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Total Synthesis of (±) Mutisianthol and (±) *epi*-Mutisianthol via Intramolecular Oxidative Heck Cyclization Approach

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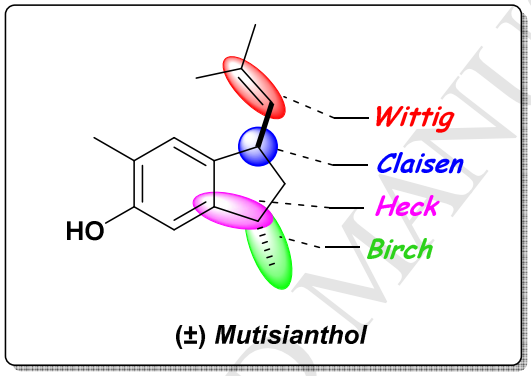
(Dedicated to the late Prof. M. G. Kulkarni, Department of Chemistry, SPPU, Pune for his pioneering work in the field of Wittig olefination–Claisen rearrangement protocol.)

Graphical abstract



Abstract

A simple and straight forward synthesis of (±) mutisianthol and its epimer is described. Implementation of 4-pentenal derivative for palladium catalyzed intramolecular 5-*endo-trig* Heck cyclization is effective. Other key steps involved are Wittig olefination with allyloxymethylenetriphenylphosphorane, [3,3] sigmatropic rearrangement and chemoselective reduction of double bond.

Keywords

Wittig olefination, Claisen rearrangement, Oxidative coupling, Heck reaction, Stereoselective hydrogenation, chemoselective reduction.

1. Introduction

Palladium catalyzed oxidative Heck reaction is an effective tool for carbon-carbon bond forming reactions since its discovery[1] and its intramolecular version was found to be more useful

in the synthesis of natural products and pharmaceutically important bioactive compounds including different types of carbacycles, *O*-heterocycles and *N*-heterocycles.[2] Indane or indanone carbacycles are the important motifs because of their presence in many natural products (Figure 1) and due to their great medicinal significance such as antitumour,[3] antiviral,[4] and anti-inflammatory[5] properties. Various methods are available for the construction of indane framework.[6] In the recent years many research groups have implemented intramolecular oxidative Heck coupling reaction strategy for synthesis of various indane scaffolds.[7] Although the synthesis of substituted indanes remains challenging task.

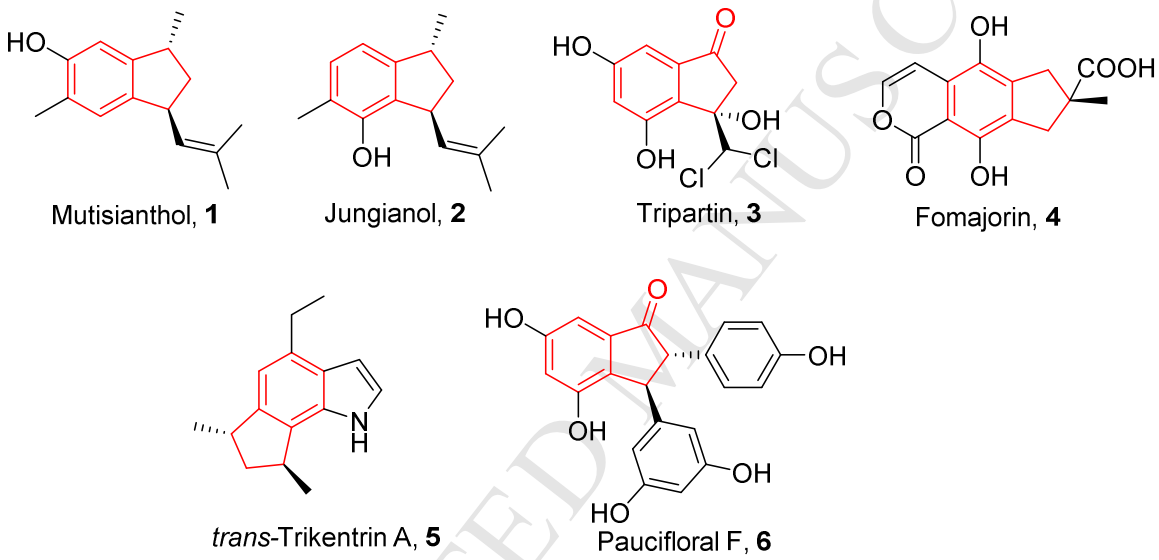
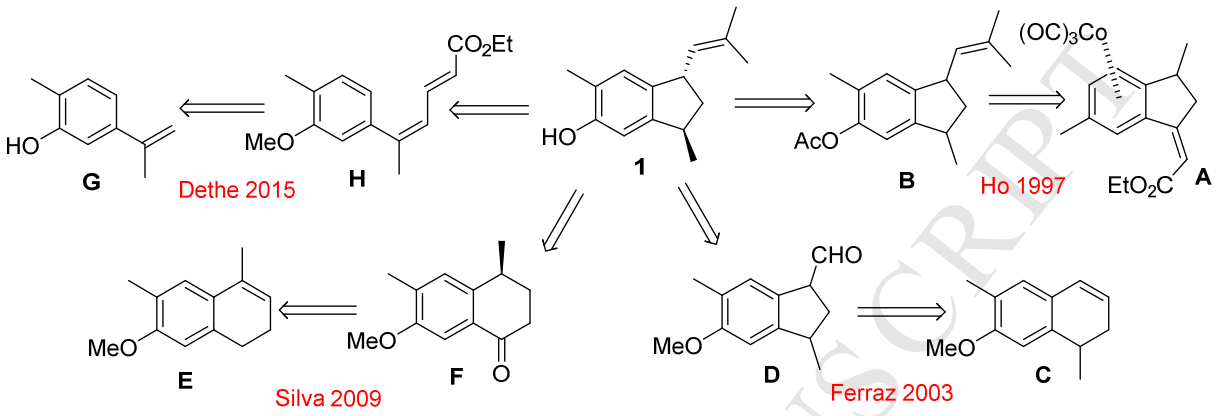


Figure 1: Some natural indane representatives.

