JOC The Journal of Organic Chemistry

Article

Regio- and Diastereo-selective Synthesis of Dihydropyrans and Pyrano-Pyrans via Oxonium-ene Reaction of #-allenols and Aldehydes

Ngangbam Renubala Devi, Sabera Sultana, Madhurjya Borah, and Anil K. Saikia

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02244 • Publication Date (Web): 21 Nov 2018

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Regio- and Diastereo-selective Synthesis of Dihydropyrans and Pyrano-Pyrans *via* Oxonium-ene Reaction of *β*-allenols and Aldehydes

Ngangbam Renubala Devi,[a] *Sabera Sultana,*[b] *Madhurjya Borah*[a] *and Anil K. Saikia**[a]

[a]*Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati - 781039, India. Fax: +91-361-2690762; E-mail: asaikia@iitg.ernet.in*

[b]*School of Chemical Engineering, Yeungnam University, Gyeongsan 38541, Republic of Korea.*

RECEIVED DATE (will be automatically inserted after manuscript is accepted).

ABSTRACT: Bismuth trifluoromethanesulfonate ($Bi(OTf)_3$) can be efficiently used for the preparation of dihydropyrans from *β*-allenols and aldehydes by oxonium-ene reaction in good yields. The reaction is highly regioselective. On the other hand, the same reaction with trimethylsilyl trifluoromethanesulfonate (TMSOTf) at -45 ^oC affords hexahydropyrano[4,3-*b*]pyran skeleton in moderate yields.

INTRODUCTION

The dihydro-, tetrahydro- and pyrano-pyrans are core units of many biologically and pharmaceutically active compounds (Figure 1). For example, Laulimalide (**1**) is a macrolide obtained from a marine sponge which exhibits potent cytotoxicity toward numerous cancer cell lines and microtubule stabilizing activity similar to that of paclitaxel and the epothilones.[1] Aspergillide (**2**), a natural product obtained from fungus Aspergillus ostianus strain 01F313, exhibits cytotoxicity against mouse lymphocytic leukemia cells (L1210).[2] Martiriol (**3**), another natural product found in genus Laurencia that belongs to red algae, shows potent activity against various tumor cell lines.[3] Importantly, the olefinic bond of the

dihydropyran ring can be converted into various polyfunctional tetrahydropyrans.[4] They are also considered as useful starting material for the synthesis of homoallylic alcohols.[5] In addition to these applications, 2, 4-disubstituted dihydropyrans are used as additive for enhancing flavor and aroma of foodstuffs.[6]

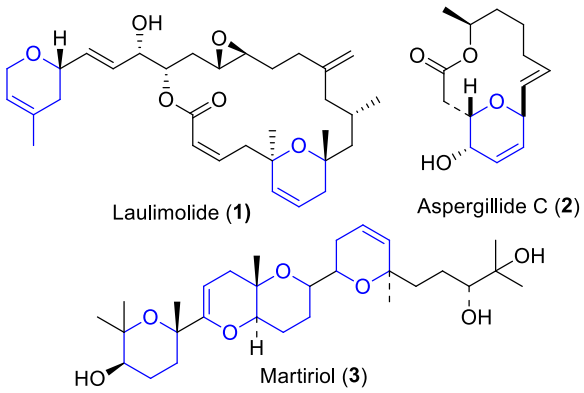
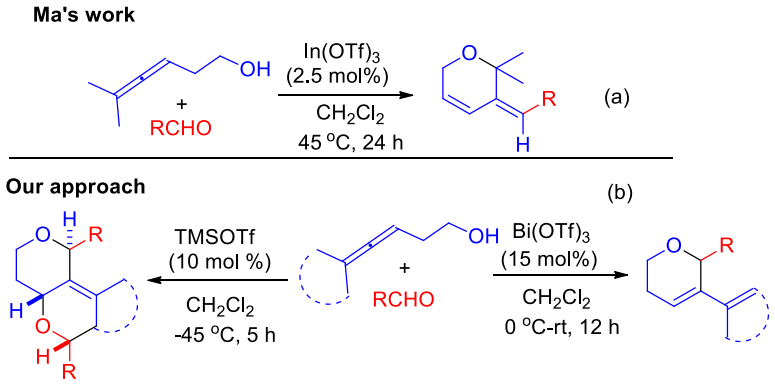


Figure 1: Biologically active compounds containing dihydropyran and tertahydropyran rings

Over the years many synthetic procedures have been evolved to construct dihydropyran ring such as hetero-Diels−Alder cycloaddition,[7] ring closing metathesis,[8] cyclization of dienols,[9] coupling-cyclization of crotylsilanes with aldehydes,[10] gold catalyzed cyclization of allenic alcohols,[11] Prins,[12] silyl-Prins[13] and oxonium-ene cyclization reactions.[14] Recently, Ma group has reported the $In(OTf)_3$ catalyzed Prins type cyclization of 5,5-disubstituted 3,4-allenols and aldehydes to synthesize 3,6-dihydro-2*H*-pyrans (method a, Scheme 1).[15] Although a variety of methods for the synthesis of dihydropyrans have been developed, more facile and efficient synthetic strategies are still desirable. Herein, we report $Bi(OTf)_3$ catalyzed and TMSOTf catalyzed cyclization reaction of allenic alcohol with aldehydes for the synthesis of 3,6-dihydro-2*H*-pyrans and hexahydropyrano[4,3-*b*]pyrans, respectively, *via* oxonium-ene cyclization reaction in moderate to good yields (method b, Scheme 1).

Scheme 1. Cyclization of *β*-allenols and aldehydes

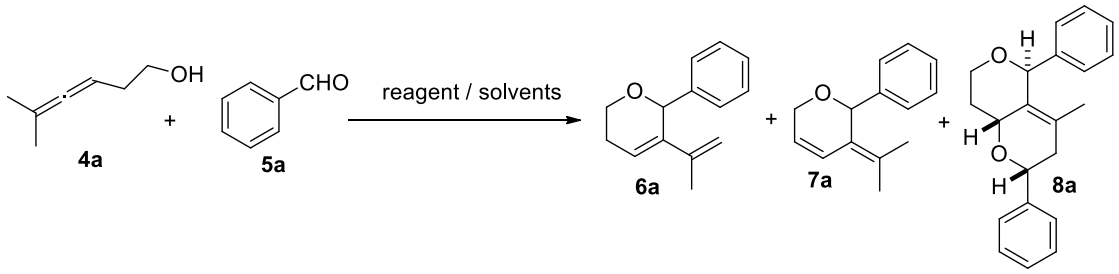


RESULTS AND DISCUSSION

To start with 5-methylhexa-3,4-dien-1-ol (**4a**) (1.0 equiv.) was subjected to react with benzaldehyde (**5a**) (1.0 equiv.) in the presence of borontrifluoride etherate ($BF_3{\cdot}OEt_2$) (1.2 equiv.) in dichloromethane at 0 °C to room temperature for 12h and a complex mixture was obtained (Table 1, entry 1). The reaction failed to provide any products in presence of TfOH (10 mol%) at 0 °C-room temperature (Table 1, entry 2). However, decreasing the temperature to -45 °C provided two inseparable products 2-phenyl-3-(propan-2-ylidene)-3,6-dihydro-2*H*-pyran (**7a**) and 4-methyl-2,5-diphenyl-2,3,5,7,8,8a-hexahydropyrano[4,3-*b*]pyran (**8a**) in 57% overall yield with ratio (**7a**: **8a**:: 5:2) (Table 1, entry 3). Further screening the reaction with other reagents such as TMSOTf (10 mol%) in dichloromethane at room temperature also provided **7a** with 48% yield (Table 1, entry 4). However, the reaction with TMSOTf (10 mol%) at -45 °C afforded the product 4-methyl-2,5-diphenyl-2,3,5,7,8,8*a*-hexahydropyrano[4,3-*b*]pyran (**8a**) with 40% yield (Table 1, entry 5). In an attempt to increase the yield of **8a,** the reaction was carried out at - 78 °C with TMSOTf (10 mol %), but the reaction was not found to be fruitful (Table 1, entry 6). There was no reaction when the solvent is changed from dichloromethane to 1,2-dichloroethane (Table 1, entry 7). Increasing the loading of TMSOTf to 20 mol% and 3,4-dien-1-ol **4a** from 1.0 equiv. to 1.5 equiv. in dichloromethane at -45 °C could not produce higher yield of **8a** (Table 1, entry 8). On the other hand, increasing the amount of benzaldehyde (**5a)** from 1.0 equiv. to 2.0 equiv. also did

not increase the yield (Table 1, entry 9). Similarly, various Lewis acids such as $In(OTf)_3$, $FeCl_3$, AgOTf, $Sc(OTf)_3$, $Zn(OTf)_2$ and $Bi(OTf)_3$ were next screened (Table 1, entries 10-15), amongst which $Bi(OTf)_3$ (10 mol %) at 0 ^oC to room temperature for 12h in dichloromethane gave compound **6a** with 41 % yield (Table 1, entry 15). Further increase in catalytic amount of $Bi(OTf)_3$ from 10 mol% to 15 mol% proved to be fruitful with 75% yield of the desired

Table 1. Optimization of the reaction[a]



Entry.	Reagent (equiv)	Solvent	Temp./ ^oC	Time/h	Product(%) yield[b]
1	$BF_3.OEt_2$ (1.2)	DCM	0 ^oC -rt	12	c
2	TfOH (0.1)	DCM	0 ^oC -rt	12	d (80)
3	TfOH (0.1)	DCM	-45 ^oC	5	**7a**+**8a** (57)
4	TMSOTf (0.1)	DCM	rt	12	**7a** (48)
5	TMSOTf (0.1)	DCM	-45 ^oC	5	**8a** (40)[e]
6	TMSOTf (0.1)	DCM	-78 ^oC	5	**8a** (32)[e]
7	TMSOTf (0.1)	DCE	-45 ^oC	5	c(75),[e]
8	TMSOTf (0.2)	DCM	-45 ^oC	5	**8a**(38)[e]
9	TMSOTf (0.2)	DCM	-45 ^oC	5	**8a**(38)[f]
10	$In(OTf)_3$ (0.2)	DCM	0 ^oC -rt	24	**6a** (27)[d,e]
11	$FeCl_3$ (1.2)	DCM	0 ^oC -rt	12	d
12	AgOTf (0.2)	DCM	rt	12	c
13	$Sc(OTf)_3$ (0.2)	DCM	rt	12	c
14	$Zn(OTf)_2$ (0.2)	DCM	rt	24	c
15	$Bi(OTf)_3$ (0.10)	DCM	0 ^oC -rt	12	**6a** (41)
16	$Bi(OTf)_3$ (0.15)	DCM	0 ^oC -rt	12	**6a** (75)[e]
17	$Bi(OTf)_3$ (0.15)	DCM	-45 ^oC	12	d (85)[e]
18	$Bi(OTf)_3$ (0.15)	DCE	0 ^oC -rt	24	d (82)[e]

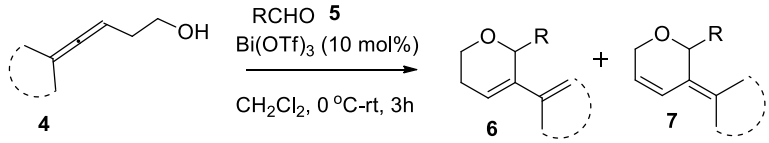
[a]Reaction conditions: **4a** (1.5 equiv), **5a** (1.0 equiv), solvent (4 mL). [b]Yields are isolated yield. [c]complex mixture. [d]starting material recovered. [e]1.5equivalents of alcohol. [f]2.0 equivelants of benzaldehyde **5a**.

