

# The First Synthesis of *p*-Cl- and *p*-F-Phenylverbenene

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**Abstract:** The first synthesis of 4'-X-phenylverbenene (X = F and Cl) via reaction of myrtenal with 4'-X phenylmagnesium bromide and Bi(NO<sub>3</sub>)<sub>3</sub> is described. Verbenene is formed due to the electron-withdrawing effect of the 4'-electronegative group, either fluorine or a Cl-Bi complex.

**Keywords:** Myrtenal, verbenene, bismuth nitrate, pinane, lewis acid.

In recent years, bismuth compounds have attracted great interest in organic synthesis. Although their chemistry is not well known, bismuth salts have been widely used as Lewis acids to catalyze numerous reactions, mainly functional group deprotections, oxidations, reductions, rearrangements and C-C bond formation [1]. The last of these reactions can be achieved by Friedel-Crafts acylation, aldolic and Knoevenagel condensations, Diels-Alder cycloaddition, and Michael addition, to mention just a few possibilities [2]. Recently, bismuth has also been used in the chemistry of natural products [3]. Studies on the chemistry of natural products of pinene derivatives have increased in recent years because of the wide biological activity that this group of compounds presents. One of these derivatives is verbenene **2** (Fig. 1), which is found as a secondary metabolite in many medicinal plants and has been investigated as a beetle attractor [4, 5]. Verbenene has also been used in the study of cycloadditions on account of its restricted stereochemistry and can also be viewed as a precursor in the formal synthesis of verbenone, which can provide a possible starting point in the synthesis of the A ring of taxol and other interesting compounds [6-10]. Verbenene has been synthesized through an electron transfer from  $\alpha$ - or  $\beta$ -pinene to 2,3,5,6-tetrachlorobenzoquinone on sensitized irradiation where a radical cation rapidly deprotonates to give verbenene with retention of chirality [11].

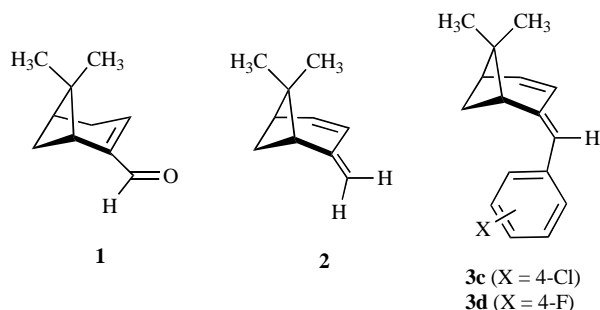


Fig. (1).

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To study the mechanism of bismuth-catalyzed additions to double bond carbonyl-activated systems, in the present work we examined the addition of Grignard reagents to myrtenal **1** catalyzed by Bi(NO<sub>3</sub>)<sub>3</sub>. We found no difference in diastereoselectivity, but surprisingly observed the production of phenylverbenenes **3c** and **3d** in good yield when 4'-Cl- or 4'-F-phenylmagnesium bromide was added at 0°C (Scheme 1). Under the same conditions but in the presence of methyl iodide, alcohols **4** and **5** (**c** and **d**) give **3** (**c** and **d**) respectively) in 98% yield (Scheme 1).

