Research Article

Synthesis and Characterization of GSK-3 Inhibitors

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ABSTRACT

Glycogen Synthase Kinase-3 (GSK-3) inhibitors are gaining prominence as they are found to be effective in treatment against Alzheimer's disease, cancer, inflammation, type II diabetes, bipolar disorders etc. In this study, we have designed and synthesized new potent GSK-3β inhibitors based on literature are characterized and isolated for further studies.

Keywords: Glycogen Synthase Kinase-3, Alzheimer's disease, bipolar disorder.

1. INTRODUCTION

Glycogen Synthase Kinase (GSK)-3 is a ubiquitous and highly conserved Serine-Threonine protein kinase that is involved in a variety of cellular processes and pathways including glucose metabolism, development, metabolic, homeostatic, neuronal growth and differentiation, cell polarity, cell fate and apoptosis.[1] Dysregulation of GSK-3 activity has been associated with a wide variety of human disorders. GSK-3 signaling pathway plays a key role in the pathogenesis of highly prevalent disorders such as Alzeimer's disease[2] and cancer.[3] Therefore, GSK-3 constitutes a highly attractive therapeutic target for the development of selective inhibitors as novel promising drugs for the treatment of these pathological conditions.

Natural products have been playing a crucial role in the discovery and development of new therapeutic agents.[4,5] Marine organisms serve as a rich source of potent drug candidate (secondary metabolites) and have been subject of intensive exploration for identifying novel biologically active compounds.[6] In recent years, several small molecules extracted from marine organisms have been recognized as promising candidates for the development of effective GSK-3 inhibitors. The chemical synthesis of highly selective and potent small molecules derived from marine organisms as a potential GSK-3 inhibitor, which would act as a drug, and help in understanding the molecular basis of biological disorders associated with the alterations in the GSK-3 pathway has gained wide interest. Till date, a few compounds derived from marine organisms have already reached phase II clinical trials as potential GSK-3 inhibitor drugs. [7, 8]

GSK-3 generally opposes the actions of insulin, thus GSK-3 inhibits glycogen synthesis and glucose homeostasis that has been reported in type II diabetics and in animal models. Consequently, GSK-3 inhibitors have been demonstrated to have anti-diabetic[9] effects *in vitro* and in animal models. However, the challenge possess for inhibition of GSK-3 by achieving selectivity involved in various pathways with multiple substrates that may lead to side effects and toxicity. GSK-3 was first identified over 20 years ago as a consequence of its phosphorylation activity toward glycogen synthase, the rate-limiting enzyme of glycogen biosynthesis. GSK-3 is also a key component of the Wnt signalling pathway[10], which is a central process at many stages of development and is highly conserved between species. Molecular cloning revealed that there were two closely-related isoforms, GSK-3α and GSK-3β which give rise to proteins of 51 and 47 kDa, respectively, that display a high degree of sequence identity (98% within their catalytic domains). The main differences between GSK-3α and GSK-3β isoforms are found in the N- and C-terminal regions.[11] Within the ATP pocket of GSK-3 where most drugs bind to and compete with ATP, there appears to be only a single amino acid difference (Glu196 in GSK-3α, Asp133 in GSK-3β) making it difficult to identify an inhibitor that can distinguish the two isoforms. GSK-3 also regulates cell survival, as it facilitates a variety of apoptotic mechanisms. Lithium is indicated as a preferential treatment for bipolar disorders[12], and the ability of this cation to inhibit GSK-3 has been proposed as a potential mechanism of action. Due to this therapeutic potential, identification of GSK-3

inhibitors is a focus of research for both pharmaceutical companies and academic centers. The availability of GSK-3β crystal structures enables structure based lead discovery and optimization.[13, 14]

A number of publications describing the molecules that inhibit GSK-3 have been reported. Considerable efforts have been made into the discovery and development of GSK-3 inhibitors. Several chemically diverse families have emerged including peptides[15], metal ions[16] and diverse small heterocycles.[17, 18] These studies interested us to pursue our knowledge further in this field. In this paper, we have focused on the development of GSK-3 inhibitors which were readily synthesized in the laboratory as shown in table 1.