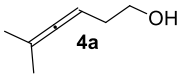
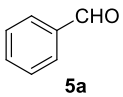
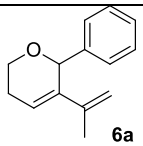
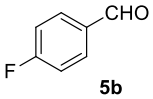
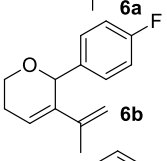
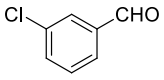
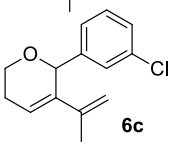
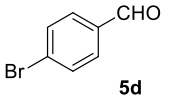
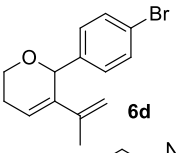
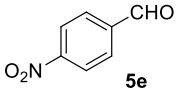
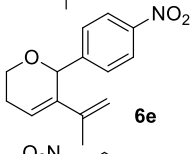
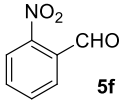
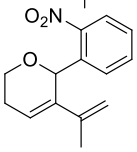
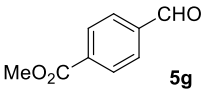
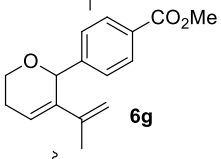
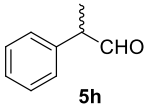
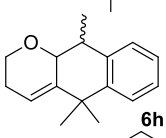
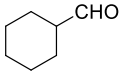
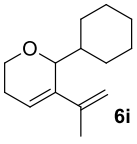
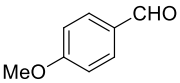
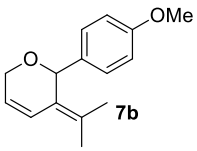
product (Table 1, entry 16). With the same reaction conditions but at -45 ^{o}C, starting material was recovered with 85% yield (Table 1, entry 17). When dichloromethane was changed to 1,2-dichloroethane no desired product was obtained even after 24h of the reaction (Table 1, entry 18). Thus, **4a** (1.5 equiv.), **5a** (1 equiv.) and $Bi(OTf)_3$ (15 mol %) in dichloromethane at 0 ^{o}C – room temperature for 12h was found to be the most suitable reaction condition.

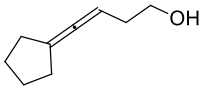
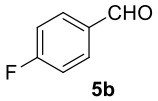
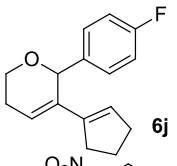
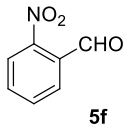
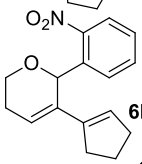
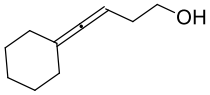
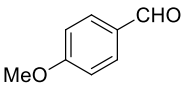
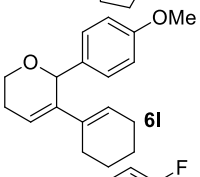
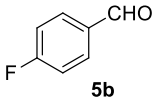
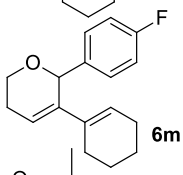
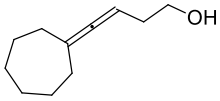
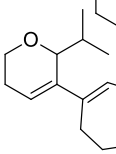
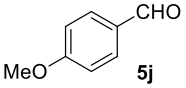
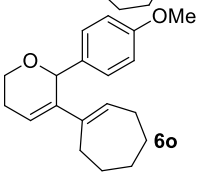
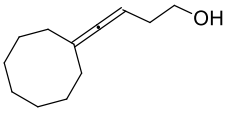
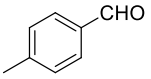
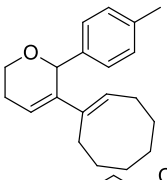
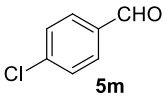
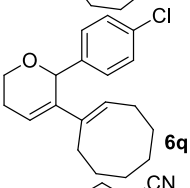
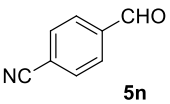
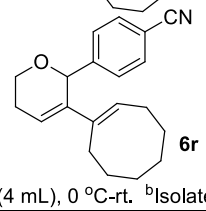
With this established optimum conditions, the utility of the reaction was further investigated with different aldehydes **5a-5n** bearing electron-donating and/or withdrawing groups as well as with various *β*-allenols **4a-4e** as shown in Table 2. The reaction of aldehydes **5b-5d** bearing moderately electron-withdrawing group such as 4-F, 3-Cl and 4-Br on the benzene ring with **4a** afforded the products **6b-6d** in 46-70% yields (Table 2, entries 2-4). The reaction was also found to be feasible with aromatic aldehydes **5e-5f** bearing a strong electron-withdrawing $–NO_2$ group and afforded the 3-prop-1-en-2-yl substituted dihydropyrans **6e-6f** in 78-82% yields (Table 2, entries 5-6). Similarly, treatment of methyl 4-formylbenzoate (**5g**) with **4a** also provided the 3-prop-1-en-2-yl substituted dihydropyran **6g** in 61% yield (Table 2, entry 7). Intrestingly, treatment of 2-phenylpropanal (**5h**) furnished tricyclic compound **6h** in 62 % yield (Table 2, entry 8). Aliphatic aldehyde cyclohexylcarboxaldehyde **5i** (Table 2, entry 9) afforded **6i** with 45 % yield. Substituents having strong electron donating functional group on the aromatic ring of the aldehyde **5j** surprisingly gave compound **7b** 2-(4-methoxyphenyl)-3-(propan-2-ylidene)-3,6-dihydro-2*H*-pyran instead of 3-prop-1-en-2-yl substituted dihydropyran (Table 2, entry 10). Aliphatic aldehyde isobutyraldehyde **5k,** also reacts with **4d** to give the desired product but with low yield (43 %). To demonstrate the versatility of the reaction, further reactions using various *β*-allenols and aldehydes were next carried out. Treatment of 4-cyclopentylidenebut-3-en-1-ol (**4b**) with aldehydes **5b** and **5f** produced the products **6j**-**6k** in 46-85% yields (Table 2, entries 11-12). Reaction of 4-cyclohexylidenebut-3-en-1-ol (**4c**) with aldehydes **5b** and **5j** afforded the corresponding products **6m-6l** in 65-73% yields (Table 2, entries 13-14). Similarly,

expansion of the ring of alcohol such as 4-cycloheptylidenebut-3-en-1-ol (**4d**) and 4-cyclooctylidenebut-3-en-1-ol (**4e**) could also react with aldehydes **5k**, **5j** and **5l-5n** and

Table2. Synthesis of dihydropyrans[a]



Entry	Substrates alcohol **4**	aldehyde **5**	Product **6/7**	Yield (%)[b]
1	 **4a**	 **5a**	 **6a**	75
2	**4a**	 **5b**	 **6b**	46
3	**4a**	 **5c**	 **6c**	70
4	**4a**	 **5d**	 **6d**	47
5	**4a**	 **5e**	 **6e**	78
6	**4a**	 **5f**	 **6f**	82
7	**4a**	 **5g**	 **6g**	61
8	**4a**	 **5h**	 **6h**	62
9	**4a**	 **5i**	 **6i**	45
10	**4a**	 **5j**	 **7b**	62

Entry	Substrates: alcohol **4**	aldehyde **5**	Product **6/7**	Yield (%)[b]
11	 **4b**	 **5b**	 **6j**	46
12	**4b**	 **5f**	 **6k**	85
13	 **4c**	 **5j**	 **6l**	73
14	**4c**	 **5b**	 **6m**	65
15	 **4d**	 **5k**	 **6n**	43
16	**4d**	 **5j**	 **6o**	47
17	 **4e**	 **5l**	 **6p**	66
18	**4e**	 **5m**	 **6q**	72
19	**4e**	 **5n**	 **6r**	46

[a]Reaction conditions: 4 (1.5 equiv), 5 (1.0 1.0 equiv), CH_2Cl_2 (4 mL), 0 °C-rt. [b]Isolated yield.

provided the corresponding products **6n-6r** in 43-72% yields (Table 2, entries 15-19). The stereochemistry of compounds was determined from nOe experiment of compounds **6g** and **6k** as well as X-ray crystallographic analysis of **6k** (Figure 2).[16]

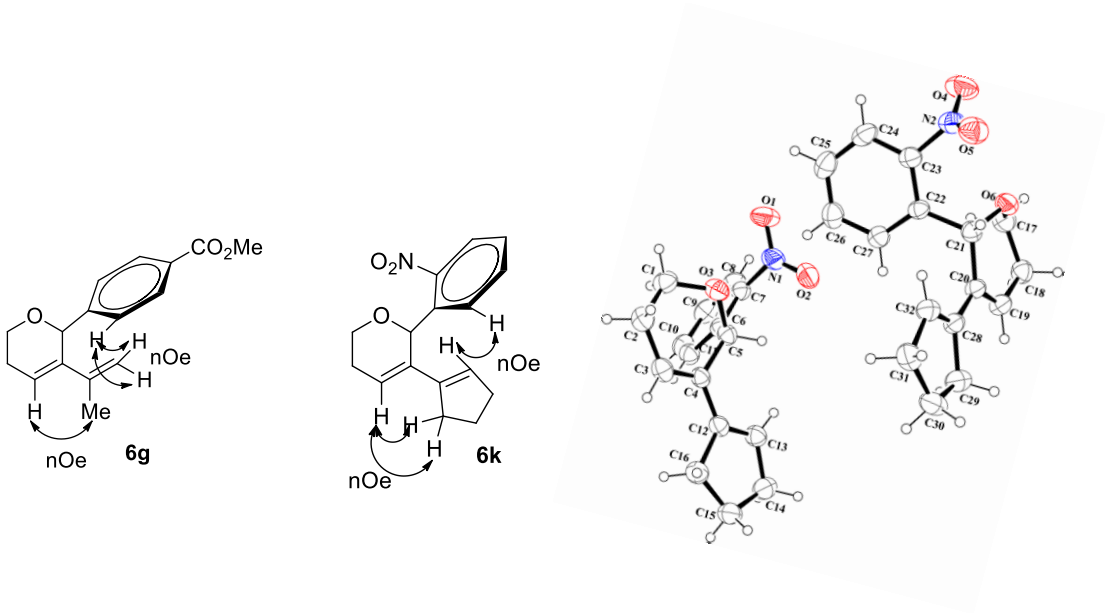
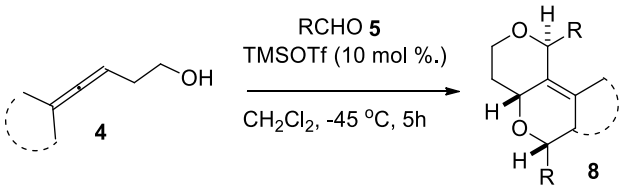


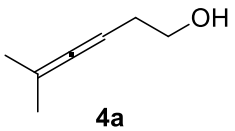
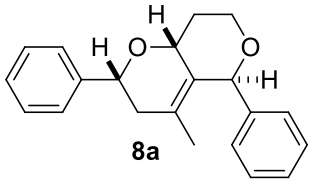
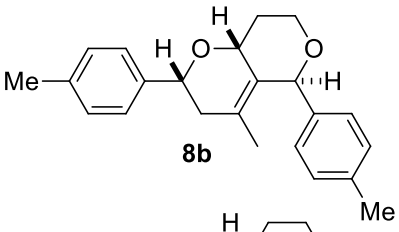
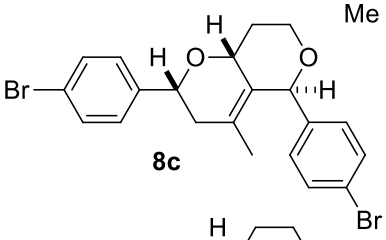
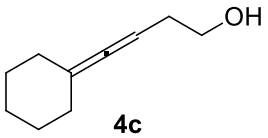
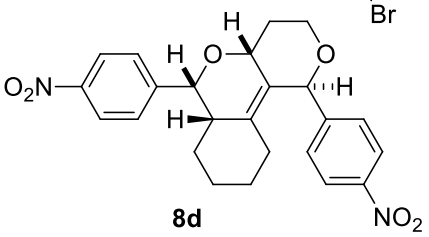
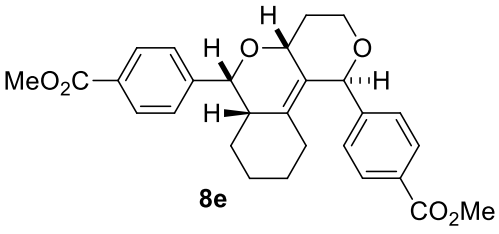
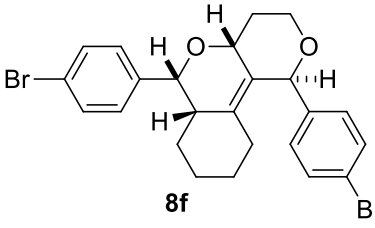
Figure 2. nOe of compounds **6g**, **6k** and X-ray crystallographic structure of **6k** (35% probability ellipsoid)