The phenolic sesquiterpene mutisianthol (**1**) having *trans* 1,3 disubstituted benzocyclopentyl (indane) unit was first isolated in 1979 from the roots of *Mutisia homoeantha* by Bohlmann's group.[8] The initial stereochemistry was assigned as *cis* for two substituents on five membered ring of mutisianthol (**1**). In the early of 1997, Ho and co-workers accomplished the first total synthesis of mutisianthol (**1**) and revised its structure by assigning the relative stereochemistry to *trans* for two substituents on five membered ring of mutisianthol.[9]

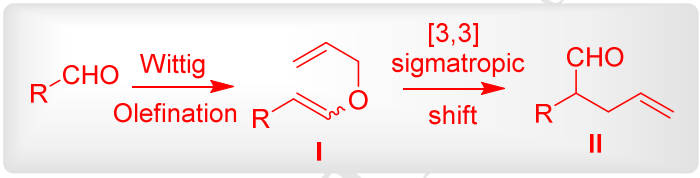
Later, very few research groups have worked on synthetic study of mutisianthol (figure 1). Ferraz *et al* achieved the total synthesis of mutisianthol exploiting thallium mediated ring contraction strategy for 1,2-dihydronaphthalene derivative.[10] Same group later also accomplished its enantioselective synthesis through asymmetric hydrogenation and thallium mediated ring contraction of thus generated tetralin motif.[11] Very recently, Dethe *et al* reported the total

synthesis of mutisianthol employing the Lewis acid catalyzed Nazarov type cyclization.[12] However, use of intramolecular Heck cyclization remains untouched in the synthesis of this natural indane which initiate us to embark on its total synthesis.



Scheme 1: Summery of the reported strategies for mutisianthol.

Since two decades, our group has been involved in the Wittig olefination on a range of aldehydes followed by Claisen rearrangement of resulted allyl vinyl ether (**I**) strategy and their exploration to the target-oriented synthesis with maximum use of resultant functionalized 4-pentenal derivatives **II** (Scheme 2).[13]



Scheme 2: Outline for generation of 4-pentenal derivative.

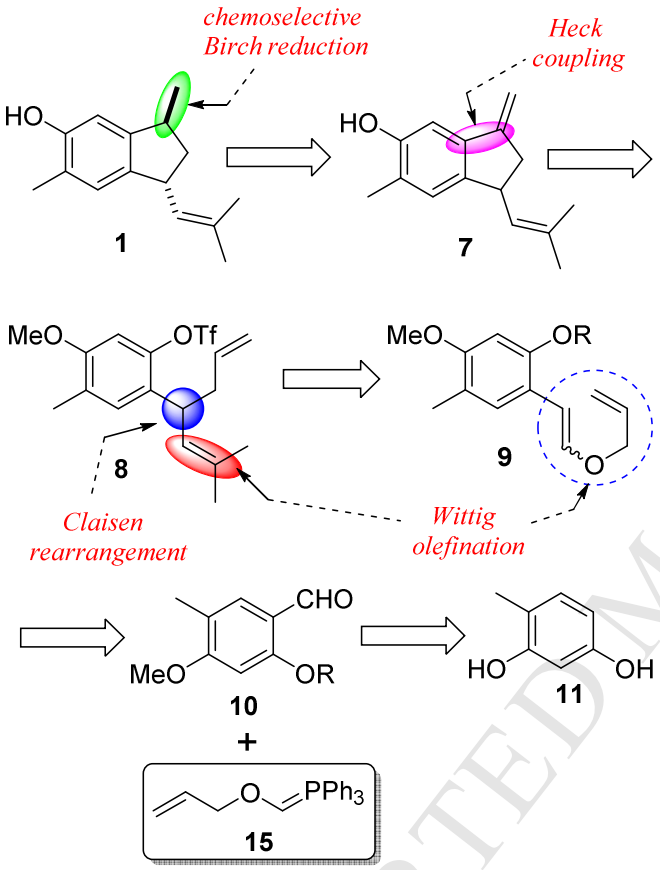
In continuation of our these efforts, herein, we report a simple and efficient synthetic method for indane natural product mutisianthol (**1**), by the use of thus generated 4-pentenal derivative for oxidative 5-*endo-trig* Heck cyclization resulting into indene framework.

