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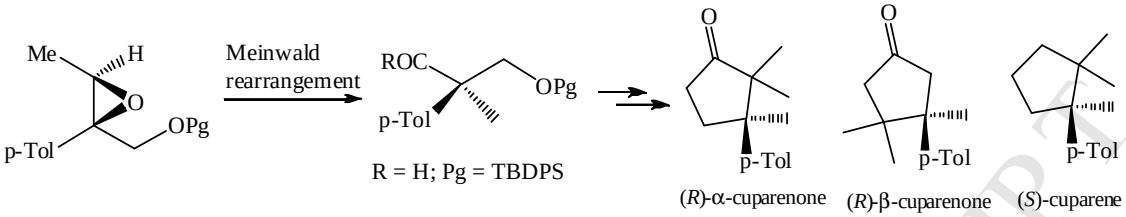

Asymmetric total synthesis of (*R*)-α-cuparenone, (*S*)-cuparene and formal synthesis of (*R*)-β-cuparenone through Meinwald rearrangement and ring closing metathesis (RCM) reaction

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Abstract: Asymmetric synthesis of enantiopure cuparenoid sesquiterpenes (*R*)-α-cuparenone, (*S*)-cuparene and a formal synthesis of (*R*)-β-cuparenone was presented in this article. Meinwald rearrangement of an enantiopure trisubstituted 2,3-epoxy alcohol derivative was the key reaction employed to construct the quaternary streocenter in the target molecules. Ring closing metathesis (RCM) reaction was explored in the final stage of synthesis to access the cyclopentane core of the natural products.

Introduction

A family of sesquiterpenes known as cuparenoids containing the hypothetical cuparane skeleton has been isolated from various natural sources. α and β-Cuparenones (**1** and **2**) are cyclopentanoid sesquiterpenes isolated from the essential oil of leaves from *Thuja orientallis* (Commonly known as "Morpankhi", Family- *Cupressaceae*) by Sukhdeb and coworkers in 1964.[1] *Thuja orientalis* is an evergreen, monoecious tree or shrub growing to 10-60 feet tall. Their leaves contain essential oils (consist of several terpenoids as an essential components) used to treat fungal infections, cancer, moles and parasitic worms. In addition *Thuja orientalis* is used internally in the treatment of coughs, hemorrhages, excessive menstruation, bronchitis, asthma, skin infections, mumps, bacterial dysentery, arthritic pains and premature blandness. Later on both the sesquiterpenes (*R*-enantiomer) was isolated from the liverworts *Mania fragrans* in 1976 by Benesova *et al*.[2] Whereas cuparene (**3**) the deoxygenated product of the α/β-cuparenone, another sesquiterpene was isolated by Erdtman *et al* [3] in 1958 and no significant biological activity was reported so far for the molecule (Fig-1).

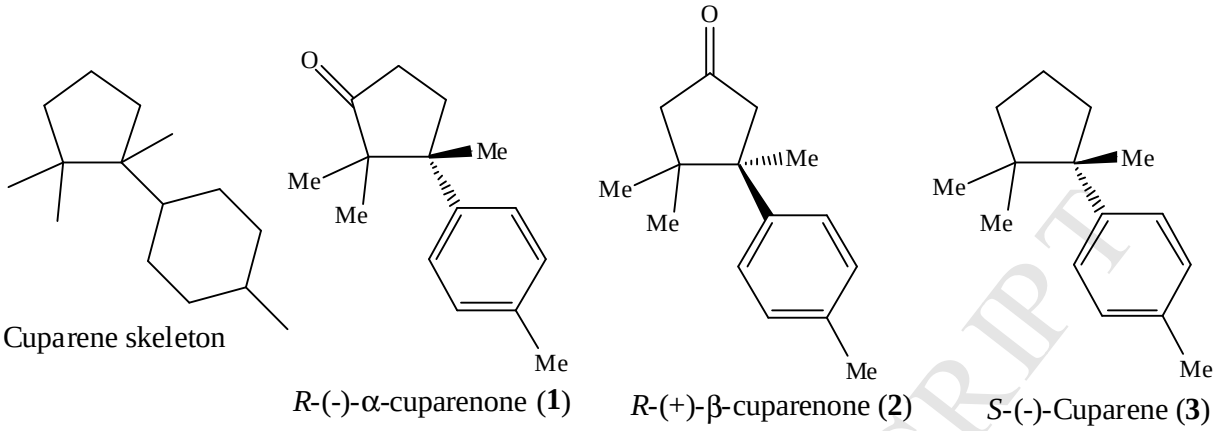


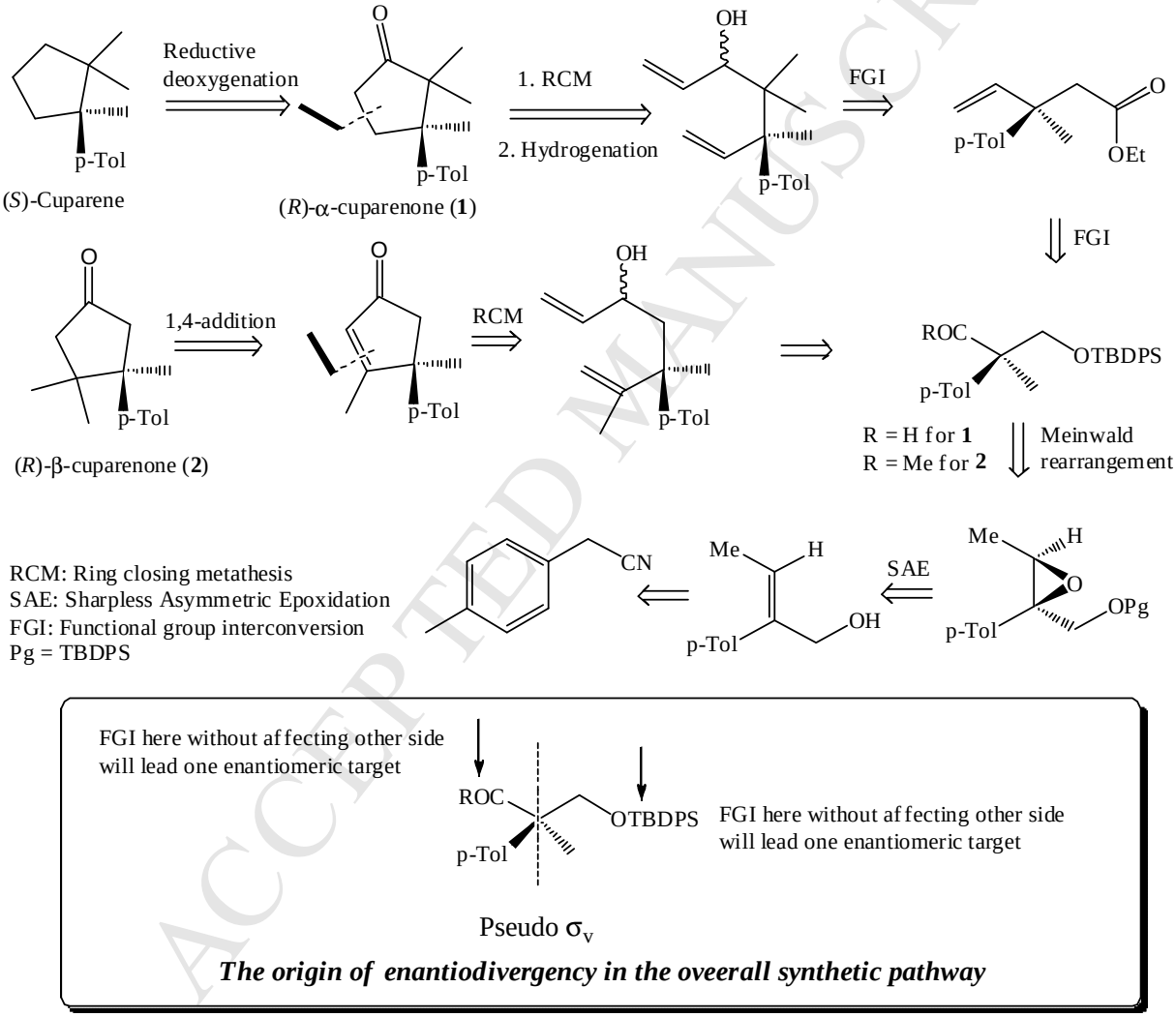
Figure 1: Structure of cuparenones and cuparene

Presence of two contiguous quaternary carbon (one being stereogenic) in the above molecules make them valuable synthetic targets. Though numerous synthetic reports were documented in the literature for the total synthesis of the above sesquiterpenoids, [4-6] the presence of two adjacent quaternary carbon atoms in the cuparenoid skeleton often poses a dreadful synthetic challenge. In the quest for relatively unexplored synthetic strategies for cuparenoids, herein we wish to report the asymmetric synthesis of α/β-cuparenones and (*S*)-cuparene from a common intermediate. We envision that Meinwald rearrangement [7] of an enantiopure epoxide will lead to the stereogenic quaternary carbon present in the target molecules and was never attempted before.