2. RESULTS AND DISCUSSION

The synthesis of compound **1** was done by brominating commercially available citronellol with phosphorous tribromide in ether to give compound **10** with 90% yield. Compound **10** was then treated with tetronic acid **11** in the presence of *n*-butyl lithium to furnish the product **1** in 48% yield (Scheme1).

Likewise, commercially available geraniol was also brominated with phosphorous tribromide in ether to give compound **12** which was then treated with triphenylphosphine in ethyl acetate to yield the phosphonium salt **13**. Wittig olefination strategy was applied on aldehydes **14**, **15** and ketone **16** to obtain subsequent compounds **2**-**4** in reasonably good yields (Scheme 2).

Compounds **5**-**9** (Scheme 3) were synthesized through a series of reactions originally starting from geraniol following known procedures involving Sharpless epoxidation[19] with D-diethyl tartarate and reductive ring opening to give 3-alkyl 1,2-diol **17** with both relative and absolute stereocontrol with an overall yield of 80% with exclusively single diastereomer[20] which was confirmed by ^{13}C and ^{1}H NMR .

Protection of the diol **18** was carried out with 2,2- dimethoxypropane followed by oxidation with selenium dioxide, salicylic acid and tertiary butylperoxide to give allylic alcohol **5** in 44% yield.

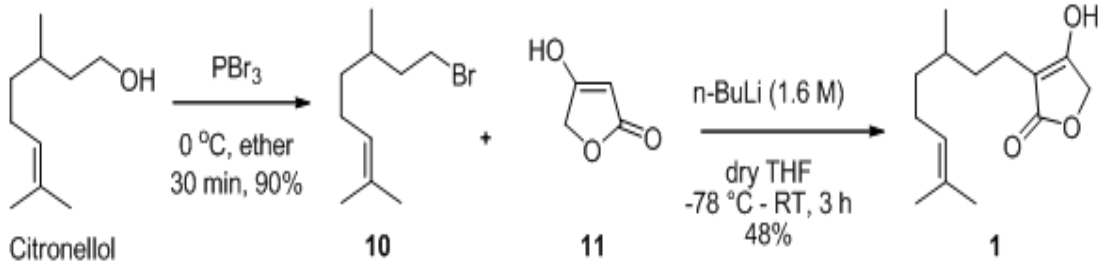
Compound **5** was then protected with *tert* butyldiphenylsilyl chloride to obtain compound **6** in 92% yield.

The acetonide deprotection of compound **6** with 80% acetic acid furnished compound **7** with 57.8% yield.