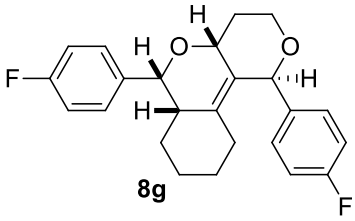
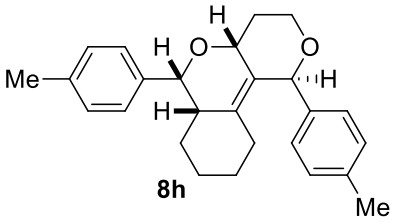
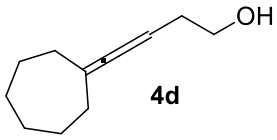
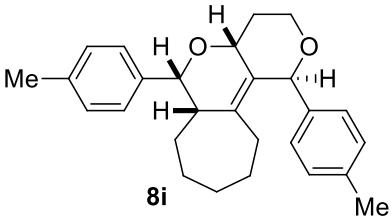
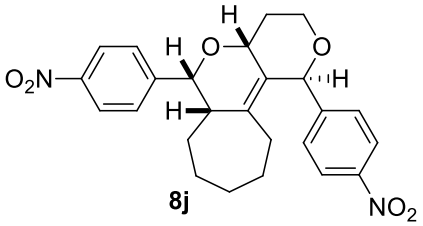
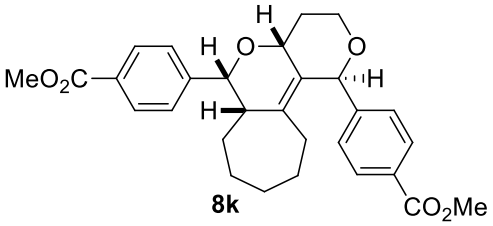
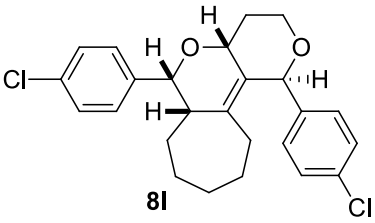
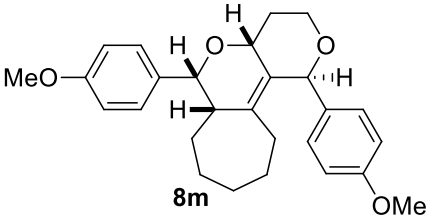
The methodology was also extended for the synthesis of pyranopyrans by using TMSOTf (Table 3). It may be mentioned that pyranopyran skeleton is found in many biologically active natural products[17] and they are also used as synthetic intermediates for the synthesis of polycyclic ethers such as marine toxins.[18] The scope of the reaction with TMSOTf was studied using different substrates as shown in Table 3. Treatment of alcohol **4a** with simple phenyl, electron donating methyl substituted and moderately electron withdrawing bromo-substituted aldehydes **5a**, **5l**, and **5d** could afford the corresponding pyranopyran products **8a, 8b** and **8c,** respectively with 40-58% yields (Table 3, entries 1-3). Reaction of 4-cyclohexylidenebut-3-en-1-ol (**4c**) with aldehydes having electron withdrawing groups **5e**, **5g**, **5d, 5b** and electron donating group on the aromatic ring **5l** afforded the corresponding pyranopyrans **8d-8h** in 40-55% yields (Table 3, entries 4-8). It was observed that substrates having highly electron withdrawing groups on the aromatic ring of the aldehydes gave better yields than moderately electron withdrawing and electron donating group. Further reaction of alcohol **4d** with aldehydes **5l**, **5e**, **5g**, **5m** and **5j** provided the products **8i-8m** in 46-52% yields (Table 3, entries 9-14). In this case there is no role of electronic effects of the substituent groups of the aromatic aldehyde on the rate of the reaction. However, aliphatic aldehydes did not give the desired product. The structure and

stereochemistry of pyranopyrans are determined from NMR spectrometry and X-ray crystallographic analysis of compound **8e** and **8k** (see the Supporting Information).[19]

Table3. Synthesis of pyranopyran[a]



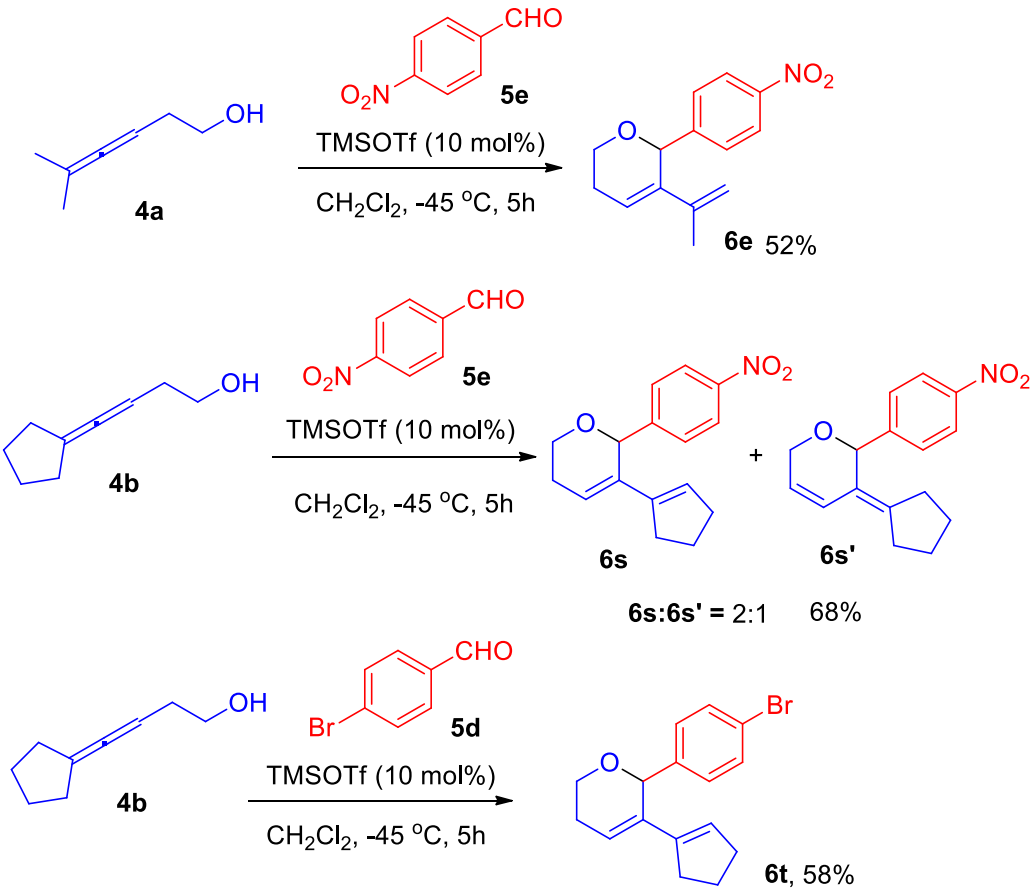
entry	alcohol	aldehyde	product	(%) yield[b]
1	 **4a**	**5a**	 **8a**	40
2	**4a**	**5l**	 **8b**	46
3	**4a**	**5d**	 **8c**	58
4	 **4c**	**5e**	 **8d**	55
5	**4c**	**5g**	 **8e**	50
6	**4c**	**5d**	 **8f**	41

entry	alcohol	aldehyde	product	(%) yield[b]
7	**4c**	**5b**	 **8g**	40
8	**4c**	**5l**	 **8h**	42
9	 **4d**	**5l**	 **8i**	46
10	**4d**	**5e**	 **8j**	52
11	**4d**	**5g**	 **8k**	47
12	**4d**	**5m**	 **8l**	48
13	**4d**	**5j**	 **8m**	47

[a]Reaction conditions: 4 (1.5 equiv), 4 (1.0 equiv), CH_2Cl_2 (2 mL), -45 ^oC. [b]Isolated yield. Compounds are characterized by ^1H, ^{13}C and mass spectrometric analysis

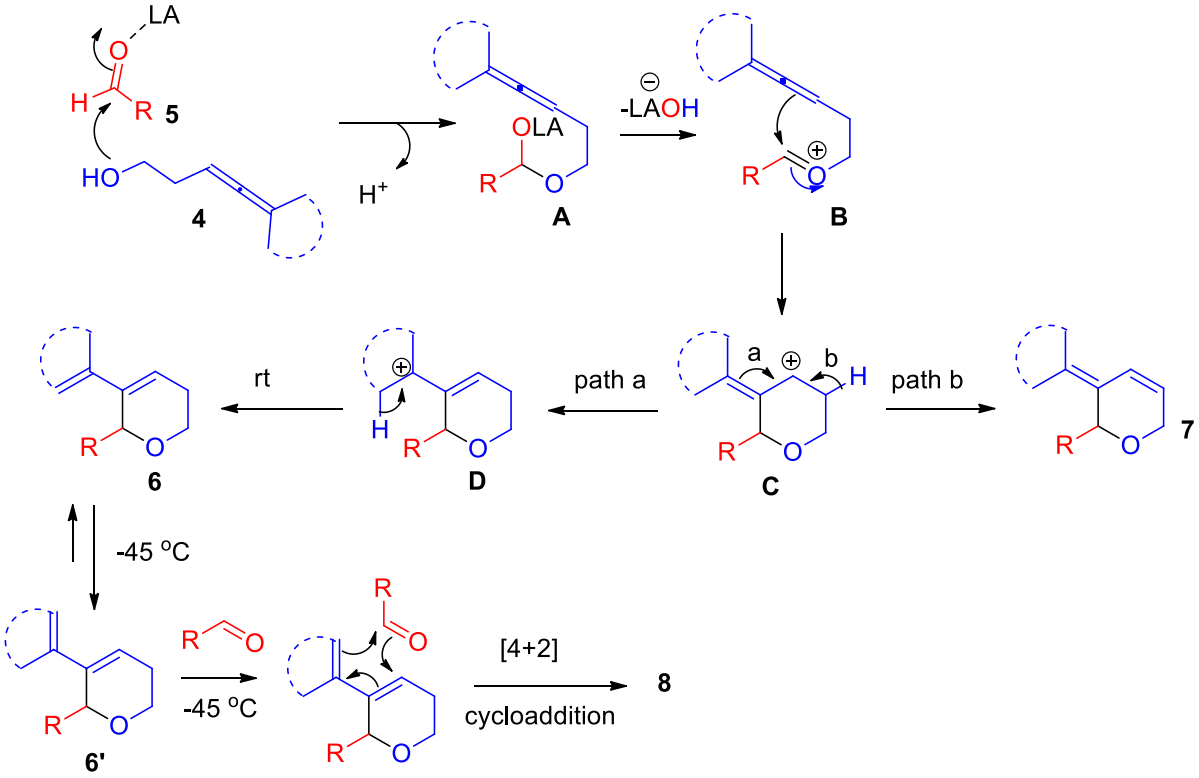
However, the reaction of 4-nitrobenzaldehyde **5e** with acyclic allenol **4a** could not produce desired pyranopyran instead dihydropyran **6e** was obtained in 52% yield. This might be due to the electronic effect of the strongly electron-withdrawing nitro group present in the aldehyde molecule. Similarly, five membered cyclic allenols **4b** was also found to be not good substrate for the formation of pyranopyrans unlike six and seven membered cyclic allenols. The reaction of allenol **4b** with aldehydes **5e** gave an isomeric mixture of **6s** and **6s′** with a ratio of 2:1 with 68% overall yield. The substrate **4b** is found to be not a good substrate for the synthesis of tricyclic compound as evident from the reaction of **4b** with **5d** which produces **6t** with 58% yield (Scheme 2). This unusual behavior of **4b** might be due to the presence five membered ring in the tricyclic ring which destabilizes the overall configuration of the molecule.

Scheme 2: Reaction of 4-nitrobenzaldehyde **5e** with allenols **4a-4b**.