Our proposed retrosynthesis was outlined in Scheme 1, (*S*)-cuparene was thought to be synthesized from (*R*)-α-cuparenone through reductive deoxygenation method. RCM (ring closing metathesis) reaction was planned at the final stage of the synthesis to construct the cyclopentane core of the target molecules. Meinwald rearrangement of enantiopure epoxide was envisioned as a crucial disconnection to construct the quaternary sterocenters in the target molecules. The enantiopure epoxides was planned to be synthesized by Sharpless asymmetric epoxidation reaction of suitable allylic alcohol. The allylic alcohol was synthesized by employing an aldol reaction of 4-methylbenzyl cyanide with acetaldehyde (Scheme 1).

The proposed synthetic strategy was very flexible and can be regarded as enantiodivergent also as both the enantiomer of all the target molecules can be accessed from the intermediate obtained

after Meinwald rearrangement of the enantiopure epoxide. The intermediate **8** (Scheme 2) containing the required all carbon quaternary stereocenter can be regarded as pseudo symmetric (having pseudo σv in its structure; -CH_2OTBDPS and –CHO/COMe functional group are regarded as enantiotopic and interconvertable to each other by standard FGI). The origin of divergency from intermediate **8**, made the overall synthetic strategy very reliable and flexible as both the enantiomer of the target compounds can be accessed by following same sequence of reactions.



Scheme 1: Retrosynthetic analysis of cuparenones through exploration of Meinwald rearrangement and RCM reaction.

Present work:

Synthesis of (*R*)-α-cuparenone and (*S*)-cuparene: The synthesis was initiated from 4-methylbenzyl cyanide, which on aldol reaction with Me-CHO in presence of K_2CO_3 afforded *E*-acrylonitrile (**4**) as a major product in 90% yield.[8] The *E*-geometry was confirmed by 2D-NOESY analysis as shown in Scheme 2. Compound **4** upon reduction with DIBAL-H followed by acid hydrolysis and further $NaBH_4$ reduction afforded *E*-allylic alcohol (**5**) as a major product in 85% yield. The *E*-geometry in compound **5** was also reconfirmed with the help of NMR analysis (2D-NOESY). Sharpless asymmetric epoxidation [9,10b] of **5** with D-DET afforded enantiopure epoxide **6** in 82% yield. The free hydroxyl group in **6** was then protected as its TBDPS ether by treatment with TBDPS-Cl and imidazole to afford compound **7** in 90% yield. Lewis acid promoted semipinacol type rearrangement of epoxides through 3,2-migration (referred as Meinwald rearrangement) induced by epoxide ring opening was widely used in the field of natural product synthesis.[10] Suitably substituted 2,3-epoxy alcohol derivative can undergo 1,2 or 2,3 (even 3,2) migration in a stereoselective fashion to lead quaternary stereocenters in presence of Lewis acids. A schematic diagram for such migration was outlined in Figure 2.

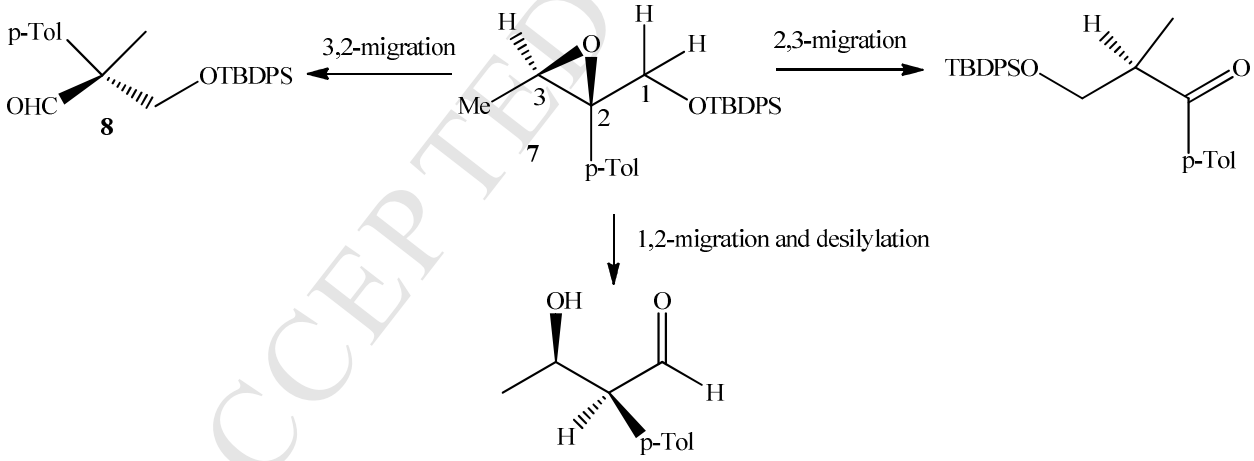


Figure 2: Lewis acid mediated Meinwald rearrangement of enantiopure epoxide **7**.

As envisioned in Figure 2, Meinwald rearrangement of compound **7** was then attempted with a series of Lewis acids as presented in Table 1.

Table 1: Meinwald rearrangement of enantiopure 7 with different Lewis acids.

Entry	Lewis acid used	Reaction condition (temp, solvent, time)	Product distribution (yield%) [a]
1	BF_3:OEt_2	-78°C, DCM, 1h	Only **8** (30%)
2	$MgBr_2$	-78°C, DCM, 1h	NR
3	$Hg(OCOCF_3)_2$	-78°C, DCM, 1h	Only **8** (40%)
4	Et_2AlCl	-78°C, DCM, 1h	Only **8** (55%)
5	Me_3Al	-78°C, DCM, 1h	Only **8** (50%)
6	Me_3Al	-78°C, toluene, 1h	Only **8** (40%)
7	Et_3Al	-78°C, DCM, 1h	Only **8** (40%)
8	Et_3Al	-78°C, toluene, 1h	Only **8** (38%)
9	$Ti(O^iPr)_4$	-78°C, DCM, 1h	Only **8** (32%)
10	MAD	-78°C, DCM, 1h	Only **8** (95%)

