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Total synthesis and assignment of the absolute stereochemistry of xanthoangelol J: development of a highly efficient method for Claisen–Schmidt condensation

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Dedicated to Late (Dr.) Jadab C. Sarma on his 55th birthday on first May 2013

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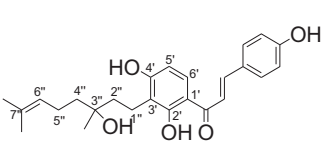
ABSTRACT

The first total synthesis of cancer chemopreventive terpenyl hydroxychalcone xanthoangelol J isolated from *Angelica keiskei* was accomplished with asymmetric epoxidation, aromatic C-alkylation and Claisen–Schmidt condensation via enol mode as key steps. The crucial Claisen–Schmidt condensation has been accomplished by a novel green method using $KHSO_4$–SiO_2 as a recyclable catalyst under microwave activation. The absolute configuration of the molecule was also determined.

1. Introduction

In their search for potential cancer chemopreventive agents from natural sources, Akihisa et al. isolated xanthoangelol J (**1**) from *Angelica keiskei* stem exudates along with 11 other compounds like xanthoangelol I (**2**) and deoxydihydroxanthangelol H (**3**).[1] Its gross structure was determined on the basis of detailed spectral analysis but the stereochemistry of the 3″-C was not assigned. In preliminary screening for cancer chemopreventive potential this compound was found to possess potent inhibitory effects on the induction of Epstein–Barr virus early antigen (EBV-EA) by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in Raji cells.[1] Epstein–Barr virus (EBV) a human herpes virus that causes infectious mononucleosis and is associated with many malignant diseases including nasopharyngeal carcinoma, B-cell and T-cell lymphomas[2] and post transplant lymphoproliferative diseases.[3] The title compound also showed potent inhibitory effect against activation of (±)-(*E*)-methyl-2-[(*E*)-hydroxyimino]-5-nitro-6-methoxy-3-hexemide (NOR 1), a nitrogen oxide (NO) donor.[1]



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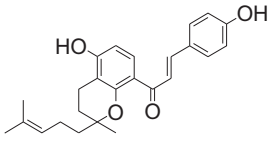

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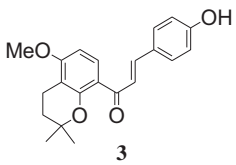

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In a project on bioactive molecules we studied the synthesis and bioactivity of a variety of chalconoids.[4] Working on terpenylated chalcones, the promising cytotoxic potential, very low isolation yield (0.067%)[1] and interesting structural features of the molecule

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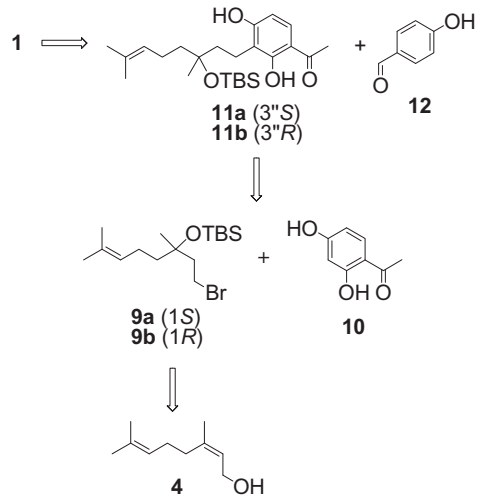
xanthoangelol J attracted us to develop a route for its synthesis. Both the (*R*)- and (*S*)-isomers of the molecule were prepared for biological studies and from comparison of their analytical data the natural isomer was identified to be (*S*)-(+)-xanthoangelol J. A key step involved in the synthetic scheme is the Claisen–Schmidt condensation between the chiral arylketone (**11a**/**b**) and 4-hydroxybenzaldehyde. When hydroxybenzaldehyde is a substrate, acid catalysed methods are preferred over base catalysed versions of Claisen–Schmidt condensation as prior protection of the hydroxy groups is a prerequisite via the later.[5] But in this very case it was not possible to realise the condensation using reported methods with catalysts like BF_3–Et_2O,[6] I_2,[7] $SOCl_2$–EtOH,[8] I_2–Al_2O_3,[4a] etc. It prompted us for the development of a new method of Claisen–Schmidt condensation with wide applicability. $KHSO_4$ is considered as a green catalyst[9] and has been successfully utilised in many organic transformations in supported form over SiO_2.[10] Our premeditated efforts resulted in the development of new rapid method of Claisen–Schmidt condensation using $KHSO_4$–SiO_2 as a reusable catalyst under microwave activation in green reaction conditions.