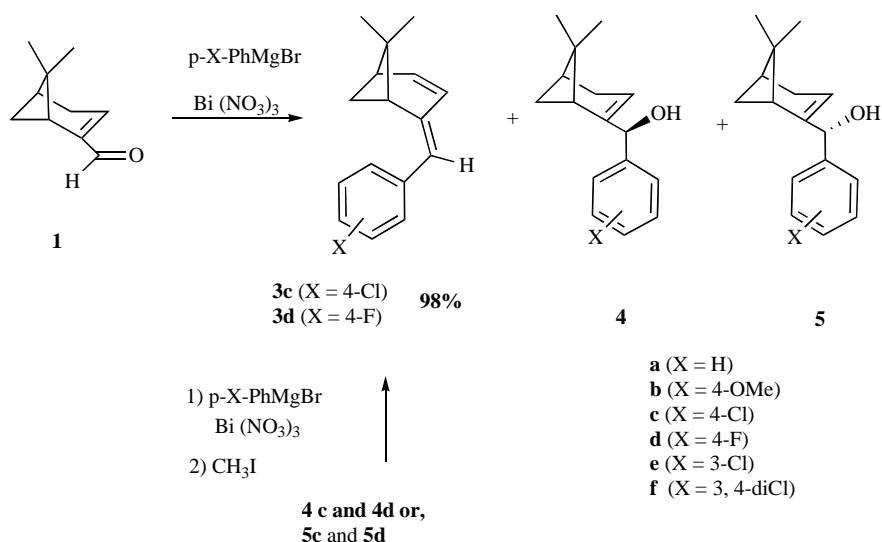
## RESULTS AND DISCUSSION

We used (1*R*)-(-)-myrtenal as a model system because some of its derivatives are good chiral auxiliaries that induce high enantiomeric excess because of the conformational restriction that is present in the bicyclic system [12-16]. Results of the addition of 4'-MeO-, 4'-Cl- or 4'-F-PhMgBr to myrtenal in the presence or absence of bismuth(III) nitrate at three temperatures (0°C, 25°C and reflux) are listed in Table 1.

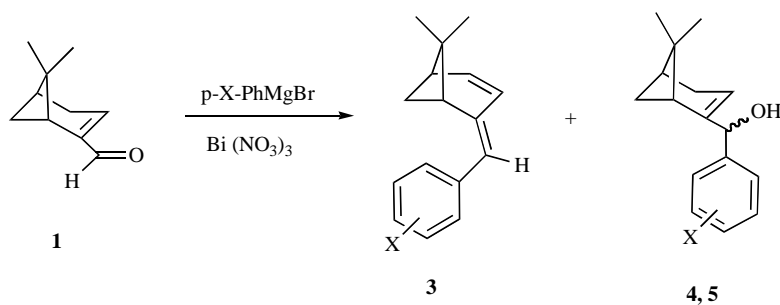
The results show no significant difference in diastereoselectivity among the various reactions, and the bismuth salt does not have any effect on the reaction. Although no significant diastereoisomeric excess was observed, an unexpected product was obtained in good yield in entries 5, 7 and 8 at 0°C. These compounds, which have not been previously reported, were characterized as the phenylverbenenes **3c** (entry 5) and **3d** (entries 7 and 8); the spectroscopic data of these compounds correlated with those recorded for their verbenene parent [17] (Table 2).

The <sup>1</sup>H NMR resonances of **3c** and **3d** were examined by NOESY, it is important to mention that only the (*Z*)-isomer was detected and isolated in the crude reaction mixture.

To see the effect of the bismuth salt as a Lewis acid, myrtenal was reacted with the MCl<sub>x</sub> salts shown in Table 3. From the results, it is clear that a Lewis acid was necessary, although the best results were obtained when the bismuth salt was present. The improvement obtained when bismuth was present may be due to its high affinity for chlorine, as has been shown in many x-ray structures of chloride derivatives [18].

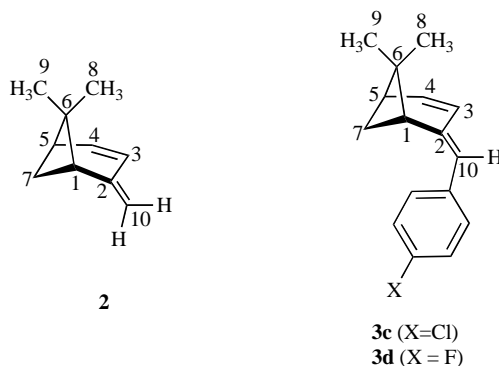


Scheme 1. Addition of Grignard reagents to myrtanal.

Table 1. Yields from the Addition of Grignard Reagents to Myrtanal in the Presence and Absence of Bi(NO<sub>3</sub>)<sub>3</sub> in Different Conditions