[a] : Isolated yield after purification; NR: No reaction; DCM: dichloromethane

From Table 1 it was observed that use of MAD (methyl aluminum bis(4-methyl-2,6-di-*tert*-butylphenoxide) as Lewis acid afforded the best result in which the desired aldehyde **8** was obtained in 95% yield as a sole product (3,2 migration as the major product due to stability of generated carbocation type intermediate). Wittig olefination of aldehyde **8** with $Ph_3P{=}CH_2$ (generated from $Ph_3P^+MeI^-$ and LHMDS) furnished olefin **9** in 90% yield. Removal of TBDPS functionality in compound **9** by TBAF followed by Dess-Martin periodinane (DMP) [11] oxidation afforded aldehyde **10** in 88% yield (two steps). The aldehyde **10** was next converted to acid **11** by adopting a two stage protocol.[12] In first step Wittig reaction with $Ph_3P{=}CHOMe$ (generated from $Ph_3P^+CH_2OMeCl^-$ and *n*-butyl lithium at -15 °C) followed by acidic hydrolysis yielded its higher homologue aldehyde, which on Pinnick oxidation [13] in second step afforded acid **11** in 60% yield (in two steps). Esterification of acid **11** with EtOH and $SOCl_2$ afforded ester **12** in 80% yield. Installation of the gem-dimethyl group was accomplished by treating compound **12** with LDA and excess MeI [14] to furnish compound **13** in 75% yield (brsm). $LiAlH_4$ reduction of **13** followed by Dess-Martin periodinane (DMP) oxidation afforded aldehyde **14** in 85% yield. Treatment of $CH_2{=}CHMgBr$ with aldehyde **14** at -78°C furnished RCM precursor **15** in 90% yield as diastereomeric mixture. Finally RCM reaction of **15** in presence of G-I catalyst [15] in

refluxing DCM followed by Dess-Martin periodinane (DMP) oxidation furnished cyclopentenone **16** in 85% yield. Hydrogenation with Pd-C/H_2 afforded (*R*)-α-cuparenone in almost quantitative yield (Scheme 2; overall yield = 9.4% from 4-mehylbenzyl cyanide). Reductive deoxygenation of (*R*)-α-cuparenone under Huang-Minlon condition (hydrazine hydrate, hydrazine dihydrochloride and KOH) [16] furnished (*S*)-cuparene (**3**) in 80% yield (overall yield = 7.5% from 4-methylbenzyl cyanide). The analytical data of our synthesized compounds (^{1}H-NMR, ^{13}C-NMR, HRMS and $[\alpha]_D$) matches perfectly with those of reported values. The ORTEP presentation (CCDC 1502182) of α-cuparenone was also presented in Figure-3.

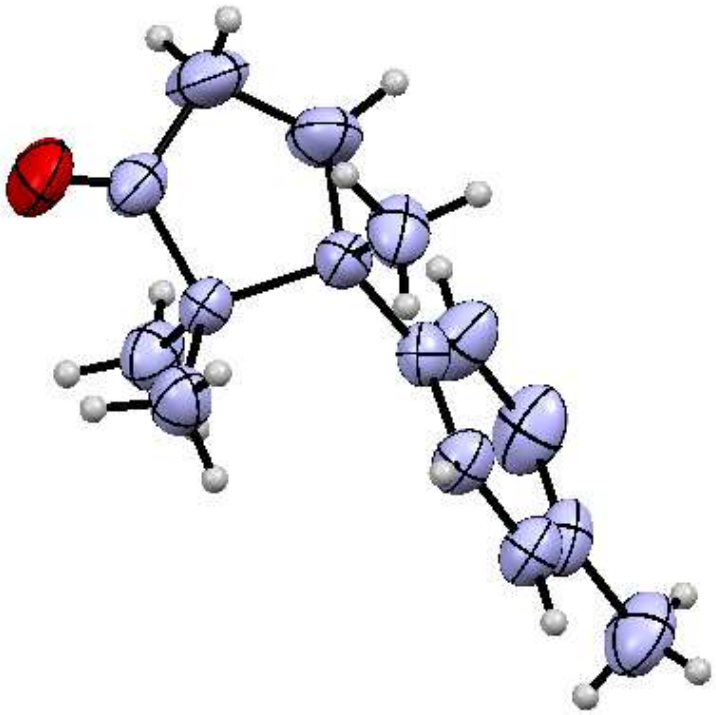
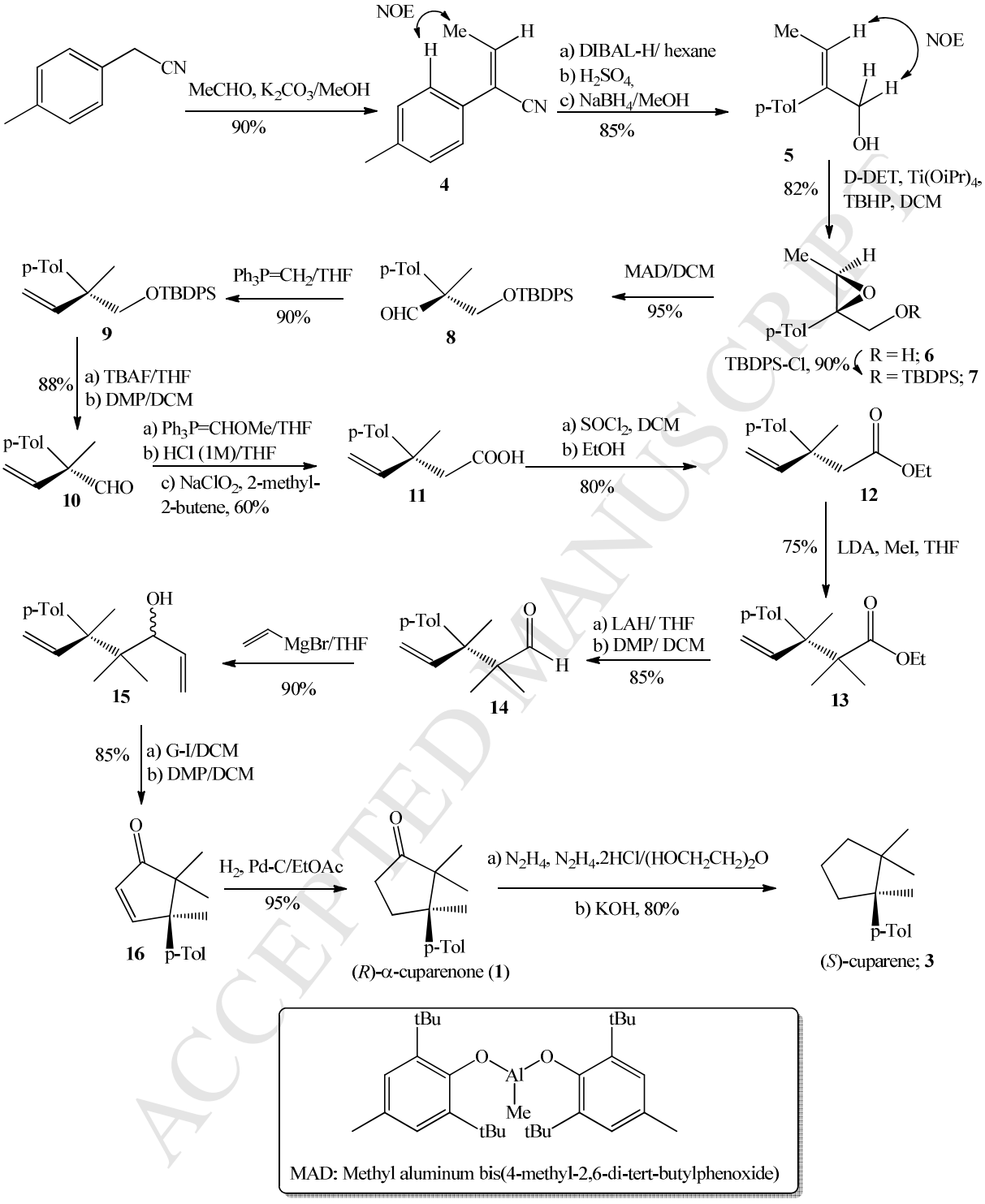
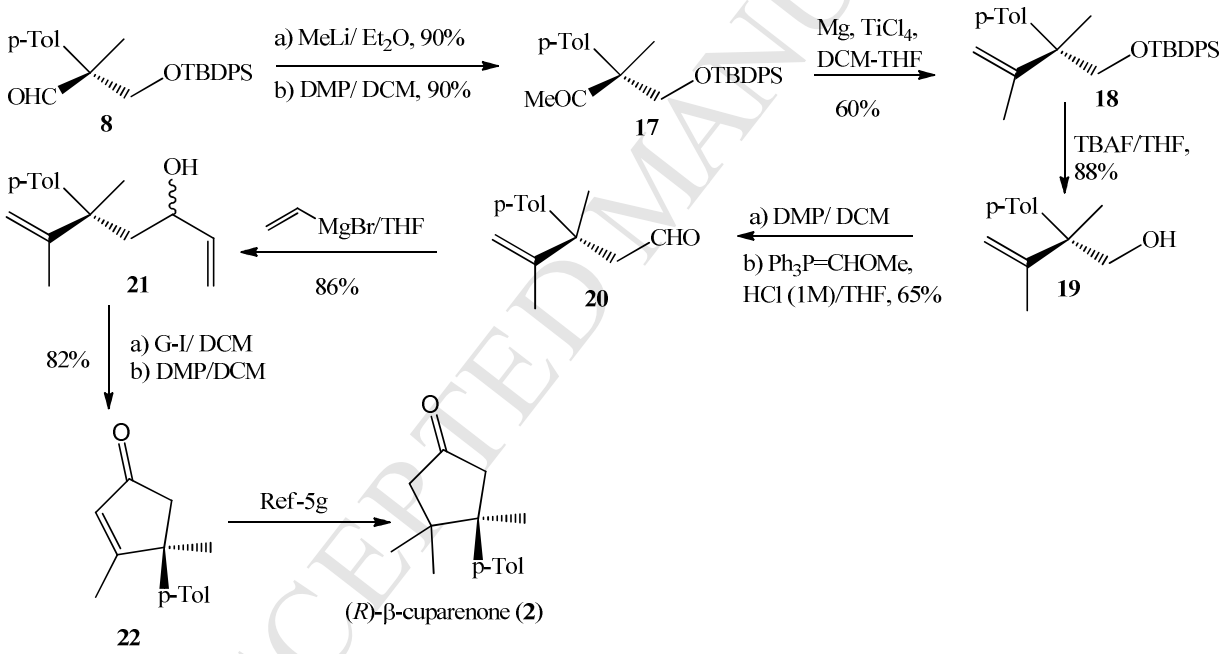