2. Result and discussion

2.1 Retrosynthetic analysis

Synthetic plan towards mutisianthol (**1**) is outlined in Scheme 3. Intramolecular Heck cyclization reaction of triflate **8** and subsequent regio and stereoselective olefine hydrogenation of **7** could be the key steps for the final construction of the target molecule **1**. We envisaged that substitution pattern in triflate **8** would be obtained from allyl vinyl ether **9** through sequence of

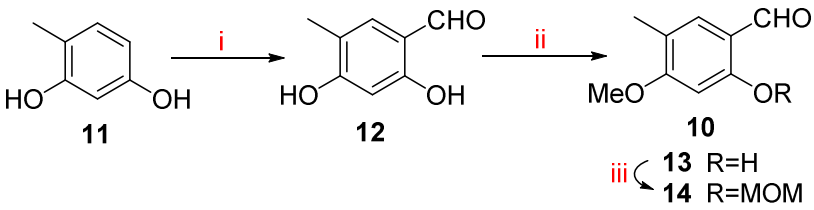
reactions such as Claisen rearrangement and olefination. The allyl vinyl ether **9** in turn could be prepared from appropriately substituted benzaldehyde **10** by using Wittig reaction with allyloxymethylenetriphenylphosphorane **15**. The required substitution in aldehyde **10** could be easily prepared from known 2,4-dihydroxy toluene **11**.



Scheme 3: Retrosynthetic plan for mutisianthol.

2.2 Synthesis of precursor aldehyde 14 with appropriate substitution.

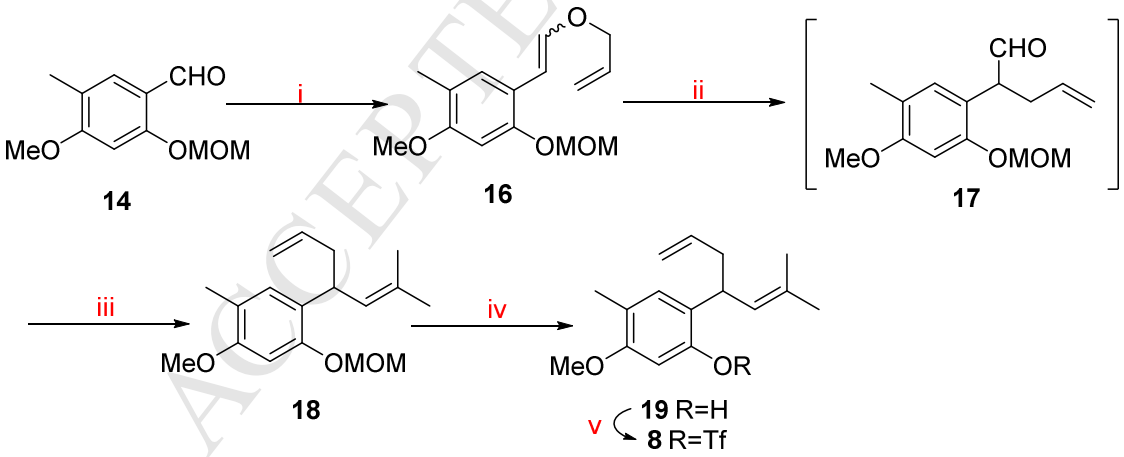
Synthesis of required aldehyde **14** commenced from 2,4-dihydroxytoluene **11. U**nder standard Vilsmeier-Haack condition ($POCl_3$/DMF), compound **11** provided coressponding aldehyde **12** with poor reaction yield.[14] However, more than 90% yield of **12** obtained when this reaction was carried out in acetonitrile instead of DMF itself. The regioselective protection of hydrogen bonding free hydroxyl group of **12** as methyl ether **13** was achieved by dimethyl sulphate and K_2CO_3. Subsequent, protection of remaining hydroxyl group as methoxy methyl ether provided coressponding fully protected benzaldehyde **14** in 94% yield.



Scheme 4: *Reagents and conditions*: (i) $POCl_3$, DMF, MeCN, 0 ºC to rt, 5 h, 93%; (ii) Dimethylsulphate, K_2CO_3, MeCN, rt, 12 h, 95%; (iii) MOMCl, NaH, THF, 0 ºC, 30 min, 94%.

2.3 Wittig olefination followed [3,3]-sigmatropic rearrangement strategy for the synthesis of triflate 8.

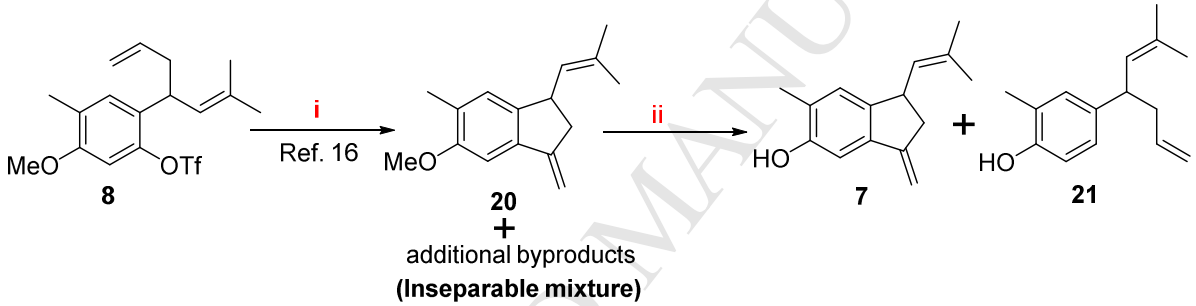
The Wittig reaction of **14** with allyloxymethylenetriphenylphosphorane (**15**)[15] was performed using standard reaction condition previously developed in our lab,[13b, 13c] to provide allyl vinyl ether **16** with *E/Z* ratio 1:1.5 in 72% yield (Scheme 5). The solvent free [3,3]-sigmatropic rearrangement was then effected by heating **16** neat at 180 ºC for 5 min, to produce the 4-pentenal derivative **17**, which was directly used for next step without purification by treating it with isopropyltriphenylphosphorane at -10 ºC gave dialkene derivative **18** in excellent yield. Deprotection of MOM ether in **18** by catalytic HCl in MeOH and subsequent treatment of thus generated phenol **19** with trifluoromethanesulphonic anhydride, triethylamine and catalytic DMAP afforded triflate **8** in 82% yield.