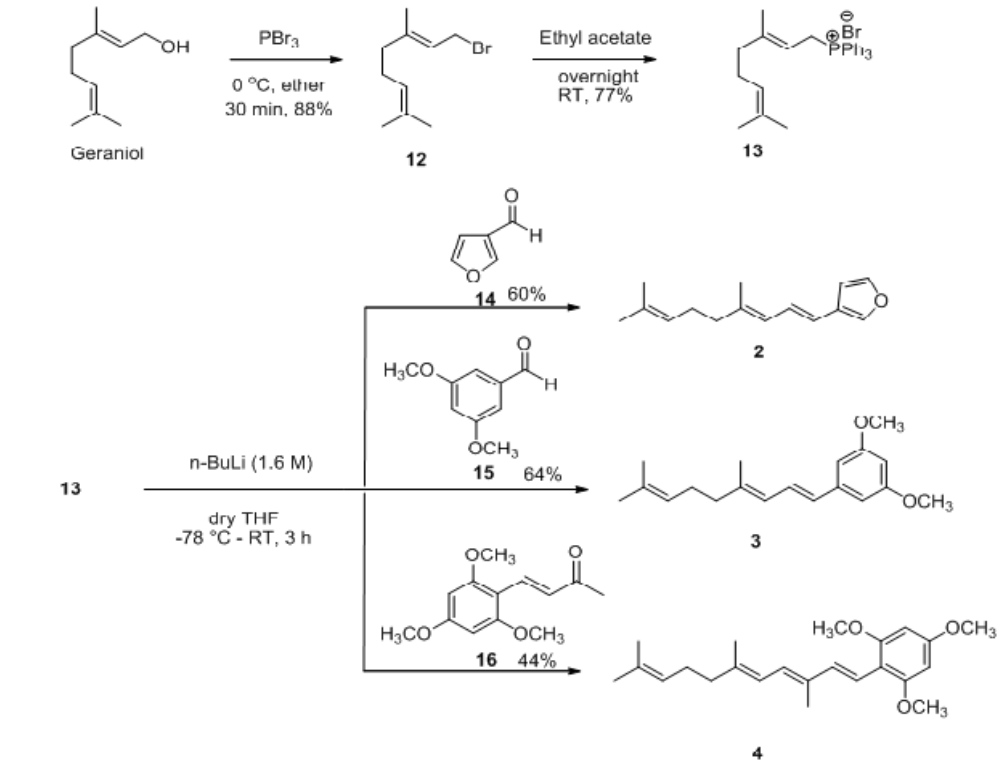
Oxidative cleavage of compound **7** with sodium metaperiodate gave an intermediate aldehyde which was subsequently converted to compound **8** (ester) using Wittig olefination with 87.6% yield.

Finally, the reduction of ester **8** by DIBAL-H (diisobutyl-ammonium hydride) afforded compound **9** in 64% yield.

Scheme 1



Scheme 2



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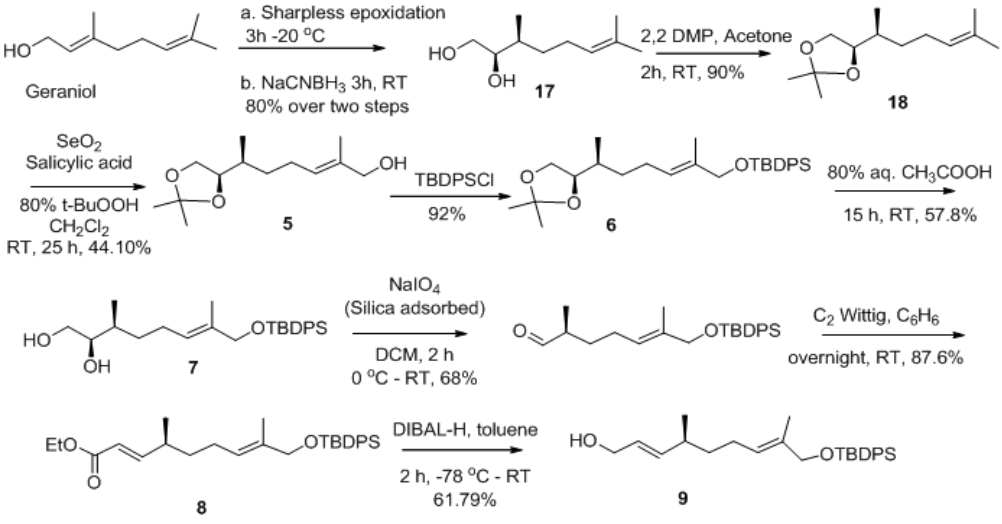


3. CONCLUSION

This paper gives the brief illustration of the compounds synthesized and characterized which can act as GSK-3 inhibitors. Further investigations on biological studies and other applications are currently under progress and will be published accordingly.

4. ACKNOWLEDGMENTS

MP thanks CSIR, New Delhi, for research fellowship. SC and PSM are grateful to the Council of Scientific and Industrial Research (CSIR)-New Delhi for research funding under the ORIGIN programme of the XII-five year plan projects.