Figure-3: ORTEP presentation of compound **1** (drawn at 30% probability).



Scheme 2: Asymmetric synthesis of (*R*)-α-cuparenone and (*S*)-cuparene.

Synthesis of (*R*)-β-cuparenone: The synthesis of another target terpenoid was accomplished as depicted in Scheme 3. The synthetic journey began with aldehyde **8** (Scheme 2), addition of MeLi followed by DMP oxidation afforded the ketone **17** in 81% yield. Attempted olefination with standard protocol such as Wittig, Tebbe and Peterson reaction failed miserably with substrate **17**. Direct methylenation (transfer of -CH_2 group) of compound **17** was carried out with CH_2Cl_2 in presence of Mg and $TiCl_4$ by following Yan's protocol [17] to furnish olefin **18** in 60% yield. The rest of the synthetic steps were almost similar as depicted in Scheme 2 for the synthesis of (*R*)-α-cuparenone. Ring closing metathesis reaction of **21** with G-I catalyst in refluxing DCM followed by DMP oxidation furnished cyclopentenone **22**. The synthesis of (*R*)-β-cuparenone from **22** was reported elsewhere [5g] hence the formal synthesis of the target molecule was achieved.



Scheme 3: Synthesis of (*R*)-β-cuparenone

In conclusion we have described an efficient asymmetric synthesis of cuparenoid sesquiterpenes α/β-cuparenones and cuparene. Lewis acid mediated Meinwald rearrangement of an enantiopure epoxy compound was the key reaction employed to generate the quaternary stereocenter in the target molecules. The enantiopure epoxide was synthesized by employing Sharpless asymmetric epoxidation reaction. Finally late stage ring closing metathesis (RCM) reaction was used to construct the cyclopentane core of the target molecules.

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Experimental Section

Materials and methods: All oxygen and/or moisture-sensitive reactions were carried out under N_2 atmosphere in glassware that had been flame-dried under vacuum (ca. 0.5 Torr) and purged with N_2 prior to use. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF, diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (DCM), hexane were distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Silica gel 100-200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 600, 400 & 200 MHz spectrometers at 25 $^{\circ}$C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ, ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^{1}H and ^{13}C, respectively. Coupling constants (*J*) are reported in hertz (Hz) and the resonance multiplicity abbreviations used are s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons. Mass spectrometric analysis was performed in the CRF, IIT-Kharagpur (TOF analyzer). Optical rotations were measured on a digital polarimeter.

(*E*)-2-*p*-tolylbut-2-enenitrile (4):

To a stirred solution of *p*-xylyl cyanide (5.0 g, 38.2 mmol) in MeOH (50 mL) were added K_2CO_3 (5.3 g, 38.2 mmol) and acetaldehyde (2.15 mL, 38.2 mmol) sequentially at room temperature, and the reaction mixture was stirred at 65 °C for 2 h. TLC analysis indicated the disappearance of the starting material after that reaction mixture was filtrated and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to afford the compound **4** (5.4 g) as a colorless oil in 90% yield.

R_f = 0.6 (EtOAc/ hexane, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.41 (d, 2H, *J* = 8.4 Hz), 7.19 (d, 2H, *J* = 8.4 Hz), 6.84 (q, 1H, *J* = 7.2 Hz), 2.36 (s, 3H), 2.19 (d, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 140.9, 139.0, 130.6, 129.8, 129.7, 125.5, 117.0, 21.3, 17.9.

HRMS (ESI) for $C_{11}H_{12}N$ $[M + H]^+$, calculated: 158.0969; found: 158.0972.

(*E*)-2-*p*-tolylbut-2-en-1-ol (5):

To a solution of **4** (12.6 g, 80.1 mmol) in dry hexane (200 mL) at -30 °C was added DIBAL-H (1.5 M toluene solution, 54 mL) over 20 min. After 2 h at 0 °C, the reaction mixture was quenched with dropwise addition of ice cold 3 N H_2SO_4 (54 mL) at 0 °C. The resulting solution was stirred at 0 °C for 0.5 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with saturated $NaHCO_3$ and dried, filtered, and concentrated in vacuo. The residue in MeOH (200 mL) was treated with $NaBH_4$ (3.0 g, 80.0 mmol) at 0 °C for 30 min. TLC analysis indicated the disappearance of the starting material and the reaction was quenched with dropwise addition of saturated ammonium chloride solution. MeOH was evaporated under reduced pressure, the content of the flask was then extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to afford the crude alcohol. Purification of the crude product by silica gel chromatography (EtOAc/hexane, 1:8) afforded compound **5** (11.0 g) as a colorless oil in 85% yield.

R_f = 0.3 (EtOAc/ hexane, 1:8).

^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 7.21 (d, 2H, *J* = 7.8 Hz), 7.15 (d, 2H, *J* = 7.8 Hz), 5.83 (q, 1H, *J* = 6.6 Hz), 4.32 (s, 2H), 2.39 (s, 3H), 1.67 (d, 3H, *J* = 6.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 140.9, 136.8, 135.2, 129.2, 128.7, 123.3, 68.3, 21.3, 14.5.

HRMS (ESI) for $C_{11}H_{15}O$ $[M + H]^+$, calculated: 163.1123; found: 163.1128.

((2*R*,3*R*)-3-methyl-2-*p*-tolyloxiran-2-yl)methanol (6):

Diethyl D-(-)-tartrate (1.26 mL, 7.4 mmol) and titanium tetraisopropoxide (1.69 mL, 5.7 mmol) were added sequentially to a mixture of powdered activated 4 Å molecular sieves (4.5 g) and

dichloromethane (100 mL) at 0 °C with stirring. The reaction mixture was cooled to -20 °C, *tert*-butyl hydroperoxide (2.7 M in dichloromethane, 54.8 mL, 148.2 mmol) was added dropwise over 0.2 h, and the resulting mixture was stirred at -20 °C for 1 h. Compound **5** (9.2 g, 57 mmol) dissolved in dichloromethane (55 mL) was then added dropwise over 0.2 h. After stirring for 15 h at -20 °C, the reaction mixture was poured into a freshly prepared ferrous sulfate solution (33 g of $FeSO_4 \cdot 7H_2O$ and 11 g of citric acid in 100 mL of H_2O) at -20 °C and stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layer was concentrated in vacuo. To the residue in Et_2O (200 mL) was added 30% NaOH (10 mL), and the resultant mixture was stirred at 0 °C for 1 h. The two phases were then separated, and the aqueous phase was extracted twice with Et_2O. The combined organic phases were washed with brine and dried over $MgSO_4$. The organic solution was filtered and then concentrated in vacuo. Purification of the crude product by silica gel chromatography (EtOAc/hexane, 1:5) afforded compound **6** (8.3 g) in 82% yield as a colorless oil.

