosphoric acid (prepared from phosphorus pentoxide 2.5 g and *ortho* phosphoric acid 2.0 g was added the above tertiary alcohol, 0.19 g and stirring was continued for additional 1 hour. It was then decomposed by addition of ice-cold water and extracted with ether. The ether extract was washed with water, dried and ether removed to give ar-himachalene. 0.14 g (64 %) It was purified by column chromatography over silica gel. Elution with pet. ether furnished pure ar-himachalene.

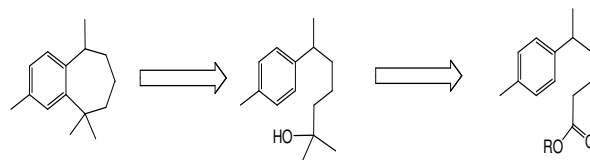
IR spectrum, ν, cm^{-1} : 2927 (C-H), 1600 (C=C).

$^1\text{H NMR}$, δ , ppm: 0.9 d (1H, -CH-CH₃), 1.1-1.4 m (12H, (CH₃)₂-CH and (CH₂)₃), 2.3 s (3H, Ar-CH₃), 2.6 m (1H, (CH₃-CH-CH₂)), 6.8-7.2 m (3H, Ar-Hs).
 $^{13}\text{C NMR}$, δ , ppm: 14.2, 21.1, 21.4, 22.8, 29.77, 32.0, 122.7, 123.0, 126.8, 128.9, 129.1.

Results and Discussion

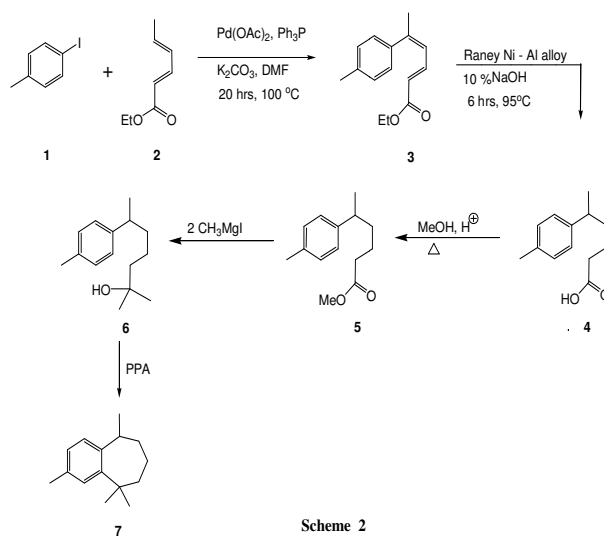
The retrosynthetic approach of ar-himachalene suggest that the preparation of carboxylic acid or ester as the key step of the synthesis because the ester on Grignard reaction with methyl magnesium iodide followed by cyclodehydration using PPA would give ar-himachalene (Scheme-1). This observation prompted us to check a new

short route towards the synthesis of same acid or ester using our experience with Heck reaction.



Scheme 1

We envisaged that palladium catalyzed Heck reaction of *p*-iodotoluene 1 with ethyl sorbate 2 was carried out in DMF in presence of triphenylphosphine as ligand and potassium carbonate as a base yielded ethyl 5-(4'-methylphenyl)sorbate 3 in moderate yield. This conjugate ester was reduced with Raney-nickel alloy in NaOH under reflux condition, which upon acidification and work-up furnished 5-(4'-methylphenyl) hexanoic acid 4. The resultant acid 4 was converted into corresponding ester, methyl 5-(4'-methylphenyl) hexanoate 5 by known procedure. The saturated ester was subjected to Grignard reaction with methyl magnesium iodide, which gave the corresponding tertiary alcohol 6-(4'-Methylphenyl)-2-methylheptan-2-ol 6 in good yield. The crude tertiary alcohol on removal of ether was directly subjected to cyclodehydration with PPA to yield ar-himachalene 7 (Scheme 2).



Scheme 2



The conjugated ester 3 showed IR bands at 1721 and 816 cm^{-1} indicated the formation of conjugated ester and *p*-disubstituted aromatic ring, respectively. ^1H NMR spectrum of the product indicated that compound is a mixture of two isomers. It showed two singlets at δ 2.2 and 2.3 for vinylic methyl group protons of two isomers. It also showed two doublets (each, with *J* 16 Hz) at δ 5.8 and 6.0 for one type of a proton, two doublets (each, with *J* 8 Hz) at δ 6.3 and 6.6 for two other types proton, out of that one proton exhibited doublet of doublet (each, with *J* 16 Hz and 8 Hz) at δ 7.7.

The conjugate ester was subjected to reduction with Raney-nickel under reflux condition, which upon work-up furnished 5-(4'-methylphenyl) hexanoic acid 4 and the resultant acid was converted into corresponding saturated methyl ester 5-(4'-methylphenyl) hexanoate 5 by known procedure. The saturated ester 5 showed shifting of IR frequency from 1721 to 1732 cm^{-1} indicated the formation of saturated ester. ^1H NMR spectrum showed a doublet at δ 1.4 for benzylic methyl group protons and three singlets at δ 2.3 and 3.7 and 7.1 for aromatic methyl group protons, ester methyl group protons and aromatic protons, respectively. The benzylic methine proton appeared as multiplet centered at δ 2.7 while methylene group protons β to ester group appeared at δ 3.5 as multiplet. The methylene group protons α to ester and γ to ester function appeared as a multiplet centered at δ 3.9. The absence of signals due to olefinic protons and the appearance of multiplet due to benzylic methyl (δ 1.4) and benzylic methine proton (δ 2.7) clearly indicated the formation of desired saturated ester 5. The ester 5 was subjected to Grignard reaction with methyl magnesium iodide, which gave the corresponding tertiary alcohol 6-(4'-Methylphenyl)-2-methylheptan-2-ol 6. The tertiary alcohol was directly subjected to cyclodehydration with PPA to yield ar-himachalene 7. IR spectrum of ar-himachalene showed the bands at 1383 cm^{-1} for *gem*-dimethyl group while the bands due to hydroxyl group or ester group were absent. ^1H NMR spectrum showed a doublet at δ 0.9 for benzylic methyl group protons and multiplet

between δ 1.13-1.4 for six protons of *gem*-dimethyl group and six protons of methylene groups. It also exhibited a singlet at δ 2.3 for aromatic methyl group protons, a multiplet at δ 2.6 for benzylic methine proton and multiplet at δ 6.8-7.2 for three aromatic protons. The band due to *gem*-dimethyl group in IR spectrum and benzylic methine proton in ^1H NMR spectrum substantiated the formation of desired product *viz.* ar-himachalene. ^{13}C NMR spectrum of the same compound showed the signals at δ 14.2, 21.1, 21.4, 22.8, 29.8, 32.0, 122.7, 123.0, 126.8, 126.9 and 129.1. The signal at 29.8 was due to the carbons of *gem*-dimethyl group and benzylic methyl group carbons at 22.8 was due to aromatic methyl group carbon and that at 32.0 was due to a tertiary carbon and a quaternary carbon while the signals between 14.2-29.8 ppm were due to carbons of methylene groups. This data also supported the structure of ar-himachalene. In the DEPT scan of the same spectrum the signals at 14.2, 21.1 and 21.4 were found inverted while that at 32.0 was found to be absent confirming the presence of three methylene groups as well as above assignment.

Conclusion

In conclusion, we have synthesized ar-himachalene only by four-step reaction sequence using Heck reaction first time.

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