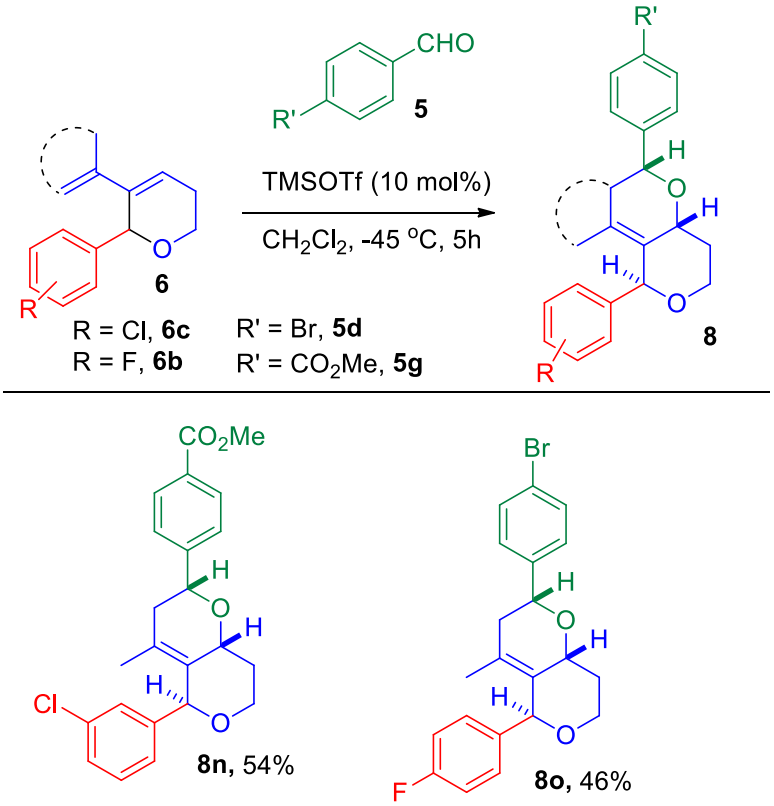
A plausible mechanism that accounts for the regioselective synthesis of **6**-**7** and **8** is depicted in Scheme 3. The Lewis acid activates the carbonyl group of aldehyde **5** for the nucleophilic attack by alcohol **4** to generate acetal **A**. The acetal after cleavage forms oxocarbenium ion **B**, which after cyclization produces intermediate carbocation **C**. The intermediate **C** after rearrangement produces carbocation **D** *via* path a, which after elimination of proton gives final S-trans products **6** at room temperature. On the other hand, carbocation **C** after elimination of proton *via* pathways b gives compound **7**. At lower temperature (-45 ^{o}C) compound **6** is in equilibrium with its S-cis product **6′**, which after reaction with aldehyde in a hetero Diels-Alder fashion gives pyranopyran **8** (Scheme 3).

Scheme 3. Plausible mechanism for ene- and [4+2] cycloaddion reactions



In order to prove the formation of compound **8** from compound **6** *via* intermediate **6′** compound **6** was reacted with **5** under similar conditions and it was observed that pyranopyrans **8** was obtained in moderate yields (Scheme 4). Accordingly, compounds **8n-o** were obtained in 54 and 46% yields, respectively.

Scheme 4. Synthesis of pyranopyrans having two different arylaldehydes



The hetero Diels Alder reaction is highly regio- and diastereo-selective. The regioselectivity can be explained by the fact that the frontier orbitals of dienes are polarized due to the presence electron donating CH_3 (in case of products **8a-8f**) or $(-CH_2-)_4$ group (in case of products **8g-8m**) as shown in Figure 3. Therefore, the HOMO of the diene interacts with the LUMO of the dienophile to give the desired regioisomers.[20]

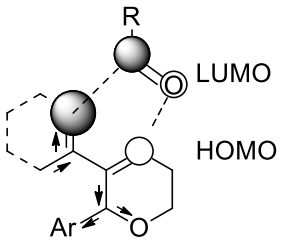
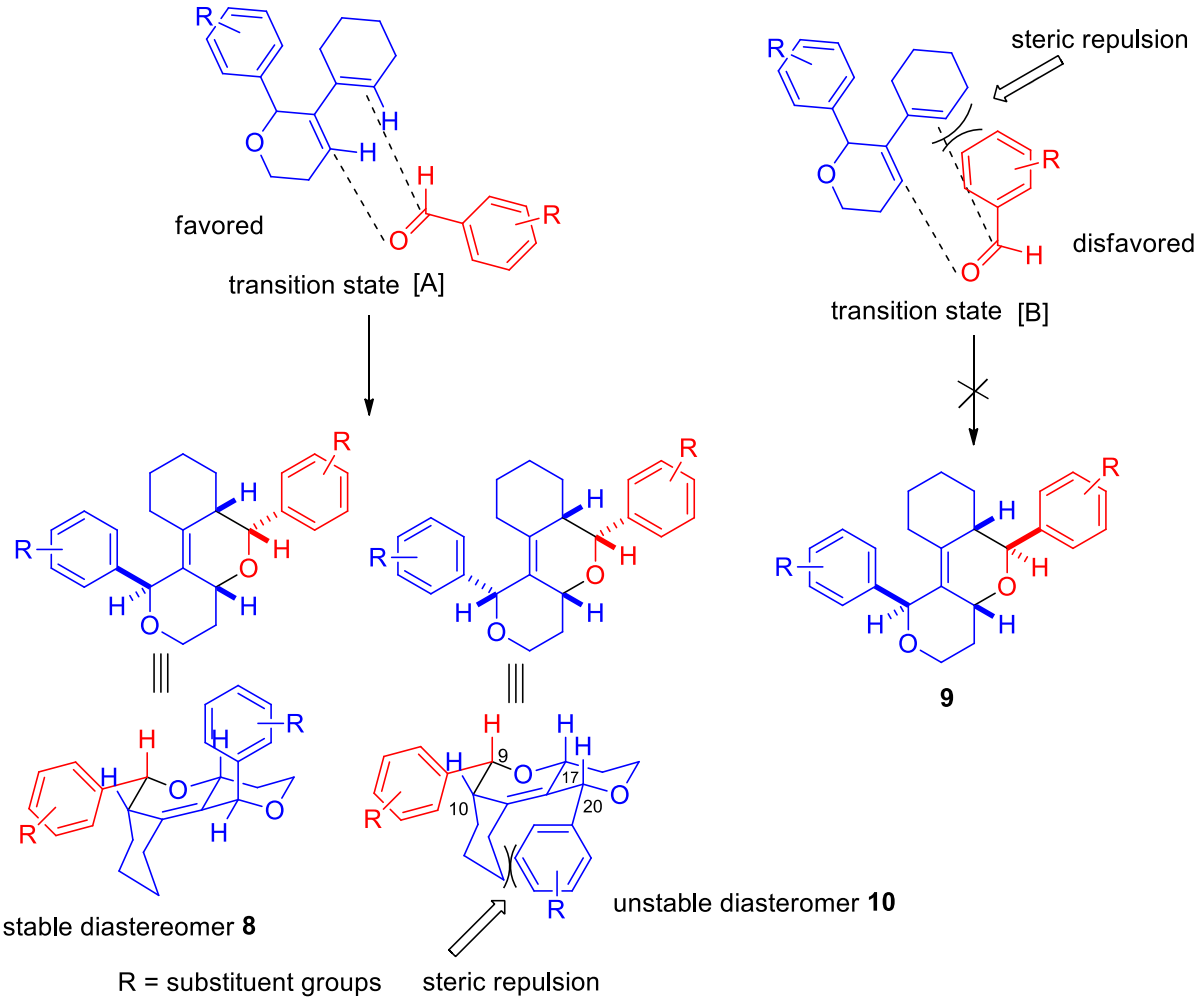


Figure 3: HOMO and LUMO interaction and regioselectivity in hetero Diels Alder reaction

The observed diastereoselectivity of the reaction is due to the formation of more stable transition sate [**A**] where there is less steric repulsion between the cyclohexene group of the dihydropyran and the

hydrogen of the aldehyde group compared to transition state [**B**], which experiences a strong steric repulsion between the cyclohexene ring and the aryl group (Scheme 5). Therefore, the desired

Scheme 5. Diastereoselectivity of the reaction



products under these circumstances might be **8** or **10** with protons at C-9H, C-10H and C-17H are in all *cis* configuration. The diastereomer **10** is not stable due to the presence of steric repulsion between cyclohexyl ring and aryl group at C-20 position. Therefore, the desired product is **8** with two phenyl groups in trans configuration.

CONCLUSION

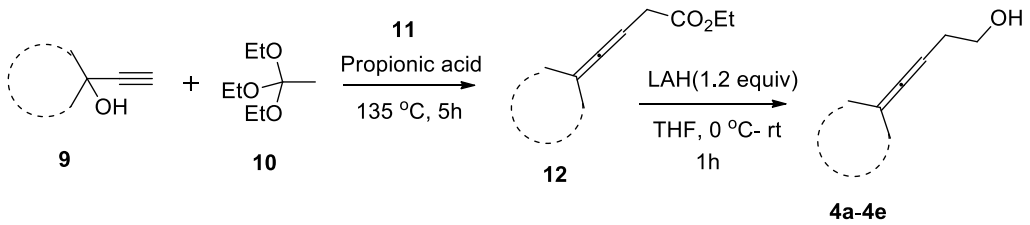
In conclusion, an efficient methodology for the synthesis of dihydropyrans starting from *β*-allenols and aldehydes has been developed with a moderate to good yields. The reaction is

highly regioselective. On the other hand, the same *β*-allenol can be used for the synthesis of hexahydropyrano[4,3-*b*]pyran skeleton in moderate yields. The reaction is highly diastereoselective.

EXPERIMENTAL SECTION

General Information: All reagents were purchased from commercial vendors as reagent grade and used without further purification. Column chromatography and TLC were performed using Silica gel (60-120 mesh size) and silica gel GF_{254} (0.25 mm), respectively. Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded on a Fourier transform-infra red (FT-IR) machine either as neat liquid or KBr pellets. NMR spectra were recorded at 400 MHz (^{1}H, 400 MHz and ^{13}C, 100 MHz) and 600 MHz (^{1}H, 600 MHz and ^{13}C, 150 MHz) machines in $CDCl_3$ using tetramethylsilane as internal standard. Chemical shifts (δ) were reported in parts per million (ppm) and spin-spin coupling constants (J) are given in Hz. High resolution mass (HRMS) were measured using Q-TOF mass analyzer. The starting allenols were prepared as per the literature procedure.[21]

General procedure for the synthesis of allenols 4a-4e:



In a round bottom flask, tertiary alcohol **9** (12.0 mmol) was taken along with triethyl orthoacetate **10** (23.5 mmol). To this solution propionic acid **11** (0.84 mmol) was added dropwise and the reaction mixture was heated at 135 °C for 5h. After completion of the reaction, the crude product was extracted with ethyl

acetate, evaporated under vacuum and finally purified by column chromatography (Hexane:EtOAc: 9:1) to give allene ester **12**. The allene ester **12** was then reduced to allenols **4a**-**4e** by lithium aluminium hydride (LAH). The reaction was treated with aqueous sodium hydroxide solution, extracted with ethyl acetate, washed with brine solution, dried (Na_2SO_4) and concentrated in rotary evaporator under vacuum. Finally the allenols were purified by column chromatography using ethyl acetate and hexane (1:9::EtOAC:Hexane) as eluent to give pure compounds **4a**-**4c**. The spectral data of these compounds are in agreement with the literature data.[21]

Procedure for the synthesis of 6-phenyl-5-(prop-1-en-2-yl)-3,6-dihydro-2*H*-pyran (6a):

To a solution of $Bi(OTf)_3$ (15 mol % 0.050 g) in dichloromethane (3 mL) at 0^o C was added benzaldehyde (0.5 mmol, 0.053 g) solution in dichloromethane (1 mL) and 5-methylhexa-3,4-dien-1-ol (0.75 mmol, 0.090 g) under N_2 atmosphere. The reaction was stirred for 12h at room temperature. After completion of the reaction as monitored by TLC, dichloromethane was evaporated, washed with brine solution and extraction with EtOAc (2x 30 mL). Finally 6-phenyl-5-(prop-1-en-2-yl)-3,6-dihydro-2*H*-pyran (**6a**) was obtained by column chromatography.

6-Phenyl-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (***6a***):

Pale yellow liquid; R_f (hexane/ EtOAc 24:1) 0.50; yield 75 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3 H), 2.15-2.24 (m, 1 H), 2.44-2.50 (m, 1 H), 3.54-3.64 (m, 2 H), 4.57 (s, 1 H), 4.78 (s, 1 H), 5.49 (s, 1 H), 6.23 (t, *J* = 4.2 Hz, 1 H) 7.12-7.34 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 25.9, 58.5, 75.6, 113.0, 124.3, 128.0, 128.4, 129.2, 137.7, 140.6, 140.7; IR (KBr, neat) 2977, 2927, 1606, 1449, 1346, 1150, 1079, 756, 698 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{17}O$ $(M + H)^+$ 201.1274, found 201.1266.