R_f = 0.2 (EtOAc/ hexane, 1:5).

$[\alpha]_D^{28}$ = +40.2 (c =1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.23 (d, 2H, *J* = 8.2 Hz), 7.19 (d, 2H, *J* = 8.2 Hz), 3.97–3.91 (m, 2H), 3.51 (t, 1H, *J* = 5.6 Hz), 2.36 (s, 3H), 1.05 (d, 3H, *J* = 5.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 137.7, 132.8, 129.2, 127.0, 66.1, 64.8, 57.0, 21.3, 14.2.

HRMS (ESI) for $C_{11}H_{14}O_2Na$ $[M + Na]^+$, calculated: 201.0892; found: 201.0899.

***Tert*-butyl(((2*R*,3*R*)-3-methyl-2-*p*-tolyloxiran-2-yl)methoxy)diphenylsilane (7):**

To a stirred solution of epoxide **6** (8.0 g, 44.9 mmol) in dry DCM (150 mL) were added imidazole (6.1 g, 89.8 mmol), *tert*-butyl(chloro)diphenylsilane (14.0 ml, 53.9 mmol) and a catalytic amount of DMAP sequentially at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. After that time water was added to the reaction mixture, the organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was then purified by silica gel column chromatography (EtOAc/hexane, 1:30) to afford the compound **7** (16.8 g) in 90% yield as a colorless oil (at room temperature).

R_f = 0.4 (EtOAc/ hexane, 1:30).

$[\alpha]_D^{28}$ = +30.8 (c =1.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.65–7.62 (m, 4H), 7.44–7.39 (m, 6H), 7.21 (d, 2H, *J* = 8.0 Hz), 7.13 (d, 2H, *J* = 8.0 Hz), 3.98–3.94 (m, 2H), 3.45–3.44 (m, 1H), 2.34 (s, 3H), 1.03 (d, 3H, *J* = 5.2 Hz), 1.02 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 137.1, 135.7, 135.5, 133.5, 133.4, 133.1, 129.6, 128.6, 127.7, 127.6, 127.4, 67.0, 65.8, 56.8, 26.7, 21.1, 19.3, 14.4.

HRMS (ESI) for $C_{27}H_{32}O_2SiNa$ $[M + Na]^+$, calculated: 439.2070; found: 439.2078.

(*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methyl-2-*p*-tolylpropanal (8):

To a solution of **7** (9.0 g, 21.6 mmol) in dichloromethane (100 mL) was added methyl aluminum bis(4-methyl-2,6-di-*tert*-butylphenoxide) (0.4 M in toluene, 108 mL) at -78 °C. After being stirred at -78 °C for 1 h, the reaction mixture was poured into a solution of cold 2 N HCl (210 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was then purified by silica gel column chromatography (EtOAc/hexane, 1:40) to afford the compound **8** (8.54 g) as a colorless oil in 95% yield.

R_f = 0.3 (EtOAc/ hexane, 1:40).

$[\alpha]_D^{28}$ = +24.6 (c =0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 9.67 (s, 1H), 7.62–7.57 (m, 4H), 7.42–7.36 (m, 6H), 7.16–7.15 (m, 2H), 7.12–7.10 (m, 2H), 4.25–4.20 (m, 1H), 3.92–3.87 (m, 1H), 2.35 (s, 3H), 1.62 (s, 3H), 1.02 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 202.1, 137.1, 135.7, 135.6, 135.3, 133.0, 129.8, 129.7, 129.4, 127.7, 127.7, 127.1, 67.8, 55.8, 26.7, 21.0 19.3, 17.6.

HRMS (ESI) for $C_{27}H_{33}O_2Si$ $[M + H]^+$, calculated: 417.2250; found: 417.2255.

(*R*)-*tert*-butyl(2-methyl-2-*p*-tolylbut-3-enyloxy)diphenylsilane (9):

To a suspension of methyltriphenylphosphonium iodide (649 mg, 1.60 mmol) in dry THF (5 mL) was added LiHMDS (1.0 M solution in THF, 1.60 mL) at 0 ºC. The yellow mixture was stirred at 0 ºC for 15 min. A solution of the aldehyde **8** (334 mg, 0.80 mmol) in 2 mL of THF was added to the reaction mixture. The yellow suspension was stirred at room temperature for further 8 h. After that the reaction was quenched with addition of water, and the layers were separated and extracted with 25 mL of ether, washed with brine. The organic solution was then dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash column chromatography (EtOAc/hexane, 1:100) to afford compound **9** (299 mg) in 90% yield as a colorless oil.

R_f = 0.6 (EtOAc/ hexane, 1:100).

$[\alpha]_D^{28}$ = +20.2 (c =0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.64–7.60 (m, 4H), 7.59–7.50 (m, 2H), 7.47–7.30 (m, 4H), 7.27 (d, 2H, *J* = 8.4 Hz), 7.16 (d, 2H, *J* = 8.4 Hz), 6.20 (dd, 1H, *J* = 10.8, 17.6 Hz), 5.21 (d, 1H, *J* = 10.8 Hz), 5.13 (d, 1H, *J* = 18.0 Hz), 3.86 (d, 1H, *J* = 9.8 Hz), 3.82 (d, 1H, *J* = 9.8 Hz), 2.38 (s, 3H), 1.52 (s, 3H), 1.06 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 144.6, 142.4, 135.7, 135.7, 135.5, 133.6, 129.5, 129.5, 128.6, 127.6, 127.6, 127.2, 113.2, 71.3, 46.5, 26.8, 22.6, 21.0, 19.4.

HRMS (ESI) for $C_{28}H_{35}OSi$ $[M + H]^+$, calculated: 415.2457; found: 415.2462.

(*R*)-2-methyl-2-*p*-tolylbut-3-enal (10):

To an ice-cooled solution of compound **9** (4.0 g, 9.6 mmol) in dry THF (20.0 mL) was added a 1 M solution of TBAF (15.0 mL, 15.0 mmol). The reaction mixture was stirred at room temperature for 12 h. After that the reaction was quenched with addition of water, THF was removed under vacuum. The content of the flask was then extracted with EtOAc, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford the crude product. The crude alcohol was used for next step without further purification.

$NaHCO_3$ (3.84 g, 40.57 mmol) was added to the solution of alcohol (1.45 g, 8.33 mmol) in 50 mL of DCM at 0 ºC, after that Dess-Martin periodinane (5.0 g, 11.18 mmol) was added to reaction mixture at the same temperature, and the reaction mixture was gradually warmed to the room temperature during 2 h. After completion of the reaction it was diluted with 60 mL of DCM. The organic part was then successively washed with 40 mL of saturated sodium thiosulfate solution, 40 mL of 5% $NaHCO_3$ and then with 60 mL of brine solution. The organic layer was then dried over anhydrous $MgSO_4$ and evaporated in vacuo to furnish the crude aldehyde. The aldehyde was subsequently purified through silica gel chromatography to afford compound **10** (1.47 g) as a colorless oil in 88% yield (for two step).

R_f = 0.6 (EtOAc/ hexane, 1:20).

$[\alpha]_D^{25}$ = +58.1 (c =1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 9.58 (s, 1H), 7.22 (d, 2H, *J* = 7.8 Hz), 7.16 (d, 2H, *J* = 7.8 Hz), 6.23 (dd, 1H, *J* = 10.8, 17.6 Hz), 5.42 (d, 1H, *J* = 10.8 Hz), 5.19 (d, 1H, *J* = 17.6 Hz), 2.37 (s, 3H), 1.55 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 199.4, 138.5, 137.2, 136.9, 129.6, 127.3, 117.1, 57.5, 20.9, 20.1.

HRMS (ESI) for $C_{12}H_{15}O$ $[M + H]^+$, calculated: 175.1123; found: 175.1129.