Entry	X-	0° C		25° C		Reflux Temperature		
		Bi(NO <sub>3</sub> ) <sub>3</sub> Equiv.	Yield 3 (%)	Yield <sup>a</sup> 4:5 (%)	Yield 3 (%)	Yield <sup>a</sup> 4:5 (%)	Yield 3 (%)	Yield <sup>a</sup> 4:5 (%)
1	H	0.05	--	(34:66)	--	(38:62)	--	(37:63)
2	H	-	--	(34:66)	--	(38:62)	--	(35:65)
3	4'-MeO-	0.05	--	(32:68)	--	(36:64)	--	(34:66)
4	4'-MeO-	-	--	(38:62)	--	(40:60)	--	(36:64)
5	4'-Cl-	0.05	<b>3c</b> (52)	--	--	(31:69)	--	(39:61)
6	4'-Cl-	-	--	(20:80)	--	(33:67)	--	(31:69)
7	4'-F-	0.05	<b>3d</b> (59)	(25:16)	--	(30:70)	--	(33:67)
8	4'-F-	-	<b>3d</b> (57)	--	--	(31:69)	--	(38:62)
9	3'-Cl-	0.05	--	(31:69)	--	b	--	b
10	3'-Cl-	-	--	(25:75)	--	b	--	b
11	3',4'-diCl	0.05	--	(32:68)	--	b	--	b
12	3',4'-diCl	-	--	(42:58)	--	b	--	b

<sup>a</sup>Isolated yield of purified product <sup>b</sup>No reaction product was detected and all of the starting material was recovered.

**Table 2.** Comparison of the NMR Spectroscopic Data of Compounds **2**, **3c** and **3d**

	<sup>13</sup> C			<sup>1</sup> H		
	<b>2</b>	<b>3c</b>	<b>3d</b>	<b>2</b>	<b>3c</b>	<b>3d</b>
<b>C<sub>1</sub></b>	43.7	45.6	45.5	2.65	3.27	3.27
<b>C<sub>2</sub></b>	150.3	145.3	144.6	---	---	---
<b>C<sub>3</sub></b>	126.7	128.3	128.3	6.03	6.08	6.09
<b>C<sub>4</sub></b>	138.4	138.6	138.2	6.32	6.40	6.38
<b>C<sub>5</sub></b>	42.9	43.4	43.3	2.31	2.36	2.36
<b>C<sub>6</sub></b>	51.9	53.6	53.5	---	---	---
<b>C<sub>7</sub></b>	36.1	36.3	36.2	H <sub>ax</sub> 1.50 H <sub>eq</sub> 2.55	H <sub>ax</sub> 1.55 H <sub>eq</sub> 2.53	H <sub>ax</sub> 1.55 H <sub>eq</sub> 2.50
<b>C<sub>8</sub></b>	22.3	22.5	22.6	0.86	0.95	0.95
<b>C<sub>9</sub></b>	26.3	26.4	26.4	1.36	1.39	1.40
<b>C<sub>10</sub></b>	107.2	122.2	128.3	4.67	6.21	6.23
<b>C<sub>Ar</sub></b>	---	136.2 131.7 129.1 128.5	130.0 130.1 133.7	---	7.18 7.26	6.98 7.13

Studies have shown that fluorine forms a weak complex with bismuth [18]. These data, in combination with the fact that fluorine induces the formation of **3** with or without a Lewis acid, indicated to us that it is the inductive effect that directs the course of the reaction in the case of chlorine, presumably by the interaction of the halogen with bismuth. To establish that bismuth plays no other role than electron withdrawal, it is important to emphasize that there was no difference in the diastereoselectivity in the formation of the alcohols. Given the high oxophilicity of the group IV and V transition metals, Bi-oxo ligands could be involved in the obtaining of **3**, however as mentioned **3d** is obtained without Bi. This suggested that the mode of interaction of the bismuth-mediated process is different, in agreement with other works, from that considering oxophilicity of the bismuth. [19, 20] This indicates that the metal is separated from the carbonyl group and that its role only involves interaction with the chloride.