*6-(4-Fluorophenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**6b**):*

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 52 mg, 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3 H), 2.16-2.23 (m, 1 H), 2.43-2.52 (m, 1 H), 3.53-3.57 (m, 1 H), 3.59-3.62 (m, 1 H), 4.54 (s, 1 H), 4.79 (s, 1 H), 5.46 (s, 1 H), 6.23 (t, *J* = 4.2 Hz, 1 H), 6.98-7.03 (m, 2 H), 7.28-7.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 25.9, 58.5, 74.8, 113.1, 115.2 (d, *J* =21.2 Hz), 124.5, 130.9 (d, *J* = 8.1 Hz), 136.7 (d, *J* = 3.2 Hz), 137.6, 140.6, 162.6 (d, *J* = 244.6 Hz); IR (KBr, neat) 2956, 2857, 1567, 1467, 1378, 1091, 855, 747 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}FO$ $(M + H)^+$ 219.1180, found 219.1196.

*6-(3-Chlorophenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**6c**):*

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.46; yield 85 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3 H), 2.20-2.24 (m, 1 H), 2.43-2.52 (m, 1 H), 3.50-3.58 (m, 1 H), 3.60-3.66 (m, 1 H), 4.54 (s, 1 H), 4.81 (s, 1 H), 5.45 (s, 1 H), 6.24 (t, *J* = 4.0 Hz, 1 H), 7.22-7.31 (m, *J* 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 25.8, 58.7, 74.9, 113.2, 124.8, 127.5, 128.2, 129.3, 129.7, 134.3, 137.1, 140.4, 142.9; IR (KBr, neat) 2964, 2925, 2865, 1639, 1595, 1573, 1471, 1427, 1287, 1252, 1184, 1087, 1032, 884, 785, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}ClO$ $(M + H)^+$ 235.0884, found 235.0876.

*6-(4-Bromophenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**6d**):*

Pale brown oil; R_f (hexane/ EtOAc 23:0.5) 0.48; yield 82 mg, 57%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.89 (s, 3 H), 2.15-2.23 (m, 1 H), 2.43-2.48 (m, 1 H), 3.52-3.56 (m, 1 H), 3.59-3.63 (m, 1 H), 4.53 (s, 1 H), 4.79 (s, 1 H), 5.43 (s, 1 H), 6.23 (t, *J* = 4.1 Hz, 1 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0, 25.9, 58.6, 74.8, 113.2, 122.1, 124.7, 131.0, 131.5, 137.3, 139.9, 140.5; IR (KBr, neat) 2925, 2860, 1587, 1481, 1373, 1256, 1118, 1074, 1003, 825, 746 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}BrO$ $(M + H)^+$ 279.0379, found 279.0377.

*6-(4-Nitrophenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**6e**):*

Brown gum; R_f (hexane/ EtOAc 24:1) 0.55; yield 96 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3 H), 2.22-2.28 (m, 1 H), 2.46-2.49 (m, 1 H), 3.50-3.54 (m, 1 H), 3.63-3.67 (m, 1 H), 4.49 (s, 1 H), 4.81 (s, 1 H), 5.54 (s, 1 H), 6.30 (t, *J* = 4.2 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 8.19 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 25.5, 59.0, 74.3, 113.0, 123.4, 125.1, 129.9, 136.5, 140.2, 147.5, 147.9; IR (KBr, neat) 2925, 2854, 1605, 1522, 1347, 1108, 1082, 1015, 854, 771 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}NO_3$ $(M + H)^+$ 246.1125, found 246.1118.

*6-(2-Nitrophenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**6f**):*

Brown gum; R_f (hexane/ EtOAc 24:1) 0.57; yield 101 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (s, 3 H), 2.12-2.20 (m, 1 H), 2.42-2.53 (m, 1 H), 3.31-3.38 (m, 1 H), 3.61-3.66 (m, 1 H), 4.67 (s, 1 H), 4.87 (s, 1 H), 6.28-6.31 (m, 2 H), 7.28 (dd, *J* = 7.8 and 1.6 Hz, 1 H), 7.43-7.48 (m, 2 H), 7.80 (dd, *J* = 7.8 and 1.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 25.8, 58.9, 69.6, 113.4, 124.8, 125.7, 129.0, 131.3, 131.7, 134.5, 136.4, 140.3, 150.2; IR (KBr, neat) 2927, 2858, 1608, 1530, 1463, 1362, 1162, 1088, 1031, 867, 743 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}NO_3$ $(M + H)^+$ 246.1125, found 246.1128.

*Methyl 4-(3-(prop-1-en-2-yl)-5,6-dihydro-2H-pyran-2-yl)benzoate (**6g**):*

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 79 mg, 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3 H), 2.18-2.26 (m, 1 H), 2.44-2.52 (m, 1 H), 3.51-3.57 (m, 1 H), 3.61-3.72 (m, 1 H), 3.91 (s, 3 H), 4.52 (s, 1 H), 4.79 (s, 1 H), 5.51 (s, 1 H), 6.26 (t, *J* = 4.1 Hz, 1 H), 7.41 (d, *J* = 8.2 Hz, 2 H), 8.00 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 25.9, 52.3, 59.0, 75.1, 113.2, 124.8, 129.3, 129.8, 129.9, 137.2, 140.6, 145.9, 167.2; IR (KBr, neat) 2925, 1720, 1606, 1435, 1360, 1279, 1108, 1070, 1017, 878, 767 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{19}O_3$ $(M + H)^+$ 259.1329, found 259.1323.

*5,5,10-Trimethyl-3,5,10,10a-tetrahydro-2H-benzo[g]chromene (**6h**):*

Pale yellow liquid; R_f (hexane/ EtOAc 23:0.5) 0.59; yield 71 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 1.45 (s, 3 H), 1.48 (d, *J* = 6.8 Hz, 3 H), 2.10-2.18 (m, 1 H), 2.23-2.32 (m, 1 H), 2.91-3.00 (m, 1 H), 3.62-3.68 (m, 1 H), 3.90-3.94 (m, 1 H), 4.00-4.08 (m, 1 H), 5.83 (t, *J* = 3.4 Hz, 1 H), 7.15-7.23 (m, 2 H), 7.30 (dd, *J* = 7.2 and 1.4 Hz, 1 H), 7.34 (dd, *J* = 7.2 and 1.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 26.0, 29.7, 35.0, 39.5, 40.4, 61.8, 75.7, 115.8, 126.2, 126.3, 126.5, 126.7, 138.8, 144.4, 145.5; IR (KBr, neat) 2966, 2924, 2854, 1602, 1488, 1463, 1371, 1263, 1102, 1028, 951, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{21}O$ $(M + H)^+$ 229.1587, found 229.1588.

*6-Cyclohexyl-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**6i**):*

Colourless oil; R_f (hexane/ EtOAc 23:0.5) 0.55; yield 45 mg, 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.48 (m, 3H), 1.56-1.69 (m, 6 H), 1.74-1.8 (m, 2 H), 1.85 (s, 3 H), 1.91-1.98 (m, 1 H), 1.24-1.27 (m, 1 H), 3.43-3.49 (m, 1 H), 3.90-3.94 (m, 1H), 4.3 (s, 1 H), 54.78 (s 1H), 4.83 (s, 1H), 5.94-5.96 (d, *J* = 6.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 25.7, 25.9, 26.7, 26.8, 27.2, 30.5, 41.1, 62.8, 78.5, 111.5, 123.0, 141.2, 143.3; IR (KBr, neat) 2924, 2851, 1449, 1377, 1250, 1103, 1053, 1012, 845, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{23}O$ $(M + H)^+$ 207.1743, found 207.1759.

*2-Phenyl-3-(propan-2-ylidene)-3,6-dihydro-2H-pyran (**7a**):*

Colorlass liquid; R_f (hexane/ EtOAc 24:1) 0.50; yield 97 mg, 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 6 H), 4.30 (t, *J* = 2.0 Hz, 2 H) 5.88-5.93 (m, 1 H), 6.43 (s, 1 H), 6.57-6.61 (m, 1 H), 7.20-7.25 (m, 3 H), 7.31-7.35 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 61.3, 73.9, 122.1, 122.8, 127.0, 128.2, 128.3, 129.6, 137.1, 139.8; IR (KBr, neat) 2977, 2927, 1638, 1492, 1360, 1124, 1078, 1015, 824, 756, 698 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{17}O$ $(M + H)^+$ 201.1274, found 201.1256.

6-(4-Methoxyphenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (***7b***):

Yellow liquid; Rf (hexane/ EtOAc 24:1) 0.50; yield 70 mg, 62%, ^{1}H NMR (600 MHz, CDCl3) δ 1.43 (s, 6 H), 3.80 (s, 3H), 4.29 (s, 2 H), 5.88 (d, *J* = 10.2 Hz, 1 H), 6.37 (s, 1 H), 6.60 (d, *J* = 10.8 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, CDCl3) δ 26.2, 55.4, 61.3., 73.9, 113.7, 122.1, 122.3, 127.6, 129.5, 130.8, 138.4, 158.6; IR (KBr, neat) 3412, 2924, 1722, 1607, 1511, 1370, 1036, 823 cm-1; HRMS (ESI) calcd. for $C_{15}H_{19}O_2$ (M + H)+ 231.1380, found 231.1378.

5-(Cyclopent-1-en-1-yl)-6-(4-fluorophenyl)-3,6-dihydro-2H-pyran (***6j***):

Colourless oil; R_f (hexane/ EtOAc 23:0.5) 0.59; yield 55 mg, 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77-1.85 (m, 2 H), 2.16-2.30 (m, 3 H), 2.41-2.53 (m, 3 H), 3.57-3.62 (m, 2 H), 5.15 (s, 1 H), 5.40 (s, 1 H), 6.04 (t, *J* = 4.1 Hz, 1 H), 6.98-7.03 (m, 2 H), 7.25-7.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 25.9, 32.5, 33.6, 58.9, 75.3, 115.2 (d, *J* = 21.2 Hz), 123.9, 127.1, 131.0 (d, *J* = 8.1 Hz), 134.5, 137.0 (d, *J* = 3.2 Hz), 140.7, 162.6 (d, *J* = 244.5 Hz); IR (KBr, neat) 2923, 1603, 1506, 1224, 1157, 1087, 829 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}FO$ $(M + H)^+$ 245.1336, found 245.1336.

5-(Cyclopent-1-en-1-yl)-6-(2-nitrophenyl)-3,6-dihydro-2H-pyran (***6k***):

Yellow solid; R_f (hexane/ EtOAc 24:1) 0.48; m. p. 115-119 ºC; yield 116 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-1.89 (m, 2 H), 2.11-2.18 (m, 1 H), 2.25-2.36 (m, 2 H), 2.42-2.59 (m, 3 H), 3.34-3.41 (m, 1 H), 3.60-3.65 (m, 1 H), 5.31 (s, 1 H), 6.10 (t, *J* = 4.0 Hz, 1 H), 6.21 (s, 1 H), 7.29 (dd, *J* = 7.8 and 1.6 Hz, 1 H), 7.40-7.48 (m, 2 H), 7.80 (dd, *J* = 7.8 and 1.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 25.7, 32.5, 33.6, 59.2, 70.0, 124.6, 124.8, 127.3, 128.9, 131.4, 131.7, 133.3, 134.6, 140.6, 150.4; IR (KBr, neat) 2925, 1528, 1360, 1253, 1180, 1086, 963, 783cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}NO_3$ $(M + H)^+$ 272.1281, found 272.1308.

5-(Cyclohex-1-en-1-yl)-6-(4-methoxyphenyl)-3,6-dihydro-2H-pyran (***6l***):

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.58; yield 100 mg, 73%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.44-1.48 (m, 2 H), 1.57-1.64 (m, 2 H), 1.86-1.94 (m, 2 H), 2.08-2.14 (m, 2 H), 2.16-2.20 (m, 1 H), 2.42-2.45 (m, 1 H), 3.52-3.58 (m, 2 H), 3.8 (s, 3 H), 5.38(s, 1 H), 5.40 (s, 1H), 6.10 (t, *J*= 4.1 Hz, 1 H), 6.84 (d, *J*= 8.7 Hz, 2 H), 7.24 (d, *J* = 8.6 Hz, 2 H) ;^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.0, 25.7, 25.8, 25.9, 55.3, 58.4, 74.9, 113.5, 120.5, 124.6, 130.5, 133.3, 134.1, 138.3, 159. IR (KBr, neat) 2927, 1608, 1509, 1461, 1172, 1089, 1035, 819 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{23}O_2$ $(M + H)^+$ 271.1693, found 271.1690 .