2. Results and discussions

The retrosynthetic analysis of xanthoangelol J (**1**) is outlined in Scheme 1. The molecule can be broken down to two main fragments—fragment **11a**/**b** and 4-hydroxybenzaldehyde (**12**). Fragment **11a**/**b** can be obtained from 2′,4′-dihydroxyacetophenone (**10**) and nerol (**4**).



Scheme 1. Retrosynthetic analysis of xanthoangelol J.

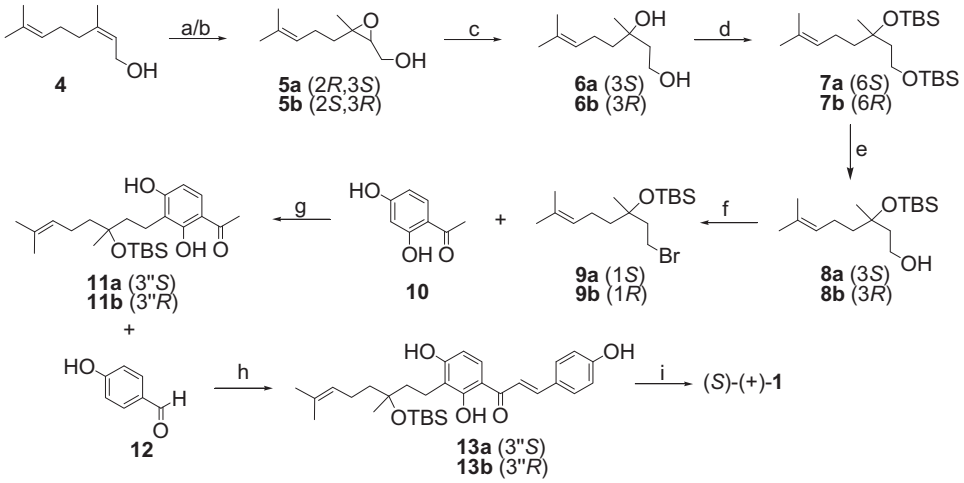
Our approach is to design a synthetic strategy using chiral intermediates of known configuration that will allow us to determine the absolute configuration of the molecule unambiguously. We planned to synthesise two enantiomeric epoxides **5a** and **b** (Scheme 2) of known configuration corresponding to the terpenyl side chain of **11a** and **b**, respectively. Commercially available nerol (**4**) was subjected to asymmetric epoxidation for this stereoselective synthesis to get **5a** with 86% ee and **5b** with 91% ee Regioselective opening of the epoxides and subsequent conversion of the primary –OH group to its bromide gave the fragments **9a** and **b**. With the requisite chiral terpenyl fragments in hand, we next focused on the 3′-C-alkylation of 2′,4′-dihydroxyacetophenone (**10**) with these. It was presumed that the presence of a couple of hydroxy groups and another two perspective aryl carbons (5′ and 6′-C) in **10** may lead to both *C*- and *O*- as well as mixture of *C*-alkylated products. To avoid a possible loss of the chiral fragment (**9a**/**b**) we studied a reaction using geranyl bromide as the alkyl halide to set the reaction conditions to get the desired alkylation occurred at 3′-*C* of **10**. Following a literature report[11] we tried the reaction using K_2CO_3 in acetone and two products were isolated. However, presence of three protons in the region between δ 6.0 and 7.0 in the ^{1}H NMR spectra of the products confirms them to be *O*-alkylated products.

In their studies on the synthesis of prenylated natural products, Lee et al.[12] used DBU in THF for C-prenylation of 2′,4′,6′-trihydroxyacetophenone with 40% product yield. We followed the same procedure for our reaction here and the 3′-*C*-alkylated product was formed in 34% isolated yield. Complete conversion of the starting materials could not be achieved even after 52 h of reaction time. With increasing time, formation of a non-polar mixture of products was observed in TLC analysis.

Now we attempted the reaction between **9a** and **10** using same reaction conditions. After continuous stirring of 60 h the desired product **11a** was isolated in 29% yield. Presence of a singlet at δ 12.9 for 2′-OH in ^{1}H NMR supported by ^{13}C NMR data for aromatic carbons nullifies the occurrence of O-alkylation in the product. Further, presence of a pair of doublets in the aromatic region integrating for two protons confirms that the alkylation occurred at 3′-C of 2′,4′-dihydroxyacetophenone.