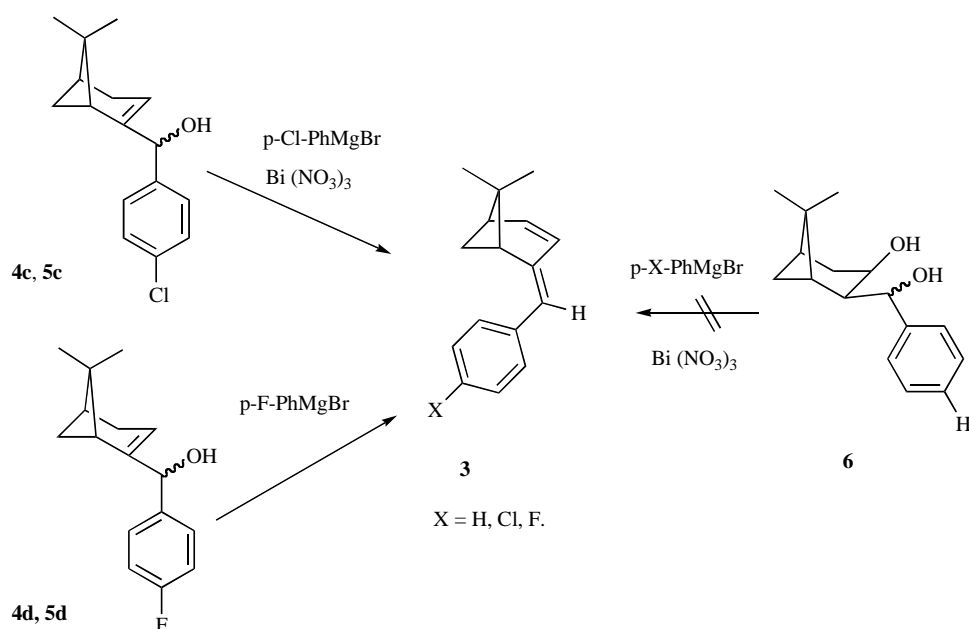
In view of the fact that phenylverbenene could result from a dehydration of the precursor alcohol or of a possible

diol intermediate, we explored the reaction of alcohols **4** and **5** as well as diol **6**, as shown in Scheme 2. Although the diol **6** was not detected in the reaction mixture, it is possible that it was present as an undetectable intermediate.

**Table 3.** Proportion of Compounds **3c** : **4c** : **5c**

Lewis Acid <sup>a</sup>	<b>3c</b> (%) <sup>b</sup>	<b>4c:5c</b> (%) <sup>b</sup>
Bi(NO <sub>3</sub> ) <sub>3</sub>	95	0
BiCl <sub>3</sub>	96	0
LiCl	13	32:68
ZnCl <sub>2</sub>	3	29:71
AlCl <sub>3</sub>	0	33:67
-----	0	20:80

<sup>a</sup>0.05 eq of Bi(NO<sub>3</sub>)<sub>3</sub> was used. <sup>b</sup>As detected from <sup>1</sup>H NMR of the crude reaction mixture.



**Scheme 2.** Addition of Grignard reagents to myrtenols in the presence of  $\text{Bi}(\text{NO}_3)_3$ .

The diastereoisomeric mixtures reacted to give the corresponding phenylverbenenes, with only the (*Z*) isomer being observed. However, no reaction product was detected when **6** was reacted with a Grignard reagent and/or bismuth salt.

The above observations can be summarized as follows: 1. Bismuth does not interact with carbonyl, 2. Only the (*Z*)-isomer was observed, 3. A dehydration of a possible diol is not involved, 4. The alcohols **4** and **5** react slowly to give **3c** and **3d** under appropriate reaction conditions, 5. A Lewis acid is necessary when  $p\text{ClPhMgBr}$  is used. And 6.  $p\text{-F-phenylmagnesium bromide}$  reacts to give **3d** without a Lewis acid. The above data suggest two possible mechanisms for the formation of **3**. As shown in Scheme 3, we suggest that in the initial step, addition of the Grignard reagent proceeds as expected by a 1,2-addition. Two pathways are therefore possible, which we designate A and B.