5-(Cyclohex-1-en-1-yl)-6-(4-fluorophenyl)-3,6-dihydro-2H-pyran (***6m***):

Colourless oil; R_f (hexane/ EtOAc 23:0.5) 0.55; yield 85 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.45- 1.5 (m, 2 H), 1.56-1.64 (m, 2 H), 1.86-1.98 (m, 2 H), 2.06-2.11 (m, 1 H), 2.13-2.22 (m, 2 H), 2.42-2.45 (m, 1 H), 3.50-3.54 (m, 1 H), 3.58- 3.62 (m, 1 H), 5.35 (s, 1 H), 5.43 (s, 1 H), 6.07 (t, *J*= 4.08 Hz, 1 H), 6.98-7.01 (m, 2 H), 7.28-7.30 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.0, 25.7, 25.8, 25.8, 58.8, 74.7, 115.1 (*J*= 14.0 Hz), 120.8, 125.0, 130.9 (*J* = 5.4 Hz), 134.1, 136.9 (*J*= 5.4 Hz), 138.1, 162 (*J*= 162 Hz); IR (KBr, neat) 2927, 1602, 1506, 1436, 1223, 1156, 1091, 1056, 924, 823 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{20}FO$ $(M + H)^+$ 259.1493, found 259.1477 .

5-(Cyclohept-1-en-1-yl)-6-isopropyl-3,6-dihydro-2H-pyran (***6n***):

Pale yellow oil; R_f (hexane/ EtOAc 23:0.5) 0.61; yield 48 mg, 43%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, *J* = 6.8 Hz, 3 H), 1.02 (d, *J* = 7.2 Hz, 3 H), 1.45-1.50 (m, 4 H), 1.71-1.76 (m, 2 H), 1.90- 1.94 (m, 2 H), 2.11-2.14 (m, 2 H), 2.19-2.24 (m, 3 H), 3.46-3.52 (*dt*, *J*= 10.4 Hz, 3.2 Hz, 1 H), 3.92 (dd, *J*= 10.4 Hz and 5.6 Hz, 1 H), 4.25 (s, 1 H), 5.67 (t, *J* = 6.8 Hz , 1 H), 5.74 (d, *J* = 6.4 Hz 1 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 20.2, 25.9, 27.0, 27.1, 28.7, 30.8, 31.9, 32.8, 63.3, 78.9, 121.0, 127.7, 144.4, 145.0; IR (KBr, neat) 2922, 2848,

1450, 1376, 1263, 1208, 1096, 1043, 941, 847, 786, 751, 476 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{25}O$ $(M + H)^+$ 221.1900, found 221.1898 .

*5-(Cyclohept-1-en-1-yl)-6-(4-methoxyphenyl)-3,6-dihydro-2H-pyran (**6o**):*

Pale yellow oil; R_f (hexane/ EtOAc 23:0.5) 0.61; yield 65 mg, 47%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27-1.32 (m, 2 H), 1.35-1.41 (m, 1 H), 1.62-1.67 (m, 3 H), 1.99-2.05 (m, 2 H), 2.16-2.22 (m, 1 H), 2.25-2.28 (m, 2 H), 2.33-2.41 (m, 1 H), 3.60-3.63 (m, 2 H), 3.80 (s, 3 H), 5.38 (s, 1 H), 5.61 (t, *J* = 6.8 Hz, 1 H), 6.03 (t, *J* = 4.0 Hz, 1 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 7.22 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.4, 26.8, 28.5, 29.9, 32.7, 55.4, 59.3, 75.7, 113.6, 121.0, 129.0, 130.6, 133.2, 140.2, 142.9, 159.3; IR (KBr, neat) 2921, 2849, 1608, 1509, 1460, 1247, 1173, 1035, 825 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{25}O_2$ $(M + H)^+$ 285.1849, found 285.1841.

*(E)-5-(Cyclooct-1-en-1-yl)-6-(p-tolyl)-3,6-dihydro-2H-pyran (**6p**):*

Pale yellow oil; R_f (hexane/ EtOAc 23:0.5) 0.58; yield 92 mg, 66%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33-1.42 (m, 5 H), 1.52-1.55 (m, 3 H), 1.99-2.02 (m, 2 H), 2.12-2.18 (m, 1 H), 2.33 (s, 3 H), 2.34-2.40 (m, 3 H), 3.54-3.59 (m, 2 H), 5.35 (t, *J* = 8 Hz, 1 H), 5.43 (s, 1 H), 6.13 (t, *J* = 4.4 Hz, 1 H), 7.12 (d, *J* = 8 Hz, 2 H), 7.24 (d, *J* = 8 Hz, 2 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 25.4, 26.0, 26.2, 27.2, 27.5, 29.3, 30.4, 58.4, 75.3, 121.5, 127.6, 128.9, 129.4, 137.4, 137.5, 137.6, 138; IR (KBr, neat) 2923, 2853, 1608, 1448, 1258, 1084, 1049, 871, 811, 737, cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{27}O$ $(M + H)^+$ 283.2056 , found 283.2044.

*6-(4-Chlorophenyl)-5-(cyclooct-1-en-1-yl)-3,6-dihydro-2H-pyran (**6q**):*

Pale yellow oil; R_f (hexane/ EtOAc 23:0.5) 0.58; yield 112 mg, 72%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34-1.54 (m, 8 H), 2.02-2.03 (m, 2 H), 2.18-2.20 (m, 1 H), 2.36-2.40 (m, 3 H), 3.49-3.53 (m, 1 H), 3.54-3.63 (m, 1 H), 5.31 (t, *J* = 8.1 Hz, 1 H), 5.43 (s, 1 H), 6.16 (d, *J* = 3.5 Hz, 1 H), 7.28 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 25.6, 25.9, 26.9, 27.2, 29.0,

30.1, 58.5, 74.5, 121.7, 127.5, 128.1, 130.5, 133.4, 136.7, 137.2, 139.3; IR (KBr, neat) 2922, 2851, 1593, 1486, 1447, 1249, 1089, 1050, 1015, 870, 820, 733 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}ClO$ $(M + H)^+$ 303.1510, found 303.1512.

*4-(3-(Cyclooct-1-en-1-yl)-5,6-dihydro-2H-pyran-2-yl)benzonitrile (**6r**):*

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.57; yield 68 mg, 46%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22-1.29 (m, 1 H), 1.31-1.45 (m, 5 H), 1.50-1.56 (m, 2 H), 1.99-2.04 (m, 2 H), 2.18-2.24 (m, 1 H), 2.35-2.40 (m, 2 H), 2.43-2.50 (m, 1 H), 3.46-3.53 (m, 1 H), 3.60-3.66 (m, 1 H), 5.27 (t, *J* = 8.2 Hz, 1 H), 5.48 (s, 1 H), 6.20 (t, *J* = 4.1 Hz, 1 H), 7.45 (d, *J* = 8.2 Hz, 2 H), 7.61 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 25.8, 26.2, 27.1, 27.4, 29.2, 30.3, 59.4, 74.9, 111.7, 119.1, 122.5, 128.0, 130.1, 132.2, 136.3, 137.5, 146.5 ; IR (KBr, neat) 2922, 2228, 1447, 1253, 1090, 1051, 871, 825, 730 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{24}NO$ $(M + H)^+$ 294.1852, found 294.1871.

*5-(Cyclopent-1-en-1-yl)-6-(4-nitrophenyl)-3,6-dihydro-2H-pyran (**6s**) and 3-Cyclopentyl-idene-2-(4-nitrophenyl)-3,6-dihydro-2H-pyran (**6s'**)(**6s**:**6s'** = 2:1):*

Dark brown solid; R_f (hexane/ EtOAc 24:1) 0.57; mixed m. p. 110-113 °C; yield 73 mg, 68%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80-1.84 (m, 3 H), 1.85-1.87 (m, 1 H), 2.20-2.29 (m, 2 H), 2.45-2.56 (m, 2 H), 3.50-3.68 (m, 2 H, major), 4.30-4.32 (m, 2 H, minor), 5.11 (s, 1 H, major), 5.48 (s, 1 H, major), 6.01-6.05 (m, 1 H, minor), 6.11 (t, *J* = 4.0 Hz, 1 H, major), 6.44 (s, 1 H, minor), 6.54-6.57 (m, 1 H, minor), 7.41 (d, *J* = 8.4 Hz, 2 H, minor), 7.50 (d, *J* = 8.6 Hz, 2 H, major), 8.17-8.20 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 22.6, 24.5, 31.3, 32.3, 34.9, 48.3, 60.4, 73.8, 83.9, 118.7, 121.1, 122.4, 122.42, 123.3, 126.0, 129.0, 129.1, 129.8, 132.3, 139.4, 140.2, 143.0, 145.3, 146.5, 147.2; IR (KBr, neat) 2962, 2853, 1638, 1520, 1408, 1345, 1260, 1090, 1060, 1018, 853, 752, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}NO_3$ $(M + H)^+$ 272.1281, found 272.1266.

*2-(4-Bromophenyl)-3-cyclopentylidene-3,6-dihydro-2H-pyran (**6t**):*

Dark brown gum; R_f (hexane/ EtOAc 24:1) 0.60; yield 72 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77-1.85 (m, 2 H), 2.15-2.30 (m, 3 H), 2.41-2.53 (m, 3 H), 3.52-3.64 (m, 2 H), 5.15 (s, 1 H), 5.38 (s, 1 H), 6.05 (t, *J* = 4.0 Hz, 1 H), 7.21 (dd, *J* = 6.8 and 1.6 Hz, 2 H), 7.45 (dd, *J* = 6.8 and 1.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 25.7, 32.4, 33.5, 58.8, 75.2, 122.0, 123.9, 127.0, 131.0, 131.4, 134.0, 140.1, 140.5; IR (KBr, neat) 2924, 2851, 1637, 1589, 1484, 1404, 1265, 1087, 962, 812, 737 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}BrO$ $(M + H)^+$ 305.0536, found 305.0545.

Procedure for the synthesis of 4-methyl-2,5-diphenyl-2,3,5,7,8,8a-hexahydropyrano[4,3-*b*]pyran (8a):

To a solution of benzaldehyde (**5a)** (1 mmol, 0.053 g) in dichloromethane (3 mL) at -45 ºC, 3-cyclohexylideneprop-2-en-1-ol (**4c)** (0.75 mmol, 0.114 g) was added under N_2 atmosphere. To this reaction mixture, TMSOTf (0.1 mmol, 0.018 g) was added after 5 minutes and then continued for 5h. It was brought to room temperature; dichloromethane was removed in a rotary evaporator, quenched with saturated sodium bicarbonate solution, and extracted with ethyl acetate (2 x 10 mL). The organic layer was washed with brine solution, dried (Na_2SO_4) and evaporated in a rotary evaporator under vacuum. The final product **8a** was obtained by column chromatography using ethyl acetate and hexane as eluents (Hexane:EtOAC::24:1).

(2R,5S*,8aR*)-4-Methyl-2,5-diphenyl-2,3,5,7,8,8a-hexahydropyrano[4,3-b]pyran* (***8a***):

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 60 mg, 40%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.78 (s, 3 H), 1.97-1.98 (m, 1 H), 2.00-2.10 (m, 1 H), 2.27-2.30 (m, 1 H), 2.51-2.56 (m, 1 H), 3.62-3.63 (m, 1 H), 3.81-3.83(m, 1 H), 4.34-4.35 (m, 1 H), 4.65-4.68 (m, 1 H), 5.9 (s, 1 H), 7.24-7.44 (m, 10 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.5, 34.7, 39.5, 60.4, 72.4, 74.2, 75.3, 126.2, 127.2,127.5, 127.9, 128.1, 128.7,128.9, 129.1, 139.2, 142.4; IR (KBr, neat)

2925, 1492, 1448, 1373, 1104, 1072, 970, 766, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}O_2$ $(M + H)^+$ 307.1693, found 307.1692.

(2R,5S*,8aR*)-4-Methyl-2,5-di-p-tolyl-2,3,5,7,8,8a-hexahydropyrano[4,3-b]pyran (**8b**):*

Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 79 mg, 46%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 3 H), 1.86-1.93 (m, 1 H), 1.95-2.00 (m, 1 H), 2.25 (dt, *J* = 17.0 and 2.6 Hz, 1 H), 2.33 (s, 3 H), 2.37 (s, 3 H), 2.48-2.56 (m, 1 H), 3.61 (dt, *J* = 12.0 and 2.0 Hz, 1 H), 3.79 (dt, *J* = 10.4 and 3.0 Hz, 1 H), 4.30-4.34 (m, 1 H), 4.63 (dd, *J* = 10.4 and 3.0 Hz, 1 H), 5.86 (s, 1 H), 7.16-7.24 (m, 4 H), 7.29-7.33 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 21.3, 21.4, 34.7, 39.5, 60.4, 72.4, 74.2, 75.2, 126.2, 127.2, 127.9, 129.2, 129.3, 129.6, 136.2, 137.1, 137.4, 139.5; IR (KBr, neat) 2924, 1511, 1460, 1371, 1265, 1077, 968, 812, 738, cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{27}O_2$ $(M + H)^+$ 335.2006, found 335.2008.