(*R*)-3-methyl-3-*p*-tolylpent-4-enoic acid (11):

The homologation of aldehyde **10** to acid **11** was performed through a two step sequence as followed without isolating any intermediate.

Step1: To a suspension (methoxymethyl)triphenylphosphonium chloride (5.5 g, 16.1 mmol) in dry THF (50 mL) was added *n*-butyllithium (1.6M, 10 ml, 16 mmol) at -15 ºC. After stirring for 5 min, a solution of the aldehyde **10** (418 mg, 2.4 mmol) in dry THF (8 ml) was added to the reaction mixture at the same temperature, and was stirred for 2 h at 0 ºC. After that the reaction solution was quenched with addition of water, and the layers were separated and extracted with 250 mL of ether. The organic solution was washed with brine and dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude enolether was then taken in THF (10 mL) and stirred with

1M HCl (10 mL) at room temperature for 1 h. Then the reaction mixture was diluted with ether and the layers were separated. The organic layer was washed with aqueous $NaHCO_3$ followed by brine and dried over anhydrous $MgSO_4$ and concentrated in vacuo.

Step 2: To a solution of homologated aldehyde (316 mg, 1.7 mmol) in tBuOH (8 ML) was added 2.0 M solution of 2-methylbut-2-ene (10.1 mL, 20.4 mmol) in THF, and the resulting solution was stirred at room temperature for 10 min. Freshly prepared solution of $NaClO_2$ (923 mg, 10.2 mmol) and NaH_2PO_4 (612 mg, 5.1 mmol) in water (8 mL) was added and the reaction mixture was stirred for further 2 h. After that time the reaction mixture was diluted with the addition of (20 mL) of water and extracted with EtOAc. The organic layer was then washed with brine and dried over anhydrous $MgSO_4$. The organic solution was then concentrated in vacuo to furnish the crude product, which was immediately purified through silica gel chromatography (EtOAc/hexane, 1:1) to afford acid **11** (295 mg) as a colorless oil in 60% yield (for two step).

R_f = 0.1 (EtOAc/ hexane, 1:1).

$[\alpha]_D^{25}$ = -5.2(c =1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.20 (d, 2H, *J* = 7.8 Hz), 7.13 (d, 2H, *J* = 7.8 Hz), 6.14 (dd, 1H, *J* = 10.8, 17.6 Hz), 5.14 (d, 1H, *J* = 10.8 Hz), 5.08 (d, 1H, *J* = 17.6 Hz), 2.80 (s, 2H), 2.33 (s, 3H), 1.55 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 177.1, 145.4, 143.0, 136.0, 129.1, 126.2, 112.6, 45.5, 43.0, 25.6, 21.0.

HRMS (ESI) for $C_{13}H_{17}O_2$ $[M + H]^+$, calculated: 205.1228; found: 205.1234.

(*R*)-ethyl 3-methyl-3-*p*-tolylpent-4-enoate (12):

To a solution of acid **11** (500 mg, 2.4 mmol) in DCM (2.0 mL) was added thionyl chloride (0.23 mL, 3.2 mmol). The mixture was stirred then for 2 h at room temperature, after that dry ethanol (24 mL) was added and the mixture was stirred for 4 h. The solvent was then evaporated under vacuum. The Purification of the crude product by silica gel chromatography (EtOAc/hexane, 1:5) afforded ester **12** (446 mg) as a colorless oil in 80% yield.

R_f = 0.6 (EtOAc/ hexane, 1:5).

$[\alpha]_D^{28}$ = -16.2(c =1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.21 (d, 2H, *J* = 8.2 Hz), 7.11 (d, 2H, *J* = 8.2 Hz), 6.14 (dd, 1H, *J* = 10.8, 17.2 Hz), 5.16–5.04 (m, 2H), 4.00 (q, 2H, *J* = 7.2 Hz), 2.77 (d, 1H, *J* = 3.0 Hz), 2.75 (d, 1H, *J* = 3.0 Hz), 2.34 (s, 3H), 1.54 (s, 3H) 1.11 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (50MHz, $CDCl_3$), δc: 171.4, 145.8, 143.2, 135.8, 128.9, 126.3, 112.2, 60.1, 45.9, 43.2, 25.6, 21.0, 14.2.

HRMS (ESI) for $C_{15}H_{21}O_2$ $[M + H]^+$, calculated: 233.1541; found: 233.1550.

(*R*)-ethyl 2,2,3-trimethyl-3-*p*-tolylpent-4-enoate (13):

Under N_2 atmosphere, LDA (lithium diisopropylamide, 2.5 M in THF, 10 mL) was slowly dropped to a stirred solution of **12** (1.8 g, 7.7 mmol) in THF (50 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1 h, and then MeI (2.6 mL, 39.5 mmol) was added. The reaction solution was then stirred for 8 h, and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The solution was then extracted with 80 mL of EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated. The residue was then purified through silica gel chromatography (EtOAc/hexane, 1:60) to furnish compound **13** (1.5 g) as a colorless oil in 75% yield.

R_f = 0.3 (EtOAc/ hexane, 1:60).

$[\alpha]_D^{28}$ = -71.6 (c =1.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.22 (d, 2H, *J* = 8.4 Hz), 7.08 (d, 2H, *J* = 8.4 Hz), 6.80 (dd, 1H, *J* = 11.0, 17.4 Hz), 5.17 (dd, 1H, *J* = 1.2, 11.0 Hz), 5.03 (dd, 1H, *J* = 1.2, 17.4 Hz), 3.99 (q, 2H, *J* = 7.2 Hz), 2.32 (s, 3H), 1.54 (s, 3H), 1.14 (t, 3H, *J* = 7.2 Hz), 1.12 (s, 6H).

^{13}C NMR (100MHz, $CDCl_3$), δc: 176.8, 143.7, 141.7, 135.8, 128.4, 128.1, 114.0, 60.4, 49.3, 48.4, 22.5, 21.4, 21.0, 14.1.

HRMS (ESI) for $C_{17}H_{25}O_2$ $[M + H]^+$, calculated: 261.1854; found: 261.1862.

(*R*)-2,2,3-trimethyl-3-*p*-tolylpent-4-enal (14):

To a solution of LAH (114 mg, 3.0 mmol,) in dry THF (9 mL) was added a solution of ester **13** (1.0 g, 3.84 mmol) in dry THF (6 mL) at 0 ºC. The reaction was then stirred at the same temperature for 4 h. TLC analysis indicated the disappearance of the starting material and the reaction was slowly quenched with dropwise addition of saturated sodium sulfate solution. The precipitate was then filtered off, and the filtrate was concentrated in vacuo. The crude alcohol was then used for next step without further purification.

According to the experimental procedure of compound **10**, the crude alcohol was then converted into aldehyde **14** (706 mg) by DMP oxidation in 85% yield (for two step) as a colorless oil.

R_f = 0.4 (EtOAc/ hexane, 1:20).

$[\alpha]_D^{25}$ = -44.2 (c =1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 9.59 (s, 1H), 7.19 (d, 2H, *J* = 8.0 Hz), 7.10 (d, 2H, *J* = 8.0 Hz), 6.58 (dd, 1H, *J* = 11.0, 17.4 Hz), 5.25 (d, 1H, *J* = 11.0 Hz), 5.10 (d, 1H, *J* = 17.4 Hz), 2.31 (s, 3H), 1.53 (s, 3H), 1.01 (s, 6H).

^{13}C NMR (50MHz, $CDCl_3$), δc: 207.0, 142.4, 140.8, 136.1, 128.5, 128.2, 115.1, 50.9, 47.7, 20.9, 20.8, 18.9, 18.8.

HRMS (ESI) for $C_{15}H_{21}O$ $[M + H]^+$, calculated: 217.1592; found: 217.1598.