Scheme 5: *Reagents and conditions*: (i) $Ph_3PCH_2OCH_2CH{=}CH_2Cl$, ^tBuOK, THF, 0 ºC, 20 min, 72% ; (ii) Neat, 180 ºC, 5 min, 100%; (iii) *i*$PrPPh_3Br$, *n*-BuLi, THF, -10 ºC, 1 h, 80%; (iv) 2 drops conc. HCl, MeOH , 1 h, 87%; (v) Tf_2O, TEA, DMAP, DCM, 0 ºC, 5 min, 82%.

2.4 The key intramolecular oxidative Heck cyclization reaction and synthesis of indene derivative 7.

After having triflate **8** in hand, we next performed the key palladium catalyzed intramolecular oxidative Heck cyclization reaction. To our disappointment, treatment of triflate **8** under various known Heck coupling conditions generated inseparable reaction products mixture containing **20** as one of the product, though appeared as homogeneous on TLC.[16] After lot of frustrating and unanticipated efforts to separate these different products, we decided to use this mixture as such for the next step. Accordingly, this mixture was treated with excess ethyl mercaptan and sodium hydride in dry DMF at 130-140 ºC for 20-24 h followed by careful column chromatographic purification, mainly afforded desired indene 5-ol derivative **7** and deoxygenated compound **21** in 56% and 14% yields respectively (Scheme 6).

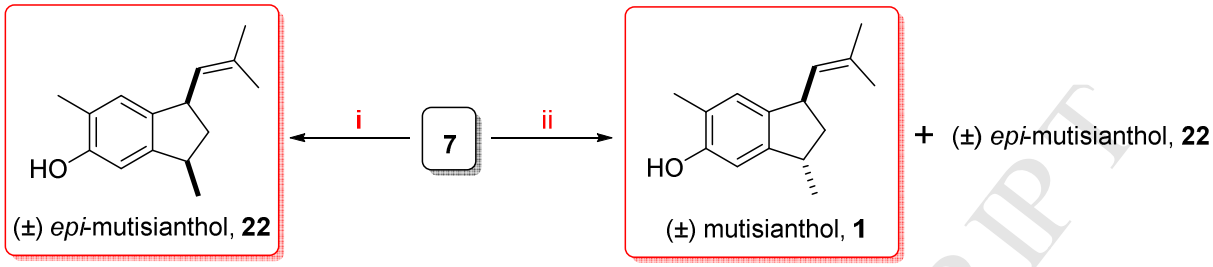


Scheme 6: *Reagents and conditions*: (i) $Pd(PPh_3)_4$, TEA, LiCl, DMF, 110 ºC, 20 h; (ii) EtSH, NaH, DMF, 130-140 ºC, 24 h, 56% (**7**) and 14% (**21**) over two steps.

2.5 Completion of total synthesis of (±) mutisianthol and (±) *epi*-mutisianthol.

The regioselective hydrogenation of benzylic exocyclic double bond of **7** by H_2, Pd/C under controlled condition (pressure and time) exclusively generated the *cis* isomer **22** in good yield (Scheme 7). The same result was observed by Dethe *et al* during the synthesis of jungianol (**2**).[17] The confirmation for *cis* stereochemistry was given by comparing the spectral data of **22** with those of reported for *epi*-mutisianthol.[12] Finally, the required stereochemistry for mutisianthol was obtained by giving temporary protection to the hydroxyl group of **7** as MOM ether followed by chemoselective reduction with Li/liq. NH_3 that resulted in 1:1 mixture of **1** and **22** after deprotection of MOM ether. The formation of *cis* and *trans* isomers in equal proportion during Li/liq. NH_3 reduction may possibly be attributed to protonation of the generated tertiary

planar radical species from both sides. The spectral data of **1** (NMR, IR, HRMS) were well accordance with the reported data for natural mutisianthol.



Scheme 7: *Reagents and conditions*: (i) H_2 (balloon), 10% Pd/C, MeOH, rt, 1 h, 84%; (ii) (a) MOMCl, DIPEA, DCM, 0 ºC to rt, 12 h, 86%; (b) Li, liq. NH_3, THF -78 ºC, 12 h, then 6 N HCl, 40% (**1**) and 40% (**22**).

3. Conclusion

In conclusion, we have developed the strategy for the construction of substituted indane framework in which intramolecular oxidative Heck cyclization was the key step. Strategy was successfully applied for the total synthesis of mutisianthol and its epimer. Synthesis was accomplished in 11 linear steps with an overall yield of 6.57% for mutisianthol and in 10 steps with overall yield of 16.05% for *epi*-mutisianthol. By the use of same strategy we are now working on the syntheses of other indanes.