(2R,5S*,8aR*)-2,5-bis(4-Bromophenyl)-4-methyl-2,3,5,7,8,8a-hexahydropyrano[4,3-b]pyran (**8c**):*

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.56; yield 125 mg, 54%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 3 H), 1.86-1.93 (m, 1 H), 1.95-2.00 (m, 1 H), 2.25 (dt, *J* = 17.0 and 2.6 Hz, 1 H), 2.48-2.56 (m, 1 H), 3.61 (dt, *J* = 12.0 and 2.0 Hz, 1 H), 3.79 (dt, *J* = 10.4 and 3.0 Hz, 1 H), 4.30-4.34 (m, 1 H), 4.63 (dd, *J* = 10.4 and 3.0 Hz, 1 H), 5.86 (s, 1 H), 7.29 (d, *J* = 8Hz, 4H), 7.49 (d, *J*= 8 Hz, 2H), 7.51 (d, *J*= 8Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 34.5, 39.4, 60.6, 72.3, 73.8, 74.6, 121.6, 121.7, 127.9, 128.3, 128.8, 129.0, 131.8, 132.0, 138.3, 141.4; IR (KBr, neat) 2924, 1485, 1397, 1074, 1010, 865, 804, cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{21}Br_2O_2$ $(M + H)^+$ 462.9903, found 462.9906.

(1S,4aR*,6R*,6aS*)-1,6-bis(4-Nitrophenyl)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-c]isochromene (**8d**):*

Pale yellow solid; R_f (hexane/ EtOAc 24:1) 0.48 m. pt 165-169 ^oC. yield 127 mg, 58%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14-1.16 (m, 1 H), 1.35-1.47 (m, 3 H), 1.80 -1.82 (m, 1 H), 1.90-1.92 (m, 2 H), 1.97-2.01 (m, 1 H), 2.08-2.11(m, 1 H), 2.36 (m, 1 H), 2.68 (d, *J*= 8.8, 1 H), 3.57 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.93 (dt, *J* = 12.2 and 2.7 Hz, 1 H), 4.23-4.25 (m, 1 H), 4.97 (d, *J* = 3.8 Hz, 1 H), 5.97 (s, 1 H), 7.54 (d, *J* = 8.6 Hz, 2 H), 7.62 (d, *J* = 8.6 Hz, 2 H), 8.24-8.27 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 29.0, 29.2, 31.2, 34.4, 44.4, 60.9, 72.2, 73.2, 76.7, 123.7, 124.1, 125.1, 126.7, 128.0, 138.4, 147.2, 147.5, 147.6, 148.0; IR (KBr, neat) 2931, 2856, 1603, 1519, 1346, 1191, 1080, 859, 726 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{25}N_2O_6$ $(M + H)^+$ 437.1707, found 437.1718.

Dimethyl 4,4'-((1S,4aR*,6R*,6aS*)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-c]isochromene-1,6-diyl)dibenzoate (**8e**):*

White solid ; R_f (hexane/ EtOAc 24:1) 0.48. m. pt 110-113 ^oC yield. 127 mg, 55%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25-1.45 (m, 4 H), 1.75-1.79 (m, 1 H), 1.81-1.89 (m, 2 H), 1.91-2.00 (m, 1 H), 2.03-2.08 (m, 1 H), 2.28-2.34 (m, 1 H), 2.62-2.68 (m, 1 H), 3.58 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.86 (dt, *J* = 12.2 and 2.8 Hz, 1 H), 3.92 (s, 6 H), 4.22-4.26 (m, 1 H), 4.92 (d, *J* = 3.8 Hz, 1 H), 5.94 (s, 1 H), 7.42 (d, *J* = 8.2 Hz, 2 H), 7.52 (d, *J* = 8.2 Hz, 2 H), 8.02-8.06 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 29.0, 29.2, 31.2, 34.6, 44.5, 52.3, 52.4, 60.8, 72.2, 73.4, 125.4, 125.9, 127.2, 128.9, 129.4, 129.7, 130.1, 138.0, 145.2, 145.9, 167.2, 167.3; IR (KBr, neat) 2928, 1722, 1611, 1436, 1280, 1109, 1018, 771, 735 cm^{-1}; HRMS (ESI) calcd. for $C_{28}H_{31}O_6$ $(M + H)^+$ 463.2115, found 463.2120.

(1S,4aR*,6R*,6aS*)-1,6-bis(4-Bromophenyl)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-c]isochromene (**8f**):*

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.59; yield 103 mg, 41%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20-1.43 (m, 4 H), 1.76-1.93 (m, 4 H), 2.00-2.05 (m, 1 H), 2.18-2.24 (m, 1 H),

2.59-2.64 (m, 1 H), 3.57 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.82 (dt, *J* = 12.2 and 2.8 Hz, 1 H), 4.21-4.25 (m, 1 H), 4.79 (d, *J* = 3.6 Hz, 1 H), 5.85 (s, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.46-7.51 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 29.0, 29.2, 31.1, 34.6, 44.5, 60.5, 72.2, 73.1, 76.8, 120.8, 121.5, 125.3, 127.7, 129.1, 131.4, 131.9, 137.9, 138.9, 139.7; IR (KBr, neat) 2927, 1485, 1403, 1254, 1090, 1068, 1011, 865, 809 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{25}Br_2O_2$ $(M + H)^+$ 503.0216, found 503.0229.

(1S,4aR*,6R*,6aS*)-1,6-bis(4-Fluorophenyl)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-c]isochromene (**8g**):*

Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 76 mg, 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.40 (m, 4 H), 1.77-1.87 (m, 3 H), 1.89-1.97 (m, 1 H), 2.01-2.05 (m, 1 H), 2.18-2.23 (m, 1 H), 2.60-2.66 (m, 1 H), 3.58 (dt, *J* = 12.4 and 1.8 Hz, 1 H), 3.80 (dt, *J* = 12.4 and 1.8 Hz, 1 H), 4.25-4.29 (m, 1 H), 4.83 (d, *J* = 3.7 Hz, 1 H), 5.89 (s, 1 H), 7.02-7.08 (m, 4 H), 7.25-7.32 (m, 2 H), 7.38-7.42 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.8, 29.0, 29.2, 31.1, 34.7, 44.7, 60.3, 72.3, 73.1, 77.5, 115.1 (d, *J* = 21.1 Hz), 127.4, 127.5, 128.8, 128.9, 135.3 (d, *J* = 3.0 Hz), 136.3 (d, *J* = 3.0 Hz), 137.7, 161.9 (d, *J* = 243.0 Hz), 162.3 (d, *J* = 244.1 Hz); IR (KBr, neat) 2929, 1508, 1224, 1154, 1079, 834 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{25}F_2O_2$ $(M + H)^+$ 383.1817, found 383.1810.

(1S,4aR*,6R*,6aS*)-1,6-di-p-Tolyl-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-c]isochromene (**8h**):*

Colourless oil; R_f (hexane/ EtOAc 24:1) 0.55; yield 80 mg, 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31-1.45 (m, 4 H), 1.75-1.84 (m, 3 H), 1.89-1.97 (m, 1 H), 2.00-2.05 (m, 1 H), 2.18-2.23 (m, 1 H), 2.34 (s, 3 H), 2.36 (s, 3 H), 2.61-2.67 (m, 1 H), 3.62 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.80 (dt, *J* = 12.2 and 2.8 Hz, 1 H), 4.27-4.32 (m, 1 H), 4.83 (d, *J* = 3.7 Hz, 1 H), 5.85 (s, 1 H), 7.14-7.25 (m, 6 H), 7.33 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

21.3, 21.4, 27.0, 29.1, 29.3, 31.0, 34.8, 44.8, 60.4, 72.3, 73.5, 77.5, 125.6, 125.9, 127.3, 128.9, 129.5, 136.5, 136.8, 137.1, 137.5, 137.7; IR (KBr, neat) 2925, 1511, 1447, 1107, 1080, 962, 817, 740 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{31}O_2$ $(M + H)^+$ 375.2319, found 375.2300 .

(1S,4aR*,6R*,6aS*)-1,6-di-p-Tolyl-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[d]pyrano[4,3-b]pyran* ***(8i)****:*

Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 90 mg, 46%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28-1.34 (m, 3 H), 1.36-1.43 (m, 1 H), 1.59-1.69 (m, 4 H), 1.85-1.96 (m, 1 H), 2.01-2.04 (m, 2 H), 2.34 (s, 3 H), 2.36 (s, 3 H), 2.39-2.44 (m, 1 H), 2.59-2.66 (m, 1 H), 3.63 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.80 (dt, *J* = 12.2 and 2.8 Hz, 1 H), 4.28-4.32 (m, 1 H), 4.83 (s, 1 H), 5.81 (s, 1 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7. 32 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 21.4, 26.0, 27.2, 27.6, 29.4, 31.3, 35.4, 44.3, 60.6, 72.8, 74.3, 77.6, 125.7, 127.2, 128.9, 129.2, 129.6, 136.1, 136.3, 136.6, 137.1, 138.4 ; IR (KBr, neat) 2925, 1512, 1451, 1109, 1080, 818, 740 cm^{-1}; HRMS (ESI) calcd. for $C_{27}H_{33}O_2$ $(M + H)^+$ 389.2475, found 389.2464.

(1S,4aR*,6R*,6aS*)-1,6-bis(4-Nitrophenyl)-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[d]pyrano[4,3-b]pyran* ***(8j)****:*

Pale yellow solid; R_f (hexane/ EtOAc 24:1) 0.48. m. pt 189-193 ^oC. yield 117 mg, 52%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27-1.37 (m, 6 H), 1.69-1.76 (m, 2 H), 1.98 (dq, *J*=12.2 and 2.7 Hz, 1 H), 2.08-2.16 (m, 2 H), 2.50-2.59 (m, 1 H), 2.68 (dt, *J* =12.2 and 1.8 Hz, 1 H), 3.60 (dt, *J*=12.2 and 2.7 Hz, 1 H), 3.92-3.97 (m, 1 H), 4.22-4.29 (m, 1 H), 4.94 (d, *J* =3.8 Hz, 1 H), 5.89 (s, 1 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 8.25 (d, *J* = 8.0 Hz, 2 H), 8.27 (d, *J* = 8.0 Hz, 2 H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.9, 26.9, 27.4, 29.3, 31.4, 35.1, 44.1, 61.2, 72.7, 73.9, 77.0, 123.7, 124.2, 126.7, 128.1, 128.5, 137.6, 146.8, 147.1, 147.6,

148.4; IR (KBr, neat) 2926, 1603, 1520, 1346, 109, 854, 738, 708, cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{27}N_2O_6$ $(M + H)^+$ 451.1864, found 451.1881.

Dimethyl 4,4'-((1S,4aR*,6R*,6aS*)-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[d]pyrano[4,3-b]pyran-1,6-diyl)dibenzoate (**8k**):*

White solid; R_f (hexane/ EtOAc 24:1) 0.45. m. pt 162-165 ºC. yield 113 mg, 47%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28-1.32 (m, 4 H), 1.40-1.45 (m, 1 H), 1.60-1.72 (m, 3 H), 1.90-1.99 (m, 1 H), 2.01-2.10 (m, 2 H), 2.45-2.53 (m, 1 H), 2.61-2.68 (m, 1 H), 3.60 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.88 (dt, *J* = 12.2 and 2.8 Hz, 1 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 4.22-4.28 (m, 1 H), 4.90 (d, *J* = 2.0 Hz, 1 H), 5.85 (s, 1 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 8.02-8.07 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 27.0, 27.5, 29.4, 31.4, 35.2, 44.1, 52.3, 52.4, 61.0, 72.7, 74.2, 77.6, 125.8, 127.2, 128.8, 128.9, 129.5, 129.7, 130.2, 137.1, 144.5, 146.4, 167.1, 167.3; IR (KBr, neat) 2928, 1722, 1611, 1436, 1281, 1109, 1019, 772, 735, cm^{-1}; HRMS (ESI) calcd. for $C_{29}H_{33}O_6$ $(M + H)^+$ 477.2272, found 477.2275.