5. Experimental Section

General: ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on 300 MHz, 500 MHz (^{1}H) or 75 MHz (^{13}C) spectrometer at ambient temperature. Chemical shifts δ is given in ppm, coupling constant *J* are in Hz. FTIR spectra were recorded as KBr thin films or neat. For low (MS) and High (HRMS) resolution, *m/z* ratios are reported as values in atomic mass units. All the reagents and solvents were reagent grade and used without further purification unless specified elsewhere. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60-120 mesh) packed in glass columns. All the reactions were performed under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring.

Spectral data for selected compounds

General procedure A for the synthesis of compound 10 and 12

To a solution of alcohol (1 mmol) in ether 20 ml at 0 °C under nitrogen atmosphere, was added phosphorous tribromide (0.5 mmol) and stirred for 30 min. After confirmation of reaction completion by TLC, quenching was done with saturated potassium bromide solution (100 mL) and extracted with diethyl ether (4 x 50 mL). The fractions were collected, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the desired product. This was directly used for the next reaction as it was unstable.

Synthesis of 8-Bromo-2,6-dimethyloct-2-ene (10)

General procedure A was followed by using citronellol (2 g, 12.98 mmol) and phosphorous tribromide (1.75 g, 6.4 mmol) for the formation of compound **10** (2.54 g, 89.43%) as a reddish brown oil.

Synthesis of (*E*)-1-Bromo-3,7-dimethylocta-2,6-diene (12)

General procedure A was followed by using geraniol (2.2 g, 14.26 mmol) and phosphorous tribromide (1.92 g, 7.1 mmol) for the formation of compound **12** (2.71 g, 87.56%) as a reddish brown oil.

Synthesis of 5-(3, 7-Dimethyloct-6-enyl)-4-hydroxyfuran-2(5*H*)-one (1)

To a solution of tetronic acid (0.23 g, 2.30 mmol) in 200 mL of dry THF under nitrogen atmosphere, was added 2.5 M n-butyl lithium in hexanes (0.37 g, 5.75 mmol) at -78 °C and stirred for 30 min until a yellow viscous solution was seen. Citronellyl bromide **10** (0.5 g, 2.30 mmol) was then added slowly and stirred for 1 h at -20 °C and 1 h at room temperature. The reaction mixture was diluted with dichloromethane (100 mL) and then hydrolyzed with water (100 mL). The solution then was acidified to pH 1.0 using 37% hydrochloric acid. Extraction was done with dichloromethane (2 x 20 mL) and the dichloromethane extracts were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude compound was purified by column chromatography was performed over silica gel (2 : 98 EtOAc/ Hexanes) to yield desired compound **1** (0.369 mg, 48 %) as syrupy liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.36 (m, 1H), 5.08-5.14 (m, 2H), 1.95-2.09 (m, 6H), 1.68 (s, 3H) 1.59-1.6 (d, 6H, *J*=4.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.6, 172.2, 143.5, 128.6, 126.4, 57.5, 48.2, 39.9, 36.5, 24.5, 20.1 and 17.6. IR (KBr, cm^{-1}): *v* 3331, 2944, 2832, 1660, 1449, 1412, 1222, 1018, 772, ESI-MS: *m/z* 239 [M+H].

Synthesis of (*E*)-(3,7-dimethylocta-2,6-dienyl) triphenylphosphonium-bromide (13)

To a stirred solution of **12** (2 g, 9.21 mmol) in ethyl acetate (30 mL), triphenyl phosphine (2.89 g, 11.05 mmol) was added and stirred overnight at room temperature which formed white solid. The reaction mixture was then filtered and the filter cake was washed with ethyl acetate (2 x 25 mL) and dried under vacuum to yield compound **13** (2.81 g, 76.9 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.8-7.87 (m, 9H), 7.68-7.74 (m, 6H), 5.12 (d, 1H, *J*=5.854 Hz), 4.89 (s, 1H), 4.47-4.54 (m, 2H), 1.97 (s, 4H), 1.58 (s, 3H), 1.51 (s, 3H) and 1.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 134.9, 133.7, 131.7, 130.1, 128.3, 124.2, 118.7, 38.8, 36.6, 28.3, 25.8, 20.2 and 18.2. IR (KBr, cm^{-1}): *v* 3357, 3054, 2966, 2916, 1731, 1658, 1587, 1484, 1438, 1219, 111,

996, 868, 770, 722, 745, 690, 532, 508, 489, ESI-MS: *m/z* 399 [M+H].