4. Experimental

4.1 General

All moisture sensitive reactions were carried out under nitrogen atmosphere using oven dried glassware unless otherwise noted. Dichloromethane, dimethylformamide and acetonitrile were distilled over CaH_2. THF was distilled over Na/benzophenone. Commercial reagents and solvents were used as received without further purification. All the reactions were monitored by thin layer chromatography (TLC)-Merck 0.25 mm silica gel 60 F_{254}. TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and/or exposure to an aqueous solution of potassium permanganate ($KMnO_4$), an acidic solution of anisaldehyde or a solution of ninhydrin in ethanol followed by heating on hot plate. Flash Chromatography was performed using silica gel (100-200 mesh) with EtOAc/pet ether solvent system distilled prior to use. Melting points were recorded with Thomas Hoover melting point apparatus and are uncorrected. ^{1}H NMR

spectra were recorded at 200, 300, 500 MHz and ^{13}C NMR spectra 50, 75, 126 MHz in $CDCl_3$ solution unless otherwise mentioned, chemical shifts are in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). High resolution mass spectra (HRMS) were recorded on Bruker impact HD ESI source. IR spectra were recorded on a Shimadzu FTIR-8400 series instrument. All the spectral analysis (IR, NMR, HRMS) were performed at CIF (Central Instrumentation Facility), Savitribai Phule Pune University, Pune.

4.2 Experimental procedures

*4.2.1. 2,4-dihydroxy-5-methylbenzaldehyde (**12**)*

To the stirred solution of 2,4-dihydroxytoulene **11** (5 g, 40.28 mmol) and DMF (6.3 ml, 80.56 mmol) in acetonitrile (70 mL) was added phosphorous oxychloride (4.6 mL, 48 mmol) dropwise over a period of 15 min at 0 ºC. The resulting yellow coloured solution was further stirred for 3 h at rt. The yellow solid obtained was then filtered, washed with cold acetonitrile 2-3 times, dissolved in hot water and heated at 50 ºC for 30 min. The red coloured liquid was then kept for overnight at room temperature and the precipitate obtained was then filtered, dried to give a brown coloured solid (5.69 g, 37.40 mmol, 92.87%). *Rf* (20% EtOAc in pet ether) 0.6 M.p. 143-147 ºC. IRυ_{max} (KBr) 3510, 3410, 2955, 2874, 1492, 1410, 1080, 995 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 11.2 (s, 1 H), 9.51 (s, 1 H), 7.20 (s, 1 H), 6.25 (s, 1 H), 5.81 (s, 1 H), 2.16 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.2, 163.8, 161.9, 134.6, 117.4, 113.6, 101.4, 14.7. HRMS (ESI) *m/z* calcd for $C_8H_8O_3Na$ [M^++Na]: 175.0371; found: 175.0383.

*4.2.2. 2-hydroxy-4-methoxy-5-methylbenzaldehyde (**13**)*

Dimethyl sulphate (3.12 mL, 32.86 mmol) was added to the stirred suspension of 2,4-dihydroxy-6-methylbenzaldehyde **12** (5 g, 32.8 mmol) and K_2CO_3 (4.5 g, 32.86 mmol) in acetonitrile (100 mL). The reaction mixture was then stirred for 12 h at room temperature. After completion of reaction, the reaction was quenched with 2 N HCl (100 mL) and extracted with ethyl acetate (3x50 mL). Combined organic solution was dried over magnesium sulphate, filtered and solvent was removed under reduced pressure. The residue was purified by column chromatography (5% EtOAc in pet ether) to yield **13** as a colorless solid (5.18 g, 31.17 mmol, 94.86%). M. P. 71-74 ºC. *Rf* (8% EtOAc in pet ether) 0.5. IRυ_{max} (KBr) 3400, 3010, 2880, 1510, 1490, 1070, 990 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 11.46 (s, 1H), 9.70 (s, 1H), 7.24 (s, 1H), 6.41 (s, 1H), 3.89 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.3, 164.9, 163.2, 134.3,

119.2, 114.1, 98.4, 55.8, 15.3. HRMS (ESI) *m/z* calcd for $C_9H_{10}O_3Na$ [M^++Na]: 189.0528; found: 189.0521.

*4.2.3. 4-methoxy-2-(methoxymethoxy)-5-methylbenzaldehyde (**14**)*

NaH (1.47 g, 61.38 mmol, 60% in mineral oil) was suspended in dry THF (25 mL) at 0 ºC. To this mixture was slowly added Phenol **13** (5.1 g, 30.69 mmol) in dry THF (20 mL) at 0 ºC and reaction mixture was stirred for 10 min. Then it was treated with chloromethyl methoxy ether (3.2 mL, 39.90 mmol) at 0 ºC and stirred for another 30 min at the same temperature. After completion of reaction as monitored by TLC, saturated NH_4Cl solution was added to quench the reaction and extracted with ethyl acetate (3x50 mL). The combined organic extract was dried over magnesium sulphate, filtered and concentrated under vacuum. The solid obtained was recrystallized from methanol to yield **14** as yellow solid (6.06 g, 28.83 mmol, 93.92%). M. P. 37-40 ºC. *Rf* (5% EtOAc in pet ether) 0.3. IRυ_{max} (KBr) 3055, 2935, 2873, 2773, 1606, 1581, 1396, 1209, 1116, 1057, 993 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.30 (m, 1H), 7.60 (s, 1H), 6.65 (s, 1H), 5.27 (s, 2H), 3.87 (s, 3H), 3.51 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.4, 163.8, 160.5, 129.6, 120.8, 118.1, .97.1, 95.0, 56.4, 55.7, 15.3. HRMS (ESI) *m/z* calcd for $C_{11}H_{14}O_4Na$ [M^++Na]: 233.0790; found: 233.0792.