(*R*)-4,4,5-trimethyl-5-*p*-tolylhepta-1,6-dien-3-ol (15):

Aldehyde **14** (1.7 g, 7.9 mmol) was taken in 16 mL of anhydrous THF. Solution of vinylmagnesium bromide (1.0 M in THF, 8.8 mL, 8.8 mmol) was added to it at -78 ºC. The reaction mixture was then kept at the same temperature for 2 h, after that time saturated NH_4Cl solution was added to it. The solution was then extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to afford the crude alcohol. Purification of the crude product by silica gel chromatography (EtOAc/hexane, 1:20) afforded an inseparable mixture of diastereomeric compound **15** (1.73 g) in 90% yield as a colorless oil.

R_f = 0.2 (EtOAc/ hexane, 1:20).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.37–7.31 (m, 1H), 7.29–7.26 (m, 1H), 7.10–7.09 (m, 2H), 6.98–6.90 (m, 1H), 5.89–5.80 (m, 1H), 5.18–5.02 (m, 4H), 4.18–4.11 (m, 1H), 2.31 (s, 3H), 1.00 (s, 3H), 0.76 (s, 3H), 0.71(s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$), δc: 146.0, 145.2, 142.8, 138.8, 138.4, 135.6, 135.5, 128.6, 128.6, 128.3, 116.2, 115.8, 113.2, 77.2, 76.5, 49.3, 48.7, 43.9, 43.6, 22.9, 22.6, 21.8, 20.9, 17.8, 17.3.

(*R*)-4,5,5-trimethyl-4-*p*-tolylcyclopent-2-enone (16):

Alcohol **15** (2.3 g, 9.4 mmol) was taken in anhydrous degassed DCM (800 mL). A catalytic amount (5 mol%) of 1st generation Grubbs' catalyst was then added to it and the solution was stirred at reflux for 4 h. The reaction mixture was then cooled to room temperature and solution was evaporated under reduced pressure. The content of the flask was then passed through a short silica gel bed to furnish the diastereomeric cyclic alcohol (1.9 g), which was pure enough to use in the next reaction without any further purification.

$NaHCO_3$ (3.6 g, 43.6 mmol) was added to the solution of alcohol (1.9 g, 8.8 mmol) in 50 mL of DCM at 0 ºC, after that Dess-Martin periodinane (4.8 g, 11.3 mmol) was added to reaction mixture at the same temperature, and the reaction mixture was gradually warmed to the room temperature during 2h. After completion of the reaction it was diluted with 250 mL of DCM. The organic part was then successively washed with 80 mL of saturated sodium thiosulfate solution, 80 mL of 5% $NaHCO_3$ and then with 60 mL of brine solution. The organic layer was then dried over anhydrous $MgSO_4$ and evaporated in vacuo. The residue was then purified by silica gel chromatography (EtOAc/hexane, 1:20) to afford cyclic ketone **16** (1.71 g) as a colorless oil in 85% yield (for two step).

R_f = 0.4 (EtOAc/ hexane, 1:20).

$[\alpha]_D^{28}$ = -32.6 (c =0.5, CH_3COCH_3).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.74 (d, 1H, *J* = 6.0 Hz), 7.14 (d, 2H, *J* = 8.0 Hz), 7.06 (d, 2H, *J* = 8.0 Hz), 6.22 (d, 1H, *J* = 6.0 Hz), 2.33 (s, 3H), 1.45 (s, 3H), 1.18 (s, 3H), 0.58 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$), δc: 215.1, 169.1, 140.5, 136.6, 129.4, 129.2, 126.9, 54.7, 51.8, 26.6, 26.0, 21.1, 20.2.

HRMS (ESI) for $C_{15}H_{19}O$ $[M + H]^+$, calculated: 215.1436; found: 215.1440.

(*R*)-2,2,3-trimethyl-3-*p*-tolylcyclopentanone (1):

A stirred solution of cyclopentenone **16** (100 mg, 0.47 mmol) and 50 mg of 10% Pd/C in 4 mL of ethyl acetate was stirred under hydrogen atmosphere (3 atm, in a Parr hydrogenation apparatus) for 3 h. The solution was then filtered through a short pad of silica gel and the solution was concentrated in vacuo. The residue was then purified by silica gel column chromatography (EtOAc/hexane, 1:10) to afford cuparenone **1** (96.5 mg) in 95% yield as a solid. R_f = 0.5 (EtOAc/ hexane, 1:10).

$[\alpha]_D^{25}$ = -160.2 (c =0.4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.29 (d, 2H, *J* = 8.0 Hz), 7.17 (d, 2H, *J* = 8.0 Hz), 2.70–2.60 (m, 1H), 2.58–2.41 (m, 2H), 2.38 (s, 3 H), 1.95–1.89 (m, 1H), 1.27 (s, 3 H), 1.20 (s, 3 H), 0.62 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 222.6, 141.9, 135.8, 128.9, 126.4, 53.2, 48.3, 33.8, 29.7, 25.3, 22.1, 20.8, 18.4.

HRMS (ESI) for $C_{15}H_{21}O$ $[M + H]^+$, calculated: 217.1592; found: 217.1599.

(*S*)-1-methyl-4-(1,2,2-trimethylcyclopentyl)benzene (3):

A mixture of the ketone **1** (480 mg, 2.2 mmol), hydrazine hydrate (7.0 mL, 99%), hydrazine dihydrochloride (1.9 g) and diethylene glycol (20 mL) was heated to 125 °C in an inert atmosphere and kept at that temperature for 2 h. The reaction mixture was then cooled to 80 °C and solid pellets of potassium hydroxide (3.2 g) were added. The temperature was gradually raised to 210 °C by distilling off low boiling materials. The reaction mixture was maintained at 210-220 °C for further 3 h. The reaction solution was then cooled, poured into water (30 mL), and extracted with ether (3 x 60 mL). The distillate containing the low boiling materials was also diluted with water (25 mL) and extracted with ether (3 x 40 mL). The combined ethereal extract was washed with cold dilute hydrochloric acid (30 mL, 3N), water (2 x 50 mL). The organic extract was then dried over $MgSO_4$ and the filtrate was concentrated in vacuo. The residue was

then purified by silica gel column chromatography (EtOAc/hexane, 1:100) to afford (*S*)-cuparene **3** (356 mg) as a colorless oil, in 80% yield.

R_f = 0.7 (EtOAc/ hexane, 1:100).

$[\alpha]_D^{28}$ = -60.5 (c =0.4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.25 (d, 2H, *J* = 8.0 Hz), 7.09 (d, 2H, *J* = 8.0 Hz), 2.51–2.48 (m, 1H), 2.32 (s, 3H), 1.81–1.79 (m, 2H), 1.77–1.70 (m, 2H), 1.58–1.54 (m, 1H), 1.26 (s, 3H), 1.06 (s, 3H), 0.56 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 144.5, 134.7, 128.1, 126.9, 50.2, 44.1, 39.7, 36.8, 26.4, 24.3, 24.2, 20.8, 19.7.

HRMS (ESI) for $C_{15}H_{23}$ $[M + H]^+$, calculated: 203.1800; found: 203.1807.

(*R*)-4-(*tert*-butyldiphenylsilyloxy)-3-methyl-3-*p*-tolylbutan-2-one (17):

Aldehyde **8** (2.2 g, 5.2 mmol) was taken in 16 mL of anhydrous diethylether. Solution of methyllithium (3.0 M in diethoxymethane, 1.9 mL, 5.72 mmol) was added to it at 0 ºC. The reaction mixture was kept at the same temperature for 2 h, after that time saturated NH_4Cl solution was added to it. The solution was then extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to afford the crude alcohol this alcohol was used for next step without further purification.

$NaHCO_3$ (1.9 g, 22.85 mmol) was added to the solution of alcohol (1.97 g, 4.6 mmol) in 22 mL of DCM at 0 ºC, after that Dess-Martin periodinane (2.5 g, 5.9 mmol) was added to reaction mixture at the same temperature. The reaction mixture was gradually warmed to the room temperature during 2 h. After completion of the reaction it was diluted with 150 mL of DCM. The organic part was then successively washed with 40 mL of saturated sodium thiosulfate solution, 40 mL of 5% $NaHCO_3$ and then with 30 mL of brine solution. The organic layer was then dried over anhydrous $MgSO_4$ and evaporated in vacuo. Purification by flash column chromatography (EtOAc/hexane, 1:15) afforded ketone **17** (1.82 g) as a colorless oil in 81% yield (for two step).