We tried different Lewis acids for the Claisen–Schmidt condensation between **11a** and **12** but ended up with disappointing results. Interestingly with the use of $SOCl_2$/EtOH as a source of in situ generated HCl,[8] the starting materials got consumed with the formation of 11% of the desired product along with a complex mixture (TLC). This signifies that instead of Lewis acids, the condensation may be best induced using a mild Brönsted acid. Therefore we studied the catalytic ability of a general laboratory reagent $KHSO_4$ to bring about the condensation between acetophenone and benzaldehyde in ethanol. To our delight, 44% product formation was observed after 12 h of room temperature stirring with 20 mol % catalyst. With the same substrates we tried to find the optimal reaction conditions in different solvents with catalytic amount of $KHSO_4$. Maximum product formation was observed in the reaction in PEG compared to the reactions in the lower alcohols or in water (Table 1). But it took as long as 42 h for completion with 91% of isolated product yield. To reduce the reaction time, the reaction was carried out under microwave irradiation. Use of microwave at different powers (200–350 W) in different time (1–7 min) durations could enhance the yield only up to 73%. Further enhancement of microwave power or reaction time resulted in the decomposition of the product formed. Then we tried the reaction using $KHSO_4$ in supported form. For this $KHSO_4$ was supported over silica gel for column chromatography and used in catalytic amount to catalyse the model reaction in PEG. This time 100% conversion was achieved after 6 min of microwave irradiation. Presence of the solvent was found obligatory since a reaction carried out without solvent keeping other reaction conditions unchanged resulted only traces of the product. To study the necessity of supporting $KHSO_4$ over silica, the reaction was carried out with same amount of $KHSO_4$ and silica gel as a mixture, but only traces of the product was formed. This suggests the existence of a synergistic effect between the two when silica gel is used as a support. It may be understood that the solid support provides a very high surface area for the catalysis making the reaction faster.

With this excellent catalytic system in hand we studied the applicability of the same with a variety of substituted aryl aldehydes and aryl ketones (Table 2). Irrespective of the nature of substituents in the aryl rings, chalcones were synthesised in moderate to excellent yields without any side product using this protocol. Products were purified by simple recrystallisation, found to be geometrically pure and configured trans.[13]



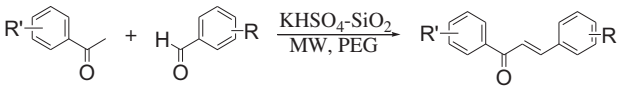
Scheme 2. Synthetic scheme of (*S*)-(+)-**1**. Reagents and conditions: (a) Ti(O-^{i}Pr)$_4$, (−)-DET, TBHP, DCM, 4 Å mol. Sieves, 91.5%; (b) Ti(O-^{i}Pr)$_4$, (+)-DET, TBHP, DCM, 4 Å mol. Sieves, 89%; c) $LiAlH_4$, THF, −40 °C, 87%; (d) $^{t}BuMe_2SiOTf$, 2,6-Lutidine, DCM, −20 °C, 76.9%; (e) *p*-TsOH, MeOH, 87.4%; (f) CBr_4, Ph_3P, DCM, 87.0%; (g) DBU, THF, 60h, 29%; (h) $KHSO_4$–SiO_2, MW, 56.5%; (i) TBAF, DMPU, 4 Å mol. sieves, 80 °C, 8 h, 92%.

Table 1
Optimisation of solvent and catalyst loading

Entry	Catalyst loading (mol %)	Solvent	Time (h)	Yield[a] (%)
1	20	EtOH	12	44
2	20	MeOH	12	22
3	20	H_2O	12	NR[b]
4	20	PEG	12	47
5	20	EtOH–H_2O	12	43
6	20	MeOH–H_2O	12	39
7	20	PEG-H_2O	12	43
8	20	—	6	Trace[c]
9	30	PEG	12	47
10	10	PEG	12	32
11	20	PEG	42	91

[a] Isolated pure yield.
[b] No reaction.
[c] Reaction mixture was grinded and kept in a mechanical shaker.

Table 2
$KHSO_4$–SiO_2 catalysed synthesis of chalcones



Entry	R′	R	Time (min)	Yield[a] (%)
1	H	H	6	93
2	2-OH	H	7	91
3	4-OMe	4-OMe	6	82
4	3-OH	2-NO_2	8	81
5	4-OH	4-OH	8	91
6	H	4-OH	7	92
7	4-OH	4-OMe	6	82
8	H	4-NO_2	7	80
9	2-OH	3-OMe, 4-OH	8	79
10	4-$OCH_2CH{=}CH_2$	4-OMe	5	85
11	2,4-OMe	2-NO_2	8	79
12	2,4-OH	4-OH	8	80
13	4-OH	3,4-OH	8	78
14	2,4-OMe	4-OMe	7	82

[a] Isolated pure yield.

In order to study the reusability of the catalyst it was separated from the reaction mixture by filtration through a sintered funnel, washed properly with EtOH and oven dried at 150 °C for 2 h. Thereafter it was used to catalyse the reaction between acetophenone and benzaldehyde and the process was repeated for six consecutive cycles. Although a marginal decrease of product formation was observed in the sixth cycle, no appreciable loss of catalytic activity was observed up to the fifth cycle (Fig. 1).