General Procedure B for the synthesis of analogues 2, 3 and 4

To a solution of Geranyl Wittig salt **13** (1 mmol) in dry THF (25 mL) under nitrogen atmosphere, was added 1.6 M (1.2 mmol) at -78 °C dropwise to yield reddish yellow color. After stirring for 30 min, a solution of aldehyde or ketone (0.9 mmol) in dry THF was added dropwise and left for stirring at -78 °C for 1 h and at 0 °C for 2 h. After completion of the reaction, monitored by TLC, it was quenched with saturated aqueous ammonium chloride solution (5 mL) and then extracted with ethyl acetate (2 x 25 mL) followed by giving brine wash (2 x 10 mL). The extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the desired compound.

Synthesis of 3-((1*Z*, 3*E*)-4,8-Dimethylnona-1,3,7-trienyl)furan (2)

Prepared according to the general procedure **B** from Phosphonium salt **13** (0.65 g, 1.35 mmol) and furan-3-carbaldehyde **14** (0.1 g,1.04 mmol) in the presence of 1.6 M *n*-butyl lithium in hexanes (0.1 g, 1.56 mmol) for 4 h to provide the title compound **2** (0.135mg, 60.26%) as a colorless semi-solid after silica gel chromatography (20 : 80 EtOAc/ Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.34-7.48 (m, 2H), 6.51-6.73 (m, 1H), 6.33-6.71 (m, 2H), 5.91-6.1 (m, 1H), 5.12 (s, 1H), 2.11-2.15 (d, 4H, *J*=10.6 Hz), 1.81 (s, 3H), 1.7 (s, 3H) and 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 143.4, 142.8, 141.2, 140.0, 131.2, 125.6, 125.1, 121.6, 119.5, 107.4, 40.6, 29.3, 22.6 and 16.5. IR (KBr, cm^{-1}): *v* 2956, 2853, 1734, 1460, 1219, 772, ESI-MS: *m/z* 217 [M+H].

Synthesis of 1-((1*E*, 3*E*)-4, 8-Dimethylnona-1, 3, 7-trienyl)-3, 5-dimethoxybenzene (3)

Prepared according to the general procedure **B** from **13** (0.5 g, 1.35 mmol) and 3,5-dimethoxy benzaldehyde **15** (0.2 g, 1.04 mmol) in the presence of 1.6 M *n*-butyl lithium in hexanes (0.075 g, 1.56 mmol) for 3 h to provide the title compound **3** (0.22 g, 63.95 %) as a yellow oil after silica gel chromatography (30 : 70 EtOAc/ Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.07-6.94 (m, 1H), 6.84-6.70 (m, 2H), 6.34-6.26 (m, 1H), 5.38 (m, 1H), 3.81-3.77 (m, 6H), 2.19-2.04 (m, 2H), 1.86-1.81 (m, 2H), 1.27-1.26 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 152.9, 151.5, 141.2, 127.6, 126.5, 125.9, 124.4, 122.7, 121.4, 116.7, 112.6, 111.4, 56.1, 55.7, 43.4, 40.3, 29.6, 29.1 and 22.4. IR (KBr, cm^{-1}): *v* 2924, 2852, 1716, 1674, 1581, 1494, 1463, 1215, 1161, 1045, 752. HRMS (ESI): *m/z* calcd. for $C_{19}H_{27}O_2$ 287.20038, found 287.20056.