*4.2.4. (E/Z)-1-(2-(allyloxy)vinyl)-4-methoxy-2-(methoxymethoxy)-5-methylbenzene (**16**)*

To a suspension of **14** (5 g, 23.78 mmol) and allylo xymethylenetriphenylphosphonium chloride[14] (11.40 g, 30.92 mmol) in dry THF (70 mL), THF solution of potassium *tert*-butoxide (5.34 g, 47.57 mmol) was added over the period of 20 minutes at 0 ºC. The reaction was stirred for another 30 minute at the same temperature. After the completion of reaction (monitored by TLC), water (150 mL) was added and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (3% EtOAc in pet ether), gave pure allyl vinyl ether **16** (*E/Z*=3:2) as colourless thick liquid (4.52 g, 17.10 mmol, 71.91%). *Rf* (5% EtOAc in hexane) 0.5. IRυ_{max} (neat) 2935, 1693, 1630, 1097, 927 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.02 (s, 2H), 6.97 – 6.88 (m, 2H), 6.65 (s, 2H), 6.16 (d, *J* = 7.2 Hz, 1H), 6.10 – 5.90 (m, 4H), 5.58 (d, *J* = 7.2 Hz, 1H), 5.44 – 5.23 (m, 6H), 5.17 (d, *J* = 2.6 Hz, 5H), 4.39 (ddt, *J* = 15.9, 5.4, 1.5 Hz, 7H), 3.82 (dd, *J* = 7.1, 1.7 Hz, 10H), 3.51 (d, *J* = 1.1 Hz, 9H), 2.19 – 2.11 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 153.9,

152.7, 151.1, 150.0, 144.1, 143.9, 135.8, 132.0, 122.2, 118.1, 118.0, 103.5, 103.4, 102.2, 101.7, 99.2, 98.4, 89.3, 78.1, 77.2, 55.7, 55.2, 16.6. HRMS(ESI) *m/z* calcd for $C_{15}H_{20}O_4Na$ [M^++Na]: 287.1259; found: 287.1268.

*4.2.5. 1-methoxy-5-(methoxymethoxy)-2-methyl-4-(6-methylhepta-1,5-dien-4-yl)benzene (**18**)*

To a stirred suspension of $(CH_3)_2CHPPh_3Br$ (4.45 g, 13 mmol) in anhydrous THF (30 mL) under nitrogen, was added dropwise *n*-BuLi (1.11 g, 17.40 mmol, 15% in hexanes) at 0 ºC. The resulting orange coloured solution was stirred for 20 min at 0 ºC to give isopropylphosphorane.

Meanwhile, the allyl vinyl ether **16** (2.30 g, 8.7 mmol) was heated neat at 180 ºC for 5 min affording corresponding aldehyde **17** (2.30 g, 8.7 mmol). After cooling to room temperature, the aldehyde was dissolved in dry THF (10 ml) and added to above stirred red solution of isopropylphosphorane. The mixture was stirred for another 1 h at 0 ºC. The reaction was quenched with H_2O (25 mL) and extracted with Et_2O (3x50 mL). The organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, giving pale yellow liquid, which was purified by silica gel column chromatography (2% EtOAc in pet ether as an eluent), afforded colorless liquid as **18 (**2.03 g, 6.99 mmol, 80.33%). *Rf* (5% EtOAc in hexane) 0.3. IRυ_{max} (neat) 2950, 2910, 2870, 1620, 1510, 1120, 980 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.70 (s, 1H), 5.83 – 5.73 (m, 1H), 5.37 – 5.32 (m, 1H), 5.24 – 5.18 (m, 2H), 5.07 – 4.95 (m, 2H), 3.98 (dd, *J* = 15.8, 8.5 Hz, 1H), 3.84 (s, 3H), 3.54 (s, 3H), 2.49 – 2.34 (m, 2H), 2.19 (s, 3H), 1.71 (dt, *J* = 12.5, 6.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 131.0, 129.4, 128.3, 125.9, 119.6, 115.1, 98.5, 95.1, 55.8, 55.4, 40.6, 36.7, 25.8, 18.1, 15.6. HRMS(ESI) *m/z* calcd for $C_{18}H_{27}O_3$ [M^++H]: 291.1882; found: 291.1883.

*4.2.6. 5-methoxy-4-methyl-2-(6-methylhepta-1,5-dien-4-yl)phenol (**19**)*

To the stirred solution of **18** (2 g, 6.89 mmol) in MeOH (25 mL) was added 2-3 drops of conc. HCl. The reaction mixture was then refluxed for 1 hour (monitored by TLC), quenched with saturated sodium bicarbonate solution (15 mL). MeOH was removed under reduced pressure and the crude product was extracted with EtOAc (3x30 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure giving pale green coloured viscous liquid. The liquid was redissolved in 10% aq. NaOH solution (100 mL) and washed with ether (3x25 mL). The aqueous layer was acidified with 2N

HCl (100 mL) and extracted with ethyl acetate (3x70 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to provide **19** as a thick gel **(**1.48 g, 6.01 mmol, 87.23%), which was used directly for next step without further purification. *Rf* (15% EtOAc in pet ether) 0.5. IRυ_{max} (neat) 3405, 2935, 2860, 1660, 1480, 1070, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.69 (s, 1H), 5.81-5.72 (m, 1H), 5.31 (d, *J* = 8.4 Hz, 1H), 5.21-5.07 (m, 2H), 4.03-3.91 (m, 1H), 3.89 (s, 3H), 2.50-2.31 (m, 2H), 2.29 (s, 3H), 1.75-1.68 (d, 10.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4, 146.6, 136.2, 132.3, 130.2, 129.0, 127.4, 126.2, 116.4, 102.0, 54.4, 41.3, 37.0, 26.1, 21.0, 18.5. HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_2K$ $[M^+ + K]$: 285.1257; found: 285.1255.