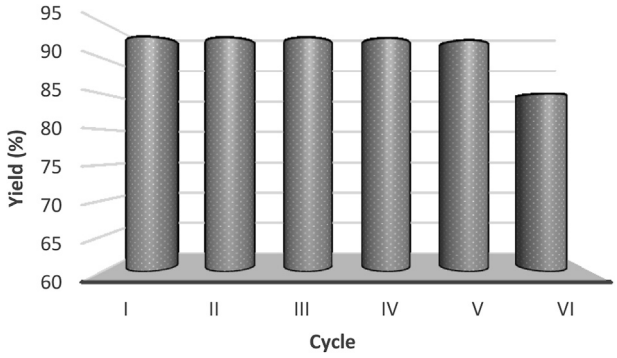


Fig. 1. Catalyst activity for six cycles.

Successful application of this new method in synthesising a variety of chalcones including polyhydroxychalcones encouraged us to apply the same for realising the condensation between **11a** and **12**. Equimolar amounts of the compounds **11a** and **12** were irradiated in MW in presence of 20 mol % catalyst. After 5 min of irradiation at 200 W power, TLC showed no further conversion of the starting material. Work up followed by column chromatography resulted in the isolation of **13a** in 56.5% yield. Finally removal of the TBS group by TBAF furnished (*S*)-(+)-**1** {$[\alpha]_D^{23}$ +28.8 (*c* 0.5, MeOH)} in 94% yield with 7.21% overall yield. (*R*)-(−)-**1** {$[\alpha]_D^{23}$ −24.0 (*c* 0.5, MeOH)} was also prepared in the same way by taking (+)-DET in the asymmetric epoxidation step of the synthetic scheme (Scheme 2). Comparison of the optical rotation values suggests the absolute configuration of xanthoangelol J {$[\alpha]_D^{25}$ +6.0 (*c* 0.1, MeOH)} to be (*S*)-(+)-xanthoangelol J.

3. Conclusion

Thus we developed the first synthetic route for the total synthesis of xanthoangelol J along with the determination of its absolute configuration. The synthesis was accomplished in eight steps with 7.2% overall yield. A new, green method was also developed for the synthesis of chalcones with wide applicability. The final step i.e., the Claisen–Schmidt condensation involved in the synthetic scheme of xanthoangelol J was realised using this green method.

Inexpensive and reusable catalyst, short reaction time, use of a green solvent PEG and use of microwave irradiation as energy source render this new endeavour as a potential alternative over the available methods of Claisen–Schmidt condensation.

4. Experimental

4.1. General remarks

All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. Melting points were determined with a Buchi B 540 apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1640 FT-IR instrument. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-300 NMR machine with TMS as the internal standard in solvents. Mass spectra were recorded on a WATERS Micro-mass ZQ 4000 (ESI Probe) spectrometer. Optical rotations were measured using a Perkin–Elmer 343 polarimeter. Elemental analyses were carried out using a Perkin–Elmer series II CSNS/O Model 2400 analyzer.

4.2. Preparation of the catalyst

$KHSO_4$ (1.0 g) was dissolved in 200 mL of distilled water. Silica gel for column chromatography (4.0 g, 60–120 mesh) was slowly added to the solution with continuous swirling. Then the mixture was kept in a hot air oven at 150 °C for 6 h and stored in a dessicator.

4.3. Representative procedure for synthesis of chalcones (Table 2)

In a typical reaction acetophenone (0.2 g, 1.66 mmol) and benzaldehyde (0.176 g, 1.66 mmol) was dissolved in PEG (8 mL) and to this solution was added 0.225 g $KHSO_4$–SiO_2 (20 mol % $KHSO_4$). Then the mixture was transferred to a sealed reaction vessel of Anton Paar Synthos 3000 microwave reactor and irradiated for 6 min at 250 W power. Maximum internal temperature observed was 92–99 °C and pressure 5.3–5.7 bar. After cooling to room temperature ethanol (10 mL) was added to the reaction mixture and filtered through a sintered funnel to separate the solid catalyst. The filtrate was concentrated under reduced pressure and the product was recrystallised from the ethanol.