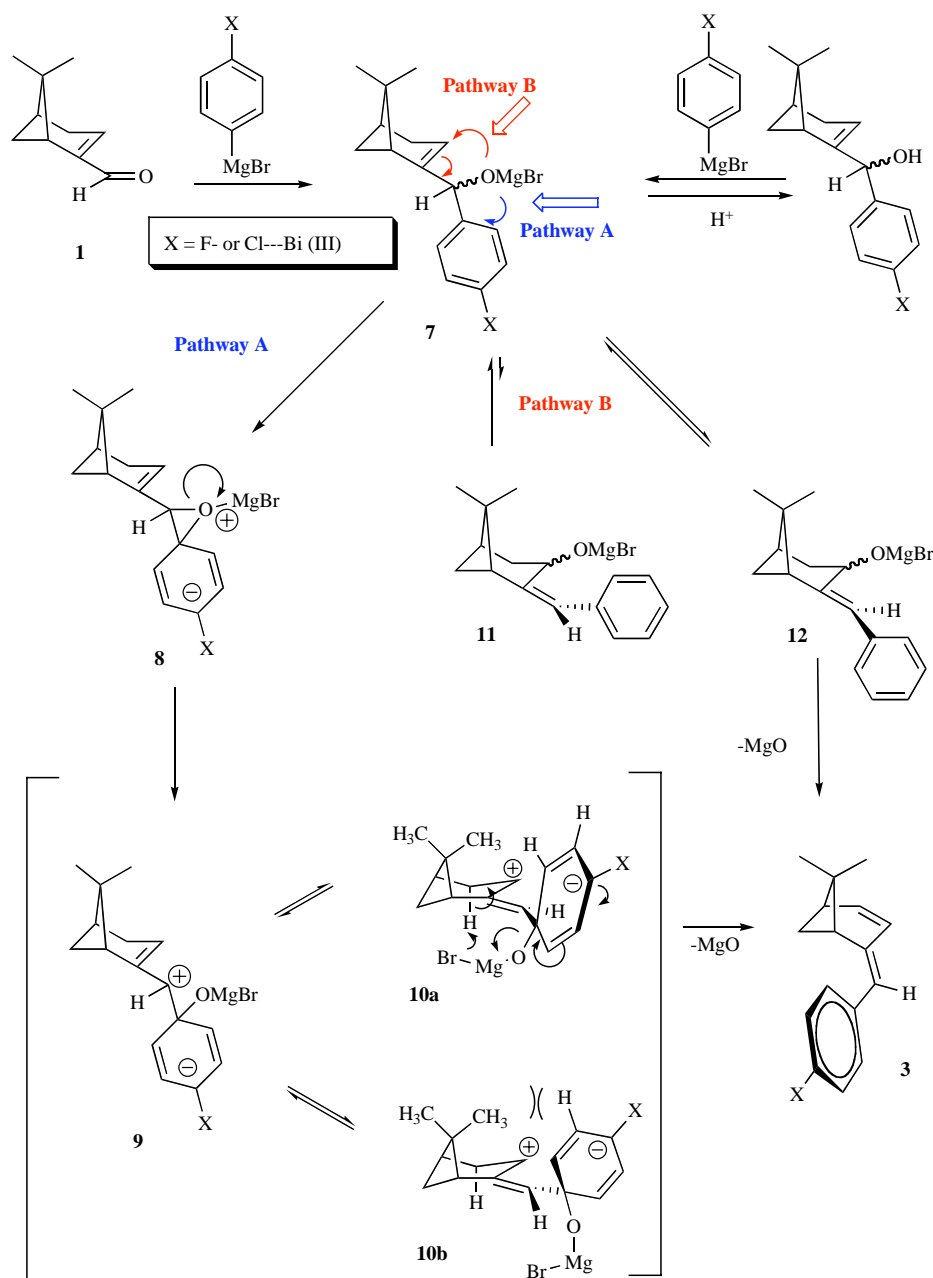
Pathway A involves a temporary loss of aromaticity of the phenyl ring. Due to the effect of the electronegative 4'-F or the 4'-Cl complexed to  $\text{Bi}(\text{III})$ , a positive electron density on C-1' allows a nucleophilic attack, generating an oxirane intermediate and breaking the aromaticity of the benzene ring, which is opened by the neighboring double bond assisted by the magnesium cation, leading to the formation of the intermediate carbocation **9**.

A recent theoretical study on 4'-F-phenylbornane derivatives, which established a long-distance effect of the fluorine to stabilize an allylic carbocation where the charge is far from the aromatic ring, supports our proposal that the positive charge is far from the 4'-Cl-Bi or F-phenyl [21]. Intermediate **9** is then able to produce two geometrical isomers, **10a** and **10b**, but for steric reasons the former is preferred. This explains why the (*Z*)-isomer is the only one observed in the reaction. Finally, a 1,2 elimination, where bromide ion behaves as a base, recovers the aromaticity and produces the diene **3**. Deoxygenation of endoxides with the elimination of magnesium oxide, using Grignard reagents, has been documented to give double bonds because of the

highly activated metallic Mg that is present, which is formed by an excess of organometallic agent to give the biphenyl Wurtz-like product explained by the Schlenk equilibrium [20]. As was expected from the proposed mechanism, the 3'-Cl-phenylmagnesium bromide compound could not produce the diene because it does not have the same ability to stabilize the positive charge at C-1' as the 4'-Cl. Contrary to expectations, however, the 3',4'-dichlorophenylmagnesium bromide did not give **3**. A possible explanation is that the presence of the meta-chlorine stabilizes the positive charge by resonance, so that the allylic carbocation cannot be formed and the positive charge is then stabilized on the aromatic ring. This effect results in a low reactivity, as can be seen in entries 9–12 in Table 1.