Synthesis of 1,3,5-trimethoxy-2-((1*E*,3*E*,5*E*)-3,6,10-trimethylundeca-1,3,5,9-tetraenyl)benzene (4)

Prepared according to the general procedure **B** from 13 (0.45 g, 1.35 mmol) and trimethoxyphenylketone **16** (0.063 g, 1.04 mmol) in the presence of 1.6 M *n*-butyl lithium in hexanes (0.075 g, 1.56 mmol) for 3 h to provide the title compound **4** (0.412 mg, 44%) as a colorless oil after silica gel chromatography (30 : 70 EtOAc/ Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.94 (d, 1H, *J*= 16.564), 7.07 (d, 1H, *J*= 16.564), 6.78 (d, 1H, *J*= 12.423) 6.12 (s, 2H), 5.12 (m, 1H), 3.88 (s, 3H), 3.85(d, 3H, *J*= 9.41), 3.85 (s, 3H), 3.79(s, 3H), 2.35 (s, 3H), 2.06(s, 3H), 1.73-1.60 (m, 4H), 1.25 (s, 3H) and 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 163.1, 161.3, 160.2, 159.3, 135.0, 134.3, 133.9, 131.5, 127.6, 121.1, 120.3, 120.0, 107.8, 90.7, 90.6, 55.7, 55.6, 55.3, 29.7, 26.9, 23.5, 22.6 and 21.4 IR (KBr, cm^{-1}): *v* 2994, 2843, 2562, 1947, 1662, 1584, 1457, 1249, 1115, 990, 831, 770. ESI-MS: *m/z* 357 [M+H].

Synthesis of (*S*, *E*)-6-((*S*)-2, 2-Dimethyl-1,3-dioxolan-4-yl)-2-methylhept-2-en-1-ol (5)

To a suspension of selenium dioxide (0.1 g, 0.9 mmol), salicylic acid (0.66 g, 4.8 mmol) and 80% tertiary butyl peroxide (23.67 mL) in dichloromethane (150 mL), **18** (30.83 g, 42.6 mmol) was added and stirred for 25 h at room temperature. After reaction completion (monitored by TLC), reaction mixture was diluted with ether (150 mL) and washed successively with 10% potassium hydroxide (80 mL), saturated sodium bicarbonate solution (80 mL), water and finally with brine (2 X 25 mL). It was dried on $MgSO_4$ and concentrated. Purification of the crude compound was done by column chromatography (20 : 80 EtOAc/Hexanes)to yield compound **5** (14.92 g, 44.10%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 5.38 (t, 1H, *J*=7 Hz, 7.2 Hz), 3.98 (s, 2H), 3.89 (q, 1H, *J*=6.8 Hz, 13.2 Hz, 13.6 Hz), 3.6 (t, 1H, *J*=7.4 Hz, 7.5 Hz), 2.95 (br s, 1H), 1.95-2.26 (m, 2H), 1.66 (s, 3H), 1.4 (s, 3H), 1.35 (s, 6H) and 0.98 (d, 3H, *J*=6.6 Hz).). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 135.1, 125.8, 108.6, 80.1, 68.8, 67.5, 35.8, 32.3, 26.5, 25.4, 24.9, 15.4 and 13.6 IR (KBr, cm^{-1}): *v* 3434, 2956, 2851, 1454 and 1246. ESI-MS: *m/z* 229 [M+H]. $[\alpha]_D^{20}$: -16.9º (*c* = 1.0, $CHCl_3$).