4.4. (2*R*,3*S*)-3-Methyl-3-((4-methylpent-3-enyl)oxiran-2-yl) methanol (5a)[14]

To a stirred suspension of crushed molecular sieves (4 Å, 0.4 g) in anhydrous CH_2Cl_2 (40 mL), L-(−)-DET (0.409 g, 1.98 mmol) and $Ti(O^iPr)_4$ (0.366 g, 1.29 mmol) were added. The suspension was then cooled to −20 °C, TBHP (3.51 mL, 19.3 mmol, 5.5 M in CH_2Cl_2) was slowly added to it and the mixture was stirred for 40 min at −20 °C. Then the suspension was further cooled to −25 °C before 2.0 g (12.9 mmol) of 3,7-dimethyl-octa-2,6-dien-1-ol (**4**) was added drop wise as a 50% solution in anhydrous CH_2Cl_2. The suspension was stirred for another 3 h at−25 °C. Then the temperature of the suspension was raised to 0 °C, 30 mL of water was added and allowed to reach room temperature. Now aqueous NaOH (30 mL, 30% solution in water, saturated with NaCl) was added to the suspension and stirred for 25 min until a clear phase separation observed. The suspension was then filtered through a sintered funnel to separate the residues of the molecular sieves from the solution. Liquid phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×40 mL). Combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Resulting thick oil was purified by column chromatography over silica gel (100–200 mesh) using EtOAc/hexane as the mobile phase to get (2.01 g, 11.8 mmol, 91.5%, 86% ee)[15] of **5a** as a colourless oil. $[\alpha]_D^{25}$ +18.3 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3427, 2968, 1672, 1647, 1450, 1380, 1257, 1218, 1033, 913; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12–5.07 (m, 1H, 6C*H*), 3.84–3.80 (m, 1H, 1C*H*H), 3.69–3.63 (m, 1H, 1CH*H*), 2.99 (dd, *J*=6.84, 4.47 Hz, 1H, 2C*H*), 2.13–2.08 (m, 2H, 5CH_2), 1.84 (br s, 1H, O*H*), 1.69 (s, 3H, 7CH_3), 1.62 (s, 3H, 7CH_3), 1.53–1.45 (m, 2H, 4CH_2), 1.34 (s, 3H, 3CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.3 (C-7), 123.2 (C-6), 64.4 (C-2), 61.5 (C-1), 61.2 (C-3), 33.1 (C-4), 25.6 (7CH_3), 19.5 (C-5), 17.6 (3CH_3), 16.9 (7CH_3); MS (ESI): *m*/*z* 171 $(M+H)^+$.

4.5. (3*S*)-3,7-Dimethyl-oct-6-ene-1,3-diol (6a)[16]

$LiAlH_4$ (0.908 g, 23.9 mmol) was slowly added to anhydrous THF (40 mL) under argon cooled to −40 °C and stirred for 5 min. Compound **5a** (1.7 g, 9.98 mmol) dissolved in THF (5 mL) was added drop wise to this solution. The reaction mixture was maintained at −40 °C for 4 h, then was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated tartaric acid (25 mL) and stirred for 1 h. After filtration through Celite, it was extracted with EtOAc (3×40 mL). The organic layer was dried over anhydrous Na_2SO_4. Chromatography over silica gel (100–200 mesh, EtOAc/hexane) yielded **6a** as a colourless oil (1.5 g, 8.7 mmol, 87%); $[\alpha]_D^{24}$ +1.61 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3536, 3382, 2969, 2928, 2883, 1557, 1451, 1376, 1342, 1216, 1116, 1067; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (t, *J*=6.9 Hz, 1H, 6C*H*), 3.87–3.84 (m, 2H, 1CH_2), 2.05–2.01 (m, 2H, 5CH_2), 1.68 (s, 3H, 7CH_3), 1.62 (s, 3H, 7CH_3), 1.56 (t, *J*=7.3 Hz, 2H, 2CH_2), 1.52–1.49 (m, 4H, 4CH_2, 1,3O*H*), 1.24 (s, 3H, 3CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.6 (C-7), 124.1 (C-6), 73.7 (C-3), 59.5 (C-1), 42.2 (C-2), 41.3 C-4), 26.4 (3CH_3), 25.6 (7CH_3), 17.5 (C-5), 16.8 (7CH_3); MS (ESI): *m*/*z* 173 $(M+H)^+$.

4.6. (6*S*)-6,8-Bis-(*tert*-butyldimethylsilanyloxy)-2,6-dimethyl-oct-2-ene[11] (7a)