R_f = 0.4 (EtOAc/ hexane, 1:15).

$[\alpha]_D^{28}$ = +28.5 (c = 0.4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.65–7.62 (m, 2H), 7.51–7.50 (m, 2H), 7.48–7.40 (m, 4H), 7.39–7.31 (m, 2H), 7.13 (d, 2H, *J* = 8.0 Hz), 7.06 (d, 2H, *J* = 8.0 Hz), 4.22 (d, 1H, *J* = 10.0 Hz), 3.89 (d, 1H, *J* = 10.0 Hz), 2.34 (s, 3H), 2.00 (s, 3H), 1.61 (s, 3H) 1.01 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 209.9, 137.9, 136.7, 135.6, 135.6, 133.3, 133.1, 129.6, 129.5, 129.3, 127.6, 127.5, 126.4, 68.9, 57.5, 26.7, 26.2, 20.9, 20.4, 19.3

HRMS (ESI) for $C_{28}H_{35}O_2Si$ $[M + H]^+$, calculated: 431.2406; found: 431.2430.

(*R*)-*tert*-butyl(2,3-dimethyl-2-*p*-tolylbut-3-enyloxy)diphenylsilane (18):

To a suspension consisting of Mg (192 mg, 8 mmol), $TiCl_4$ (379 mg, 0.21 mL, 2 mmol), and DCM (4 mL) was added a solution of ketone **17** (430.65 mg, 1 mmol) in DCM (3 mL) and THF (2 mL) at 0°C. After being stirred for 30 min at 0 ºC, the resulting green-black mixture was stirred for an additional 1 h at room temperature. The reaction mixture was cooled to 0 ºC and saturated potassium carbonate solution (10 mL) was added and the mixture was diluted with ether (20 mL). The organic layer was separated and washed with brine. The organic extract was then dried over $MgSO_4$, and the filtrate was evaporated in vacuo. Purification by flash column chromatography (EtOAc/hexane, 1:80) afforded compound **18** (258 mg) as a colorless oil in 60% yield.

R_f = 0.6 (EtOAc/ hexane, 1:80).

$[\alpha]_D^{25}$ = -10.5 (c =1.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.57–7.55 (m, 2H), 7.46–7.40 (m, 2H), 7.39–7.29 (m, 6H), 7.14 (d, 2H, *J* = 8.2 Hz), 7.07 (d, 2H, *J* = 8.2 Hz), 4.95–4.91 (m, 2H), 3.87 (d, 1H, *J* = 9.4 Hz), 3.83 (d, 1H, *J* = 9.4 Hz), 2.32 (s, 3H), 1.57 (s, 3H), 1.50 (s, 3H) 1.01 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 149.4, 142.0, 135.7, 135.3, 133.7, 133.6, 129.5, 129.4, 128.6, 127.5, 127.4, 127.0, 125.5, 111.0, 70.4, 49.0, 26.8, 22.9, 20.9, 20.5, 19.3.

HRMS (ESI) for $C_{29}H_{37}OSi$ $[M + H]^+$, calculated: 429.2613; found: 429.2619.

(*R*)-2,3-dimethyl-2-*p*-tolylbut-3-en-1-ol (19):

To an ice-cooled solution of compound **18** (100 mg, 0.23 mmol) in dry THF (1.0 mL) was added a 1 M solution of TBAF (0.3 mL, 0.3 mmol). The reaction mixture was stirred at room temperature for 12 h. After that time the reaction was quenched with addition of water. The content of the flask was then extracted with EtOAc, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (EtOAc/hexane, 1:5) afforded compound **19** (38.5 mg) in 88% yield as a colorless oil.

R_f = 0.4 (EtOAc/ hexane, 1:5).

$[\alpha]_D^{25}$ = +40.4 (c =1.2, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 7.19–7.14 (m, 4H), 5.08 (s, 1H), 4.98 (s, 1H), 3.89 (d, 1H, *J* = 10.5 Hz), 3.84 (d, 1H, *J* = 10.5 Hz), 2.34 (s, 3H), 1.58 (s, 3H) 1.24 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$), δc: 148.9, 141.1, 135.9, 129.1, 126.7, 112.0, 69.1, 49.1, 22.8, 20.9, 20.3.

HRMS (ESI) for $C_{13}H_{19}O$ $[M + H]^+$, calculated: 191.1436; found: 191.1440.

(*R*)-3,4-dimethyl-3-p-tolylpent-4-enal (20):

$NaHCO_3$ (384 mg, 4.57 mmol) was added to the solution of alcohol (175 mg, 0.92 mmol) in 5 mL of DCM at 0 ºC, after that Dess-Martin periodinane (500 mg, 1.18 mmol) was added to reaction mixture at the same temperature, and the reaction mixture was gradually warmed to the room temperature during 2 h. After completion of the reaction it was diluted with 30 mL of DCM. The organic part was then successively washed with 8 mL of saturated sodium thiosulfate solution, 8 mL of 5% $NaHCO_3$ and then with 6 mL of brine solution. The organic layer was then dried over anhydrous $MgSO_4$ and evaporated in vacuo to furnish the aldehyde.

The crude aldehyde was then used for next step without further purification. In next step according to the experimental procedure for homologation, as described in the experimental part of compound **11**, crude aldehyde (159 mg, 0.84 mmol), was converted into homologated aldehyde **20** (121 mg) as a colorless oil in 65% yield (overall yield for two step).

R_f = 0.5 (EtOAc/ hexane, 1:10).

$[\alpha]_D^{25}$ = +55.1 (c =1.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 9.56 (s, 1H), 7.25–7.08 (m, 4H), 5.02–5.01 (m, 2H), 2.80 (s, 2H), 2.38 (s, 3H) 1.62 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 203.6, 149.9, 142.4, 136.2, 129.2, 126.1, 111.7, 52.2, 45.3, 26.0, 21.0, 20.0.

HRMS (ESI) for $C_{14}H_{19}O$ $[M + H]^+$, calculated: 203.1436; found: 203.1442.

(*R*)-5,6-dimethyl-5-p-tolylhepta-1,6-dien-3-ol (21):

Compound **20** (500 mg, 2.5 mmol) was then converted to its corresponding alcohol **21** (496 mg) as a colorless oil in 86% yield in a similar way as described for the synthesis of compound **15**.

R_f = 0.4 (EtOAc/ hexane, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.19–7.10 (m, 4H), 5.90–5.84 (m, 1H), 5.17 (dd, 1H, *J* = 5.8, 17.0 Hz), 5.08–5.01 (m, 3H), 4.18 (s, 1H), 2.32 (s, 3H), 2.19–2.14 (m, 2H), 1.56 (s, 3H), 1.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 152.8, 151.3, 144.1, 143.9, 142.2, 142.0, 135.8, 135.6, 129.3, 129.1, 126.5, 126.3, 113.7, 113.6, 111.3, 70.6, 70.6, 46.5, 46.4, 46.3, 45.8, 26.1, 25.7, 21.0, 20.6, 20.3.

(*R*)-3,4-dimethyl-4-p-tolylcyclopent-2-enone (22):

Alcohol **21** (400 mg, 1.73 mmol) was then converted to cyclic ketone **22** (285 mg) as a colorless oil in 82% yield in similar way as described for the synthesis of compound **16**.

R_f = 0.2 (EtOAc/ hexane, 1:5).

$[\alpha]_D^{25}$ = +210 (c =0.4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.14–7.09 (m, 4H), 6.02 (s, 1H), 2.65 (d, 1H, *J* = 18.8 Hz), 2.53 (d, 1H, *J* = 18.8 Hz), 2.32 (s, 3H), 1.82 (s, 3H), 1.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$), δc: 208.8, 184.9, 141.3, 136.4, 130.3, 129.5, 125.7, 54.5, 50.0, 23.8, 21.0, 15.1.

HRMS (ESI) for $C_{14}H_{17}O$ $[M + H]^+$, calculated: 201.1279; found: 201.1284.

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