Synthesis of *tert*-Butyl ((*S*, *E*)-6-((S)-2, 2-dimethyl-1,3-dioxolan-4-yl)-2-methylhept-2-enyloxy)diphenylsilane (6)

To the stirred solution of **5** (14.92 g, 106.7 mmol) in dry dicholoromethane (150 mL)was added imidazole (21.85 g, 321.2 mmol) at 0 °C and stirred at room temperature for 3 h. After the reaction completion (monitored by TLC), reaction mixture was quenched with saturated ammonium chloride solution. The reaction mixture was extracted with dichloromethane (3 x 50 mL) and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the crude compound was done by column chromatography (10 : 90 EtOAc/Hexanes) to yield the title compound **6** (28.05g (92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.67-7.73 (m, 6H), 7.3-7.41 (m, 4H), 5.42 (t, 1H, *J*=6.6 Hz, 6.8 Hz), 4.06 (s, 2H), 3.97-4.01 (m, 1H), 3.88 (q, 2H, *J*=6.6 Hz, 13.6 Hz), 3.59 (t, 1H, *J*=7.5 Hz), 2-2.19 (m, 2H), 1.6 (s, 3H), 1.37 (d, 6H, *J*=14.7 Hz), 1.11 (s, 2H), 1.07 (s, 9H), 0.99 (d, 3H, *J*=6.6 Hz).). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 135.4, 134.0, 133.7, 129.5, 129.4, 128.0, 127.5, 127.4, 126.7, 125.7, 123.9, 108.3, 80.0, 68.8, 67.6, 35.8, 32.4, 26.7, 26.5, 25.4, 24.6, 19.1, 15.3 and 13.4 IR (KBr, cm^{-1}): *v* 3444, 3071, 2958, 2711, 1962, 1894, 1722, 1465, 1376, 1218, 1111, 857, 771, 704, 609, 505. ESI-MS: *m/z* 467 [M+1]. $[\alpha]_D^{20}$: +51.3º (*c* = 1.0, $CHCl_3$).

Synthesis of (2*S*, 3*S*, *E*)-8-(*tert*-Butyldiphenylsilyloxy)-3, 7-dimethyloct-6-ene-1, 2-diol (7)

Compound **6** (28.05 g, 60.06 mmol) was treated with 80% aqueous acetic acid (300 mL) at room temperature for 15 h. After the reaction completion by TLC, the reaction mixture was concentrated under reduced pressure and co-evaporated several times with toluene (300 mL). Purification of the crude compound was done by silica gel chromatography(30 : 70 EtOAc/Hexanes) to provide the title compound **7** (15.6 g, 57.8%) as a colorless oily product. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.66-7.72 (m, 6H), 7.32-7.45 (m, 4H), 5.42 (s, 1H), 4.77 (s, 1H), 4.04 (s, 1H), 3.33-3.67 (m, 5H), 1.60-1.69 (m, 3H), 1.25 (s, 4H), 1.05 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 135.6, 134.2, 133.9, 129.8, 129.6, 128.2, 127.8, 127.7, 126.9, 125.5, 124.4, 108.6, 80.3, 69.0, 67.9, 36.1, 32.6, 25.6, 24.9, 15.5 and 13.6 IR (KBr, cm^{-1}): *v* 3464, 3071, 3050, 2959, 2931, 2858, 1961, 1894, 1720, 1651, 1463, 1367, 1265, 1182, 1109, 822, 772, 703, 613. HRMS (ESI): *m/z* calcd. for $C_{26}H_{38}O_3NaSi$ 449.24824, found 449.24692.

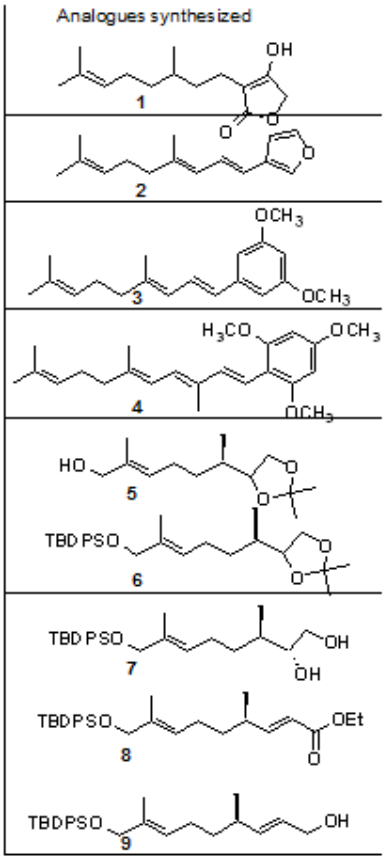
Synthesis of ((*S*, 2*E*, 7*E*)-ethyl 9-(*tert*-Butyldiphenylsilyloxy)-4, 8-dimethylnona-2, 7-dienoate (8)