To an ice cold stirred solution of **6a** (1.4 g, 8.12 mmol) in CH_2Cl_2 (50 mL), 2,6-lutidine (3.47 g, 32.4 mmol) and TBSOTf (5.15 g, 19.5 mmol) were added at 0 °C. The resulting mixture was warmed to room temperature and stirred for 12 h, and then water (40 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×40 mL). Combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by column chromatography over silica gel (100–200 mesh) using EtOAc/hexane as the mobile phase to get the product **7a** as a colourless oil (2.5 g, 6.25 mmol, 76.9%). $[\alpha]_D^{23}$ +0.68 (*c* 1.5, $CHCl_3$), IR (KBr, cm^{-1}) 2998, 2962, 2919, 2903, 1609, 1540, 1493, 1464, 1409, 1360, 1238, 1098, 991; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (t, *J*=6.71 Hz, 1H, 3C*H*), 3.71 (t, *J*=7.13 Hz, 2H, 8CH_2), 2.08–1.89 (m, 2H, 4CH_2), 1.81–1.66 (m, 2H, 7CH_2), 1.64 (s, 3H, 2CH_3), 1.61 (s, 3H, 2CH_3), 1.48–1.33 (m, 2H, 5CH_2), 1.22 (s, 3H, 6CH_3), 0.89 (s, 9H, C(CH_3)$_3$), 0.86 (s, 9H, C(CH_3)$_3$), 0.07 (s, 6H, Si(CH_3)$_2$), 0.05 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.4 (C-2), 124.7 (C-3), 74.9 (C-6), 60.1 (C-8), 44.9 (C-7), 43.1 (C-5), 28.1 (6CH_3), 26.1 (SiC(*C*H$_3$)), 26.0 (SiC(*C*H$_3$)), 25.8 (2CH_3), 23.3 (C-4), 18.4 (Si*C*(CH$_3$)$_3$), 17.1 (2CH_3), −1.9 (Si(*C*H$_3$)$_2$), −5.5 (Si(*C*H$_3$)$_2$); MS (ESI): *m*/*z* 401 $(M+H)^+$.

4.7. (3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-3,7-dimethyl-oct-6-en-1-ol (8a)

To a cooled (0 °C) solution of the bis-TBS-ether **7a** (2.4 g, 5.98 mmol) in MeOH (40 mL), *p*-TsOH (0.123 g, 0.71 mmol) was added as a solid. The reaction mixture was stirred at the same temperature for 30 min. Then it was quenched with solid $NaHCO_3$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography over silica gel

(100–200 mesh) using EtOAc/hexane as the mobile phase to isolate **8a** as a colourless oil (1.50 g, 5.23 mmol, 87.4%); $[\alpha]_D^{23}$ +2.13 (*c* 1.55, $CHCl_3$); IR (KBr, cm^{-1}) 3407, 3080, 2967, 2438, 2868, 1630, 1460, 1377, 1358, 1148, 1096; ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (t, *J*=7.1 Hz, 1H, 6C*H*), 3.80 (t, *J*=5.71 Hz, 2H, 1CH_2), 2.71 (m, 2H, 5CH_2), 1.96 (m, 2H, 2CH_2), 1.69 (s, 3H, 7CH_3), 1.60 (s, 3H, 7CH_3), 1.56 (t, *J*=5.72 Hz, 2H, 4CH_2), 1.22 (s, 3H, 3CH_3), 0.87 (s, 9H, C(CH_3)$_3$), 0.12 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.1 (C-7), 124.3 (C-6), 77.1 (C-3), 60.2 (C-1), 44.5 (C-2), 42.6 (C-4), 27.8 (3CH_3), 25.7 (7CH_3), 25.4 (SiC(CH_3), 25.3 (SiC(CH_3), 23.1 (C-5), 18.2 (SiC(CH_3)$_3$), 17.7 (7CH_3), −1.3 (SiCH_3). MS (ESI): *m*/*z* 287 $(M+H)^+$.

4.8. (1*S*)[1-(2′-Bromo-ethyl)-1,5-dimethyl-hex-4-enyloxy]-*tert*-butyldimethylsilane (9a)

CBr_4 (2.26 g, 6.83 mmol) was added under N_2 at room temperature to a solution of **8a** (1.4 g, 4.88 mmol) in anhydrous CH_2Cl_2 (50 mL). After stirring for 10 min the solution was cooled to 0 °C and Ph_3P (3.59 g, 13.7 mmol) was added. The mixture was stirred overnight and passed through a silica gel (60–120 mesh) column to separate the highly polar coloured by-products to get **9a** as brown oil (1.48 g, 4.25 mmol, 87.0%); $[\alpha]_D^{23}$ +1.9 (*c* 1.51, $CHCl_3$); IR (KBr, cm^{-1}) 2969, 2858, 1650, 1444, 1384, 1369, 1202, 1110, 840; ^1H NMR (300 MHz, $CDCl_3$) δ 5.11 (t, *J*=7.10 Hz, 1H, 4C*H*), 3.67 (t, *J*=5.70 Hz, 2H, 2′CH_2), 2.68 (t, *J*=5.73 Hz, 2H, 1′CH_2), 1.95–1.87 (m, 2H, 3CH_2), 1.68 (s, 3H, 5CH_3), 1.61 (s, 3H, 5CH_3), 1.59–1.49 (m, 2H, 2CH_2), 1.20 (s, 3H, 1CH_3), 0.86 (s, 9H, SiC(CH_3)$_3$), 0.32 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9 (C-5), 124.6 (C-4), 77.4 (C-1), 41.9 (C-2), 30.5 (1CH_3), 27.8 (5CH_3), 26.1 (C-2′), 25.8 (SiC(CH_3)), 25.5 (SiC(CH_3)), 25.3 (SiC(CH_3)), 23.0 (C-3), 18.2 (5CH_3), 18.1 (SiC(CH_3)$_3$), −1.3 (Si(CH_3)$_2$). MS (ESI): *m*/*z* 350 $(M+H)^+$.