*4.2.7. 5-methoxy-4-methyl-2-(6-methylhepta-1,5-dien-4-yl)phenyl trifluoromethanesulfonate (**8**)*

Triflic anhydride (1.48 mL, 8.83 mmol) was added to the stirred mixture of **19** (1.45 g, 5.89 mmol), TEA (1.6 mL, 11.77 mmol) and DMAP (143 mg, 1.18 mmol) in 30 mL DCM at 0 ^oC. Upon completion of reaction (5 min), diluted with water (50 mL), extracted with DCM (3x50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (1% EtOAc in pet ether as an eluent) to yield **8** as a colorless liquid **(**1.83 g, 4.84 mmol, 82.16%). *Rf* (3% EtOAc in pet ether) 0.6. IRυ_{max} (neat) 2930, 2835, 1680, 1440, 1090, 1075, 693 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.67 (s, 1H), 5.80–5.66 (m, 1H), 5.30–5.20 (d, 1H), 5.09–4.93 (m, 2H), 3.95 (m, 1H), 3.85 (s, 3H), 2.46–2.28 (m, 2H), 2.22 (s, 3H), 1.75–1.55 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 144.9, 136.0, 133.2, 129.9, 127.3, 126.2, 119.8, 116.3, 102.9, 41.0, 36.6, 25.8, 18.0, 16.0. HRMS (ESI) *m/z* calcd for $C_{17}H_{21}F_3O_4SNa$ $[M^+ + Na]$: 401.1011; found: 401.1012.

*4.2.8. Mixture containing 5-methoxy-6-methyl-1-methylene-3-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-indene 20 (**IM**)*

The mixture of **8** (300 mg, 0.792 mmol), TEA (0.32 mL, 2.386 mmol) and LiCl (33.61 mg, 0.792 mmol) in DMF (5 mL) was degased by passing argon gas for 15 min. The $Pd(PPh_3)_4$ (183 mg, 0.158 mmol, 20 mol%) was added and the reaction mixture was heated at 100-110 ^oC for 20 h. The reaction mixture was diluted with diethyl ether (10 mL) and filtered through celite bed, washed the bed with ether (3x10 mL). The combined filtrate was washed with brine solution (20 mL) followed by water (20 mL). The ether layer was dried over $MgSO_4$, filtered and concentrated to give crude reaction mixture. The crude reaction mixture was then diluted with

hexane (100 mL) and filtered through long silica bed. The bed was successively washed with hexane (3x100 mL). The combined hexane layer was then concentrated under reduced pressure to provide inseparable products mixture **IM** (152 mg) *Rf* (pet ether) 0.4, though appeared homogeneous on TLC. This mixture was as such used for next step.

*4.2.9. 6-methyl-3-methylene-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-inden-5-ol (**7**) and 2-methyl-4-(6-methylhepta-1,5-dien-4-yl)phenol (**21**)*

NaH (788 mg, 32.85 mmol, 60% in mineral oil) was washed with anhydrous pet ether under nitrogen atmosphere and suspended in anhydrous DMF (3 mL). To this mixture was slowly added a solution of EtSH (1.22 g, 19.71 mmol) in anhydrous DMF (1 mL) at 0 ºC, and the resulting solution was stirred for 30 minute at rt. A solution of **IM** (150 mg) in anhydrous DMF (1 mL) was then added dropwise, and the resulting mixture was stirred for 24 h at 130 °C. The mixture was cooled to rt, and a saturated solution of NH_4Cl was added. The mixture was extracted with Et_2O (3x20 mL), and the organic phase was washed with H_2O and brine followed by drying over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by silica gel column chromatography (2-3% EtOAc in pet ether) furnished compound **7 (**95 mg, 0.443 mmol, 55.91% from **8**) as colourless thick gel, *Rf* (10% EtOAc in pet ether) 0.5 and **21** (24 mg, 0.110 mmol, 14% from **8**) as colourless oil, *Rf* (10% EtOAc in pet ether) 0.5 as two distinct products. Spectral data for **7**: IRυ_{max} (neat) 3396, 2929, 2844, 1669, 1439, 1074, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.68 (s, 1H), 5.24 (d, *J* = 8.4 Hz, 1H), 5.06 (m, 2H), 3.97-3.86 (m, 1H), 2.56-2.38 (m, 2H), 2.21 (s, 3H), 1.74 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (126 MHz) δ 156.7, 145.0, 143.2, 136.4, 133.5, 130.1, 127.5, 126.4, 115.9, 110.4, 44.3, 39.8, 26.0, 18.1, 5.9. HRMS (ESI) *m/z* calcd for $C_{15}H_{20}OK$ $[M^+ + K]$: 253.0996; found: 253.0988. Spectral data for **21**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.10-6.97 (m, 2H), 6.7 (d, 7.8 Hz, 1H), 5.81-5.73 (m, 1H), 5.63 (d, *J* = 8.2 Hz, 1H), 5.20-5.08 (m, 2H), 4.02-3.92 (m, 1H), 2.49-2.31 (m, 2H), 2.21 (s, 3H), 1.70 (s, 6H). ^{13}C NMR (126 MHz) δ 156.2, 133.5, 133.1, 132.1, 128.9, 128.1, 127.0, 124.3, 117.1, 116.0, 49.6, 37.1, 25.8, 18.1, 16.0.