The second possible mechanism (Pathway B) also involves an oxygen transposition to C-3 with migration of the double bond, to give the sterically unstable compound **11** and the favored compound **12**, and then a deoxygenation gives phenylverbenene. In this mechanism, there is not loss of aromaticity, suggesting that this pathway would be energetically favored over pathway A. However we failed to isolate alcohols from **11** or **12**, although the crude reaction gave NMR signals that appeared to arise from the expected intermediates. We attempted to capture the alcohols by methylating them with methyl iodide at the end of the reaction; to our surprise, however, the methyl ethers were not found but the corresponding phenyl verbenenes were obtained in high yields.

It is noteworthy that the change in behavior of chlorine depending on whether bismuth is present, from a low electron-withdrawing group capable of donating electrons to a high electron-withdrawing group incapable of donating electrons, indicates that bismuth is a useful agent for temporarily protecting or inverting the reactivity of chlorine, for example in aromatic nucleophilic substitution reactions. This feature, the generalization of the method, and the role of methyl iodide are currently under study.



**Scheme 3.** Suggested mechanism for the formation of **3c** and **3d**.

## EXPERIMENTAL

### General Information

Reactions were carried out under nitrogen atmosphere. Solvents were previously distilled and dried. Column chromatography purifications were done using gel silica Merck de 70-230 mesh. NMR  $^1\text{H}$  spectra were run in a Varian Gemini 200 and Mercury 400 using  $\text{CDCl}_3$  as a solvent. Chemical shifts are given in ppm relative to TMS as an internal reference. Mass spectra were run in a Hewlett Packard 5989B. Optical rotations were measured at 589 nm using a 1 dm cell on a polarimeter 341 Perkin-Elmer.

### Preparation of **4** and **5** Typical Procedure

*p*-ClPhMgBr (2.2 ml; 2.2 mmol; 2.2 eq) were added to a solution of myrtenal (150 mg, 1 mmol, 1 eq) in 1 ml of THF

and the reaction mixture maintained at  $0^\circ\text{C}$  for 1 hour. The reaction is monitored by TLC and the reaction washed with  $\text{NH}_4\text{Cl}$  saturated solution and dried under  $\text{MgSO}_4$  anhydrous. Evaporation of the solvent gave a yellow oil that was subjected to column chromatography on silica gel eluted with hexane – ethyl acetate 90 : 10 to give pure **4c** and **5c**.

### (*S*) - (4-chlorophenyl) - [(1*R*), 6, 6 - dimethylbicyclo [3.1.1] hept-2-en-2-yl]methanol (**4c**)

Colorless oil  $^1\text{H}$  RMN ( $\text{CDCl}_3$ ):  $\delta$  7.26 (m, 4H, H-Ar), 5.61 (m, 1H, H-3), 5.12 (d, 1H, H-10,  $J = 1.6$  Hz), 2.30 (m, 2H, H-4), 2.29 (m, 1H,  $H_{eq}$ -7), 2.07 (m, 1H, H-5), 2.05 (m, 1H, H-1), 1.80 (d, 1H, OH,  $J = 3.3$  Hz), 1.20 (s, 3H, H-9), 1.05 (d, 1H,  $H_{ax}$ -7,  $J = 8.6$  Hz), 0.71 (s, 3H, C-8);  $^{13}\text{C}$  RMN:  $\delta$  149.09 (C-2), 128.22, 128.18, 127.96 (C-Ar), 119.59 (C-3), 75.94 (C10), 42.00 (C-1), 40.55 (C-5), 37.63 (C-6), 31.89

(C-7), 31.20 (C-4), 25.89 (C-9), 21.24 (C-8); MS(EI, 70eV)  $m/z = 262[M^+]$ ,  $[\alpha]_D^{20} = -24.07$  ( $c = 0.1$ ,  $CHCl_3$ ).