4.9. 1-{(3″*S*)-[3″-(*tert*-Butyl-dimethyl-silanyloxy)-3″,7″-dimethyl-oct-6-enyl]-2′,4′-dihydro-xyphenyl}-ethanone (11a)

A mixture of **9a** (1.01 g, 2.9 mmol), 2′,4′-dihydroxyacetophenone (**10**, 0.45 g, 2.9 mmol) and DBU (0.441 g, 2.9 mmol) in dry THF (30 mL) was stirred at room temperature for 20 h. Addition of 2 N HCl (15 mL), extraction with EtOAc (3×30 mL), washing with brine (1×30 mL) and removal of the solvent followed by column chromatography over silica gel (100–200 mesh) using EtOAc/hexane as the mobile phase resulted in the isolation of **11a** as a thick brown oil (0.353 g, 0.84 mmol, 29%); $[\alpha]_D^{23}$ +6.9 (*c* 0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3381, 2960, 1629, 1606, 1455, 1376, 1357, 1150, 1058, 916, 712; ^1H NMR (300 MHz, $CDCl_3$) δ 13.1 (s, 1H, 2′O*H*); 7.57 (d, *J*=8.8 Hz, 1H, 6′*H*); 6.39 (d, *J*=8.6, 1H, 5′*H*), 5.11 (t, *J*=7.41 Hz, 1H, 6″C*H*), 2.75 (t, *J*=5.81 Hz, 2H, 1″CH_2), 2.62–2.40 (m, 2H, 5″CH_2), 2.48 (s, 3H, COCH_3), 1.69 (s, 3H, 7″CH_3), 1.61 (s, 3H, 7″CH_3), 1.82–1.54 (m, 2H, 4″CH_2), 1.20 (s, 3H, 3″CH_3), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.12 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9 (*C*O), 161.4 (C-4′), 159.2 (C-2′), 132.2 (C-7″), 129.1 (C-6′), 124.3 (C-6″), 119.0 (C-1′), 117.8 (C-3′), 107.9 (C-5′), 77.2 (C-3″), 45.6 (C-2″) 41.9 (C-4″), 30.5 (3″CH_3), 27.8 (7″CH_3), 7.1 (C-1″), 25.7 (SiC(CH_3)), 25.5 (SiC(CH_3)), 25.3 (SiC(CH_3)), 23.1 (C-3″), 18.2 (7″CH_3), 18.1 (SiC(CH_3)$_3$), −1.3 (Si(CH_3)$_2$). MS (ESI): *m*/*z* 421 $(M+H)^+$.

4.10. (*E*)-1-{(3″*S*)-[3″-(*tert*-Butyl-dimethyl-silanyloxy)-3″,7″-dimethyl-oct-6″-enyl]-2′,4′-dihydroxyphenyl}-3-(4-hydroxyphenyl)-propenone (13a)