*4.2.10. (±) epi-Mutisianthol (**22**)*

To a solution of Compound **7** (20 mg, 0.093 mmol) in MeOH (2 mL)was added palladium on activated carbon (2.2 mg, 20 mol%). The reaction was stirred under hydrogen atmosphere at room temperature for two hour, whereupon TLC showed the reaction was

complete. The solid was filtered off. Evaporation of the solvent and purification of the residue on silica gel column chromatography (3% EtOAc in pet ether) furnished the product **22** as a white solid (17 mg, 0.078 mmol, 84.21%). M. P. 65-73 ºC. *Rf* (7-8% EtOAc in pet ether) 0.4. IRυ_{max} (KBr) 3404, 2952, 2929, 2870, 1490, 1454, 1420, 1375, 1284, 1180, 1154, 1054, 995 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.63 (s, 1H), 5.10 (d, *J* = 8.4 Hz, 1H), 4.57 (s, 1H), 3.85 - 3.77 (m, 1H), 3.12 - 3.02 (m, 1H), 2.50 - 2.39 (m, 2H), 2.23 (s, 3H), 1.80 (s, 3H), 1.78 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 147.4, 139.1, 132.3, 128.5, 125.9, 121.2, 109.6, 44.2, 42.5, 38.1, 25.8, 19.1, 18.1, 15.7. HRMS (ESI) *m/z* calcd for $C_{15}H_{20}ONa$ [M^{+}+Na]: 239.1412; found: 239.1413.

*4.2.11. (±) Mutisianthol (**1**)*

To the cooled solution of compound **7** (30 mg, 0.140 mmol) and DIPEA (0.05 mL, 0.280 mmol) in dichloromethane (5 mL) at 0 ºC was added chloromethyl methoxy ether (0.015 mL, 0.181 mmol). Reaction mixture slowly warmed to rt and stirred for 12 h. Upon completion, 5% aq. NaOH solution (10 mL) was added and reaction mixture was extracted with dichloromethane (3x10 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated to dryness afforded MOM ether **23** (31 mg, 0.119 mmol, 85.71%) *Rf* (5% EtOAc in pet ether) 0.6 enough pure for next step.

Lithium metal (4 mg, 0.580 mmol) was added to the stirred solution of anhydrous ammonia (25 mL) at -78 ºC. To this mixture was added a solution of **23** (30 mg, 0.116 mmol) in dry THF (6 mL) at the same temperature followed by stirring for 30 min and quenching with methanol. The ammonia was evaporated and 20 mL of 6 N methanolic HCl was added and stirred for another 90 min. Solvent was removed under reduced pressure and crude was purified by column chromatography (2-3% EtOAc in pet ether) to end up with compound **1** as a white solid (10 mg, 0.046 mmol, 39.82%) and compound **22** as a white solid (10 mg, 0.046 mmol, 39.82%). Spectral data for compound **1**: M.P. 97-100 ^{o}C. *Rf* (7-8% EtOAc in pet ether) 0.4. IRυ_{max} (KBr) 3332, 2955, 2929, 2857, 1620, 1495, 1446, 1375, 1295, 1189, 1166, 881, 861 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.61 (s, 1H), 5.12 (d, *J* = 10.4 Hz, 1H), 4.58 (s, 1H), 3.99-3.92 (m, 1H), 3.20 (m, 1H), 2.21 (s, 3H), 2.00-1.88 (m, 2H), 1.77 (s, 3H), 1.74 (s, 3H), 1.20 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 147.8, 138.6, 131.3, 128.6, 126.3,

121.6, 110.1, 42.4, 41.6, 37.9, 25.6, 20.9, 18.1, 15.9. HRMS (ESI) *m/z* calcd for $C_{15}H_{21}O$ $[M^+ + H]$: 217.1514; found: 217.1517.

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Notes and References

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16. Optimization of reaction condition for Heck reaction

	Catalyst	Base	Additive	Solvent	Time(h)	**IM**(%)[a]
1	$Pd(OAc)_2$	TEA	-	MeCN	20	Complex TLC

2	$Pd(PPh_3)_4$	TEA	-	MeCN	12	41
3	$Pd(PPh_3)_4$	K_2CO_3	-	DMF	20	Complex TLC
4	$Pd(PPh_3)_4$	DIPEA	LiCl	DMF	15	83[b]
5	$Pd(PPh_3)_4$	TEA	LiCl	DMF	20	87
6	$Pd(PPh_3)_4$	TEA	LiCl	DMSO	20	82

IM- inseparable mixture, [a] isolated yield-calculated by considering **IM** as product **20**, [b] reaction proceeded well in the presence of additive (LiCl).

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