**(R)- (4-chlorophenyl) - [(1R) 6, 6 - dimethylbicyclo [3.1.1] hept-2-en-2-yl]methanol (5c)**

Colorless oil  $^1H$  RMN ( $CDCl_3$ ):  $\delta$  7.26 (m, 4H, H-Ar), 5.60 (m, 1H, H-3), 5.09 (s, 1H, H-10), 2.32 (m, 2H, H-4), 2.26 (m, 1H,  $H_{eq-7}$ ), 2.07 (m, 1H, H-1), 2.05 (m, 1H, H-5), 1.89 (d, 1H, OH,  $J = 3.1$  Hz), 1.13 (d, 1H,  $H_{ax-7}$ ,  $J = 8.6$  Hz), 1.16 (s, 3H, H-9), 0.57 (s, 3H, H-8);  $^{13}C$  RMN:  $\delta$  149.17 (C-2), 139.35, 133.01, 129.44, 128.24 (C-Ar), 118.76 (C-3), 76.43 (C-10), 41.90 (C-1), 40.65 (C-5), 37.64 (C-6), 31.70 (C-7), 31.15 (C-4), 25.92 (C-9), 20.95 (C-8) MS (EI, 70 eV)  $m/z = 262 [M^+]$ ,  $[\alpha]_D^{20} = -13.273$  ( $c = 0.1$ ,  $CHCl_3$ ).

**(S)-[(1R)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl] (4-fluorophenyl)methanol (4d)**

Colorless oil  $^1H$  RMN ( $CDCl_3$ ):  $\delta$  7.29 (m, 2H, H-Ar), 6.99 (m, 2H, H-Ar), 5.60 (m, 1H, H-3), 5.11 (s, 1H, H-10), 2.31 (m, 1H, H-4), 2.29 (m, 1H,  $H_{eq-7}$ ), 2.07 (m, 1H, H-5), 2.05 (m, 1H, H-1), 1.86 (d, 1H, OH,  $J = 2.9$  Hz), 1.19 (s, 3H, H-9), 1.07 (d, 1H,  $H_{ax-7}$ ,  $J = 8.6$  Hz), 0.72 (s, 3H, H-8);  $^{13}C$  RMN:  $\delta$  163.18, 160.74, 127.96, 127.88, 114.94, 114.73 (C-Ar), 149.31 (C-2), 119.00 (C-3), 75.93 (C-10), 42.09 (C-1), 40.56 (C-5), 37.62 (C-6), 31.84 (C-7), 31.17 (C-4), 25.90 (C-9), 21.21 (C-8) MS (EI 70 eV)  $m/z = 246[M^+]$ ,  $[\alpha]_D^{20} = -27.718$  ( $c = 0.185$ ,  $CHCl_3$ ).

**(R)-[(1R)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl] (4-fluorophenyl)methanol (5d)**

Colorless oil  $^1H$  RMN ( $CDCl_3$ ):  $\delta$  7.28 (m, 2H, H-Ar), 7.00 (m, 2H, H-Ar), 5.61 (m, 1H, H-3), 5.09 (s, 1H, H-10), 2.35 (m, 2H, H-4), 2.33 (m, 1H,  $H_{eq-7}$ ), 2.07 (m, 1H, H-1), 2.04 (m, 1H, H-5), 1.89 (d, 1H, OH,  $J = 2.6$  Hz), 1.16 (s, 3H, H-9), 1.13 (d, 1H,  $H_{ax-7}$ ,  $J = 8.6$  Hz), 0.58 (s, 3H, H-8);  $^{13}C$  RMN:  $\delta$  163.32, 160.89, 128.26, 128.18, 115.01, 114.80 (C-Ar), 149.39 (C-2), 118.31 (C-3), 76.41 (C-10), 41.96 (C-1), 40.67 (C-5), 37.64 (C-6), 31.67 (C-7), 31.13 (C-4), 25.94 (C-9), 20.92 (C-8) MS (EI, 70 eV)  $m/z = 246[M^+]$ ,  $[\alpha]_D^{20} = -25.311$  ( $c = 0.1$ ,  $CHCl_3$ ).