11a (0.29 g, 0.69 mmol), 4-hydroxybenzaldehyde (**12**, 0.084 g, 0.69 mmol), PEG-400 (5 mL) and $KHSO_4$–SiO_2 (0.326 g) was mixed in a reaction vessel of Anton Paar Synthos 3000 MW reactor. Then the mixture was irradiated at 200 W power for 5 min (TLC showed completion of the reaction). Maximum internal temperature observed was 72 °C and pressure 5.2–5.4 bar. After cooling to room temperature, ethyl acetate (15 mL) was added to the reaction mixture and filtered through a sintered funnel to separate the solid catalyst. After aqueous washing (1×15 mL), the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography over silica gel (100–200 mesh) using EtOAc/hexane as the solvent system afforded **13a** as a yellow oil (0.204 g, 0.39 mmol, 56.5%); $[\alpha]_D^{23}$ +26.7 (*c* 0.51, MeOH); IR (KBr, cm^{-1}) 3378, 2965, 2926, 1619, 1605, 1558, 1448, 1375, 1231, 1157, 1056, 916; ^1H NMR (300 MHz, CD_3OD) δ 13.9 (s, 1H, 2′O*H*), 7.90 (d, *J*=8.7 Hz, 1H, 6′*H*), 7.78 (d, *J*=15.3 Hz, 1H, α-*H*), 7.68 (d, *J*=15.3 Hz, 1H, β-*H*), 7.65 (d, *J*=8.32 Hz, 2H, 2*H*, 6*H*), 6.86 (d, *J*=8.38 Hz, 2H, 3*H*, 5*H*), 6.44 (d, *J*=8.4 Hz, 1H, 5*H*), 5.10–5.06 (m, 1H, 6″C*H*), 2.70–2.64 (m, 1H, 1″CH_2), 2.09–2.04 (m, 2H, 5″CH_2), 1.66–1.60 (m, 2H, 2″CH_2), 1.61 (s, 3H, 7″-CH_3), 1.58 (s, 3H, 7″-CH_3), 1.50–1.42 (m, 2H, 4″CH_2), 1.19 (s, 3H, 3″-CH_3), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.12 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, CD_3OD) δ 191.0 (*C*O), 165.6 (C-4′), 163.6 (C-2′), 161.8 (C-4), 145.4 (C-β), 132.4 (C-7″), 131.8 (C-6′), 130.1(C-1), 128.1(C-2, C-6), 126.5 (C-6″), 119.0 (C-1′), 117.9 (C-3, C-5), 114.8 (C-3′), 75.0 (C-3″), 46.0 (C-2″), 41.3 (C-4″), 29.1 (3CH_3), 27.9 (7″CH_3), (SiC(CH_3)), 25.6 (SiC(CH_3)), 25.3 (SiC(CH_3)), 18.3 (7″CH_3), 7.3 (C-1″), −1.3 (Si(CH_3)$_2$). MS (ESI): *m*/*z* 524 $(M)^+$.

4.11. (*E*)-1-[2′,4′-Dihydroxy-(3″*S*)-(3″-hydroxy-3″,7″-dimethy-loct-6″-enyl)-phenyl]-3-(4-hydroxyphenyl)-propenone [(*S*)-(+)-1]

Compound **13a** (0.15 g, 0.36 mmol) was added to a 1.0 M solution of tetra butyl ammonium fluoride in THF (1.43 mL, 1.43 mmol) and the solution was concentrated in vacuo. The residual oil was dissolved in DMPU (1.5 mL) and crushed activated molecular sieves (4 Å, 0.15 g) were added to it. The resulting suspension was heated at 80 °C for 8 h. Then the reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and poured on to cold water. The solution was extracted with EtOAc (3×10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was washed with hexane to remove any residual DMPU and subjected to column chromatography over silica gel (100–200 mesh) using EtOAc/hexane as the mobile phase to afford (*S*)-(+)-**1** as a yellow solid (0.136 g, 0.331 mmol, 92%); mp 121–123 °C [lit. 120–123 °C];[1] $[\alpha]_D^{23}$ +28.8 (*c* 0.5, MeOH); IR (KBr, cm^{-1}) 3370, 2969, 2929, 1615, 1605, 1562, 1512, 1444, 1370, 1236, 1167, 1107, 980, 833, 796; ^1H NMR (300 MHz, CD_3COCD_3) δ 13.9 (s, 1H, 2′O*H*), 7.91 (d, *J*=8.8 Hz, 1H, 6′*H*), 7.78 (d, *J*=15.3 Hz, 1H, β-*H*), 7.70 (d, *J*=15.3, 1H, α-H), 7.67 (d, *J*=8.4 Hz, 2H, 2*H*, 6*H*), 6.87 (d, *J*=8.4 Hz, 2H, 3*H*, 5*H*), 6.45 (d, *J*=8.8 Hz, 1H, 5′*H*), 5.10–5.05 (m, 1H, 6″C*H*), 2.71–2.68 (m, 1H, 1″CH_2), 2.08–2.04 (m, 2H, 5″CH_2), 1.65–1.60 (m, 2H, 2″CH_2), 1.61 (s, 3H, 7″CH_3), 1.58 (s, 3H, 7″CH_3), 1.50–1.42 (m, 2H, 4″CH_2), 1.19 (s, 3H, 3CH_3); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 193.6 (*C*O), 165.7 (C-2′), 163.4 (C-4′), 161.4 (C-4), 145.4 (C-β), 132.2 (C-2, C-6), 131.8 (C-7″), 130.6 (C-6′), 128.1 (C-1), 126.5 (C-6″), 119.0 (C-α), 117.9 (C-3′), 117.3 (C-3, C-5), 114.8 (C-1′), 108.8 (C-5′), 73.0 (C-3″), 43.0 (C-4″), 41.3 (C-2″), 27.9 (3″-CH_3), 26.3 (7-CH_3), 23.9 (C-5″), 18.4 (C-1″), 18.1 (7-CH_3). MS (ESI): *m*/*z* 411 $(M+H)^+$. Anal. calcd for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37. Found: C, 73.11; H, 7.39.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.11.106.

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