To a stirred solution of **7** (10.1 g, 7.1 mmol) in benzene (200 mL) under nitrogen atmosphere, Wittig salt (4.9 g, 14.2 mmol) was added and stirred overnight at room temperature. After reaction completion, reaction mixture was dried over anhydrous Na_2SO_4,concentrated under reduced pressure and purification of the crude compound was done by silica gel chromatography (30 : 70 EtOAc/Hexanes) to provide the title compound **8** (10.4 g, 87.6%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.66 -7.71 (m, 6H), 7.34-7.42 (m, 4H), 6.83-6.91 (m, 1H), 5.78 (d, 1H, *J*=15.9 Hz), 5.4 (t, 1H, *J*=6.1 Hz, 6.8 Hz), 4.04-4.24 (m, 4 H), 3.53 (m, 1H), 2.3 (q, 1H, *J*=7.5 Hz, 12.1 Hz, 15.1 Hz), 1.65 (d, 1H, *J*=6.1 Hz), 1.58 (s, 2H), 1.29 (t, 5H, *J*=6.1 Hz), 1.06 (s, 15 H) and 0.79-0.93 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 166.9, 154.3, 135.5, 134.4, 133.9, 129.5, 127.6, 119.8, 68.9, 60.2, 36.1, 35.8, 29.7, 26.8, 25.1, 19.4, 14.3 and 13.5. IR (KBr, cm^{-1}): *v* 3429, 3070, 2960, 2930, 2857, 1960, 1720, 1651, 1589, 1463, 1368, 1175, 1043, 980, 820, 772, 704, 505. HRMS (ESI): *m/z* calcd. for $C_{29}H_{40}O_3NaSi$ 487.26389, found 487.26285. $[\alpha]_D^{20}$: +24.3º (*c* = 1.0, $CHCl_3$).

Synthesis of (*S*, 2*E*, 7*E*)-9-(*tert*-Butyldiphenylsilyloxy)-4, 8-dimethylnona-2, 7-dien-1-ol (9)

To a stirred solution of ester **8** (10.4 g, 22.41mmol) in toluene (120 mL) under nitrogen atmosphere, diisobutyl aluminium hydride (DIBAL-H) (6.37 g, 44.82 mmol)was added at -78 °C and after 2 h of stirring, the reaction mixture was quenched with saturated sodium potassium tartarate overnight. Reaction mixture was then extracted with ether (3 x 30 mL) and organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the crude compound was done by silica gel chromatography (40 : 60 EtOAc/Hexanes) to provide the title compound **9 (**5.84 g, 61.79%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.66-7.71 (m, 6H), 7.34-7.44 (m, 4H), 5.59 (t, 2H, *J*=3.8 Hz, 6.1 Hz), 5.34-5.44 (m, 1H), 4.1 (d, 2H, *J*=19.6 Hz), 4.05 (s, 2H), 2.17 (s, 1H), 2.02 (q, 2H, *J*=7.5 Hz, 14.4 Hz, 15.1 Hz), 1.59 (s, 3H), 1.22-1.38 (m, 5H) and 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 138.8, 136.1, 135.6, 133.9, 129.5, 127.5, 127.4, 36.6, 35.9, 27.2, 26.8, 25.2, 20.4 and 13.5. IR (KBr, cm^{-1}): *v* 3344, 3049, 2958, 1462, 1260, 1219, 739, HRMS (ESI): *m/z* calcd. $C_{27}H_{38}O_2NaSi$ 445.25333, found 445.25287.

Table 1:



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