**(4Z, 5R) - 4- (4 - chlorobenzylidene) - 6, 6 - dimethyl bicyclo [3.1.1]hept-2-ene (3c) (Pocedure with methyl iodide from 4c and 5c)**

$Bi(NO_3)_3 \cdot 5H_2O$  (7 mg; 0.05 eq) were added to a solution of **4c** (0.075 g; 0.28 mmol; 1.0 eq) in 1 ml of THF anhydrous and the reaction mixture maintained at  $0^\circ C$  for 40 min under inert atmosphere. After that time, *p*-ClPhMgBr (0.62 ml; 0.62 mmol; 2.2 eq) were added slowly and the resulting mixture was stirred for 30 min at the same temperature. A solution of methyl iodide (0.07 ml, 1.14 mmol, 4 eq) was added to the solution and the mixture was gradually warmed over the period of 3 hours. The reaction mixture is washed with  $NH_4Cl$  saturated solution and dried under  $MgSO_4$  anh. Evaporation of the solvent gave a yellow oil that was subjected to column chromatography on silica gel eluted with hexane – ethyl acetate 90:10 obtained a yellow oil, (90 mg, 98%)  $^1H$  RMN ( $CDCl_3$ ):  $\delta$  7.26 (m, 2H, H-Ar), 7.24 (m, 2H, H-Ar), 6.40 (dd, 1H, H-4,  $J = 6.59$  Hz,  $J = 1.8$  Hz), 6.21 (s, 1H, H-10), 6.09 (d, 1H, H-3,  $J = 8.6$  Hz), 3.28 (dt, 1H, H-1,  $J = 5.8$  Hz,  $J = 1.5$  Hz), 2.50 (dt, 1H,  $H_{eq-7}$ ,  $J = 9.984$  Hz,  $J = 4.3$  Hz), 2.35 (q, 1H, H-5), 1.56 (d, 1H,  $H_{ax-7}$ ,  $J = 8.6$  Hz),

1.39 (s, 3H, H-9), 0.95 (s, 3H, H-8);  $^{13}C$  RMN:  $\delta$  145.34 (C-2), 138.65 (C-4), 128.30 (C-3), 128.59, 128.36, 129.45, 129.91 (C-Ar), 122.28 (C-10), 53.62 (C-6), 45.67 (C-1), 43.43 (C-5), 36.35 (C-7), 26.40 (C-9), 22.59 (C-8) MS (EI 70eV)  $m/z = : 244[M^+]$ , 209(53), 203(35), 201(100), 166(79), 165(80),  $[\alpha]_D^{20} = 58.351$  ( $c = 0.15$ ,  $CHCl_3$ ).

**(4Z, 5R) - 4- (4 - fluorobenzylidene) - 6, 6 - dimethyl bicyclo [3.1.1]hept-2-ene (3d)**

*p*-PPhMgBr (2.2 ml; 2.2 mmol; 2.2 eq) were added to a solution of myrtenal (150 mg, 1 mmol, 1 eq) in 1 ml of THF and the reaction mixture maintained at  $0^\circ C$  for 3 hours under inert atmosphere. The reaction is monitored by TLC and the reaction washed with  $NH_4Cl$  saturated solution and dried under  $MgSO_4$  anh. Evaporation of the solvent gave a yellow oil that was subjected to column chromatography on silica gel eluted with hexane – ethyl acetate 90:10 to give pure **3d**. Colorless oil, 98 %  $^1H$  RMN ( $CDCl_3$ ):  $\delta$  7.13 (m, 2H, H-Ar), 6.98 (m, 2H, H-Ar), 6.38 (dd, 1H, H-4,  $J = 6.6$  Hz), 6.23 (s, 1H, H-10), 6.09 (d, 1H, H-3,  $J = 8.6$  Hz), 3.27 (dt, 1H, H-1,  $J = 5.8$  Hz,  $J = 1.5$  Hz), 2.50 (dt, 1H,  $H_{eq-7}$ ,  $J = 9.8$  Hz,  $J = 4.3$  Hz), 2.36 (q, 1H, H-5), 1.55 (d, 1H,  $H_{ax-7}$ ,  $J = 8.4$  Hz), 1.40 (s, 3H, H-9), 0.95 (s, 3H, H-8);  $^{13}C$  RMN:  $\delta$  144.64 (C-2), 138.24 (C-4), 133.72, 130.17, 130.09, (C-Ar), 128.32 (C-3), 122.38 (C-10), 53.50 (C-6), 45.57 (C-1), 43.39 (C-5), 36.25 (C-7), 26.40 (C-9), 22.61 (C-8) MS (EI, 70 eV)  $m/z = 228[M^+]$ .

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