(1S,4aR*,6R*,6aS*)-1,6-bis(4-Chlorophenyl)-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[d]pyrano[4,3-b]pyran (**8l**):*

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 100 mg, 48%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28-1.34 (m, 3 H), 1.38-1.43 (m, 1 H), 1.58-1.70 (m, 4 H), 1.85-1.95 (m, 1 H), 2.00-2.05 (m, 2 H), 2.38-2.43 (m, 1 H), 2.58-2.65 (m, 1 H), 3.58 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.82 (dt, *J* = 12.2 and 2.8 Hz, 1 H), 4.23-4.27 (m, 1 H), 4.80 (d, *J* = 2.5 Hz, 1 H), 5.78 (s, 1 H), 7.31-7.35 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 27.0, 27.5, 29.3, 31.3, 35.3, 44.1, 60.8, 72.7, 73.8, 77.6, 127.2, 128.4, 128.7, 128.8, 129.1, 132.6, 133.4, 137.0, 137.6, 139.7; IR (KBr, neat) 2927, 2855, 1488, 1263, 1088, 1014, 829, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{27}Cl_2O_2$ $(M + H)^+$ 429.1383, found 429.1382.

(1S,4aR*,6R*,6aS*)-1,6-bis(4-Methoxyphenyl)-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[d]pyrano[4,3-b]pyran (**8m**):*

Yellow oil; R_f (hexane/ EtOAc 24:1) 0.40; yield 98 mg, 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.34 (m, 3 H), 1.38-1.43 (m, 1 H), 1.62-1.69 (m, 4 H), 1.88-1.94 (m, 1 H), 2.00-2.05 (m, 2 H), 2.35-2.43 (m, 1 H), 2.59-2.66 (m, 1 H), 3.61 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.78-3.82 (m, 7 H), 4.29-4.33 (m, 1 H), 4.81 (d, *J* = 2.3Hz, 1 H), 5.78 (s, 1 H), 6.88-6.93 (m, 4 H), 7.29 (d, *J* = 8.6 Hz, 2 H), 7.34 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 27.2, 27.7, 29.4, 31.3, 35.4, 44.4, 55.4, 55.5, 60.5, 72.9, 74.1, 77.6, 113.7, 114.2, 126.9, 128.5, 129.2, 131.0, 133.6, 136.5, 158.5, 159.1; IR (KBr, neat) 2927, 1622, 1510, 1247, 1171, 1079, 832cm^{-1}; HRMS (ESI) calcd. for $C_{27}H_{33}O_4$ $(M + H)^+$ 421.2373, found 421.2386.

Procedure for the synthesis of pyrano-pyran derivatives 8n:

To a stirred solution of dihydro-2*H*-pyran **6c** (0.1g, 0.4 mmol) under nitrogen atmosphere, 3mL of dry DCM was added at -45 ^{o}C, followed by aldehyde **5g** (0.074g, 0.4 mmol). 3-cyclohexylideneprop-2-en-1-ol (**4c)** (0.75 mmol, 0.114 g) was added under N_2 atmosphere. To this reaction mixture, TMSOTf (0.010 mL, 0.04 mmol) was added after 5 minutes and then continued for 5h. The completion of the reaction was monitored by thin-layer chromatography. After cooling down to room temperature, it was evaporated and quenched with saturated $NaHCO_3$ solution. Finally, it was washed with saturated brine solution and extracted with EtOAc (2 x 10 mL). The desired product **8n** was obtained by column chromatography (Hexane:EtOAc: 24:1).

Methyl 4-((2R,5S*,8aR*)-5-(3-chlorophenyl)-4-methyl-2,3,5,7,8,8a-hexahydropyrano[4,3-b]pyran-2-yl)benzoate (**8n**):*

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.60; yield 84 mg, 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (s, 3 H), 1.85-1.96 (m, 1 H), 1.99-2.04 (m, 1 H), 2.32 (dt, *J* = 17.0 and 2.8 Hz,

1 H), 2.43-2.51 (m, 1 H), 3.59 (dt, *J* = 12.2 and 2.0 Hz, 1 H), 3.84 (ddd, *J* = 12.0, 4.6 and 1.6 Hz, 1 H), 3.91 (s, 3 H), 4.29-4.32 (m, 1 H), 4.72 (dd, *J* = 10.8 and 3.4 Hz, 1 H), 5.84 (s, 1 H), 7.26-7.33 (m, 3 H), 7.41 (s, 1 H), 7.49 (d, *J* = 8.2 Hz, 2 H), 8.04 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 34.5, 39.3, 52.3, 60.7, 72.2, 73.8, 74.7, 125.3, 125.9, 127.3, 127.8, 128.4, 128.8, 129.5, 130.0, 135.1, 141.6, 147.5, 167.1; IR (KBr, neat) 2953, 2858, 1721, 1681, 1594, 1468, 1372, 1280, 1187, 1144, 1077, 1017, 970, 858, 792, 737, 680 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{24}ClO_4$ $(M + H)^+$ 399.1358, found 399.1352.

(2R,5S*,8aR*)-2-(4-Bromophenyl)-5-(4-fluorophenyl)-4-methyl-2,3,5,7,8,8a-hexahydropyrano[4,3-b]pyran (**8o**):*

Brown gum; R_f (hexane/ EtOAc 24:1) 0.60; yield 72 mg, 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (s, 3 H), 1.83-1.90 (m, 1 H), 1.91-2.00 (m, 1 H), 2.26 (dt, *J* = 17.0 and 2.8 Hz, 1 H), 2.42-2.50 (m, 1 H), 3.57 (dt, *J* = 12.2 and 1.6 Hz, 1 H), 3.81 (ddd, *J* = 12.2, 4.8 and 1.8 Hz, 1 H), 4.29-4.31 (m, 1 H), 4.62 (dd, *J* = 10.8 and 3.4 Hz, 1 H), 5.84 (s, 1 H), 7.05-7.09 (m, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.36-7.40 (m, 2 H), 7.48 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 34.5, 60.4, 72.3, 73.8, 74.6, 115.7 (d, *J* = 84.6 Hz), 121.6, 127.8, 128.0, 128.9 (d, *J* = 8.0 Hz), 129.1, 131.8, 134.8 (d, *J* = 3.0 Hz), 141.5, 162.4 (d, *J* = 244.2 Hz); IR (KBr, neat) 2927, 2858, 1602, 1503, 1405, 1225, 1103, 1076, 1011, 823, 790, 742, 632 cm^{-1}; Anal. Calcd. For $C_{21}H_{20}BrFO_2$: C, 62.54; H, 5.00. Found C, 62.47; H, 5.02.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds, NOE spectra of compounds **6g** and **6k**, The crystal parameters and ORTEP diagram of compounds **6k**, **8e** and **8k** and HRMS of compounds **6a-t**, **7a-b** and **8a-n** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENTS

NRD gratefully acknowledges Indian Institute of Technology Guwahati for her fellowship. This work is supported by Department of Science and Technology (DST), New Delhi, (Grant No. EMR/2016/006411) and CoE, MHRD, Govt of India. Authors are thankful to Central Instrument Facility (CIF), IIT Guwahati for NMR and XRD facilities.

REFERENCES

1) (a) Uenishi, J.; Ohmi, M. Total synthesis of (-)-laulimalide: Pd-catalyzed stereospecific ring construction of the substituted 3,6-dihydro[2H]pyran units *Angew. Chem., Int. Ed.* **2005**, *44*, 2756-2760. (b) Gollner, A.; Altmann, K.-H.; Gertsch, J.; Mulzer, J. Synthesis and biological evaluation of a des-dihydropyran laulimalide analog *Tetrahedron Lett*. **2009**, *50*, 5790-5792.

2) Nagasawa, T.; Kuwahara, S. Enantioselective Total Synthesis of Aspergillide C *Org. Lett*. **2009**, *11*, 761-764.

3) (a) Souto, M. L., Gavin, J. A., Manriquez, C. P., Norte, M., Fernandez, J. J. Several new squalene-derived triterpenes from Laurencia *Tetrahedron*, **2001**, *57*, 3117-3123. (b) Soriente, A., De Rosa, M. M., Scettri, A., Sodano, G., Terencio, M. C., Paya, M. Alcarez, M. J. Manoalide. *Curr Med. Chem*., **1999**, *6*, 415-431.

4) (a) Yet, L. Metal-Mediated Synthesis of Medium-Sized Rings. *Chem. Rev*., **2000**, *100*, 2963–3007. (b) Boivin, T. L. B. Synthetic routes to tetrahydrofuran, tetrahydropyran, and spiroketal units of polyether antibiotics and a survey of spiroketals of other natural products. *Tetrahedron*, **1987**, *43*, 3309–3362. (c) Coppi, L.; Ricci, A.; Taddei, M. Lewis acid-mediated condensation of alkenols and aldehydes. A selective synthesis of tetrahydropyrans and oxepanes. *J. Org. Chem*., **1988**, *53*, 911–913. (d) Li, C.-J.; Zhang,

W.-C. Diastereoselective synthesis of 2,4-disubstituted tetrahydropyranols and ethers via a prins-type cyclization catalyzed by scandium triflate. *Tetrahedron* **2000**, *56*, 2403–2411. (e) Schmidt, B.; Westhus, M. Diastereoselectivity in a ring closing metathesis reaction with a remote stereogenic center leading to quaternary dihydropyrans. *Tetrahedron* **2000**, *56*, 2421–2421. (f) Pham, M.; Allatabakhsh, A.; Minehan, T. G. An Environmentally Benign Synthesis of cis-2,6-Disubstituted Tetrahydropyrans via Indium-Mediated Tandem Allylation/Prins Cyclization Reaction. *J. Org. Chem.*, *2008*, *73*, 741–744.

5) Mack, D. J.; Guo, B.; Njardarson, J. T. Synthesis of allylic and homoallylic alcohols from unsaturated cyclic ethers using a mild and selective C-O reduction approach. *Chem. Commun*. **2012**, *48*, 7844-7846.

6) Vinals, J. F.; Kiwala, J.; Hruza, D. E.; Hall, J. B.; Vock, M. H. A. 2-Alkyl-4-phenyl-dihydropyrans and processes for augmenting the organoleptic properties of foodstuffs and tobacco using one or more of said pyrans. US Patent 4070491, 1978.

(7) (a) Sako, S.; Kurahashi, T.; Matsubara, S. Nickel-iminophosphine-catalyzed [4+2] cycloaddition of enones with allenes: synthesis of highly substituted dihydropyrans. *Chem. Commun*. **2011**, *47*, 6150−6152. (b) Li, Z.; Jung, H.; Park, M.; Lah, M. S.; Koo, S. Manganese(III)-Promoted Tandem Oxidation and Cyclization of β-Keto Ester Derivatives of Terpenoids. *Adv. Synth. Catal*. **2011**, *353*, 1913−1917. (c) Fujiwara, K.; Kurahashi, T.; Matsubara, S. Cationic Iron(III) Porphyrin-Catalyzed [4 + 2] Cycloaddition of Unactivated Aldehydes with Simple Dienes. *J. Am. Chem. Soc*. **2012**, *134*, 5512−5515. (d) Chaladaj, W.; Kowalczyk, R.; Jurczak, J. Enantioselective Construction of Cis-2,6-Disubstituted Dihydropyrans: Total Synthesis of (-)-Centrolobine. *J. Org. Chem*. **2010**, *75*, 1740−1743.

(8) (a) Schmidt, B.; Wildemann, H. Diastereoselective ring-closing metathesis in the synthesis of dihydropyrans. *J. Org. Chem*. **2000**, *65*, 5817−5822. (b) Wildemann, H.;

Dünkelmann, P.; Müller, M.; Schmidt, B. A Short Olefin Metathesis-Based Route to Enantiomerically Pure Arylated Dihydropyrans and α,β-Unsaturated δ-Valero Lactones. *J. Org. Chem*. **2003**, *68*, 799−804. (c) Donnard, M.; Tschamber, T.; Nouën, D. L.; Desrat, S.; Hinsinger, K.; Eustache, J. Ring-rearrangement metathesis of substituted dihydropyrans and dihydrofurans. *Tetrahedron* **2011**, *67*, 339−357.

(9) (a) de la Pradilla, R. F.; Tortosa, M. Sulfoxide-Directed Enantioselective Synthesis of Functionalized Dihydropyrans. *Org. Lett*. **2004**, *6*, 2157−2160. (b) de la Pradilla, R. F.; Tortosa, M.; Lwoff, N.; del Águila, M. A.; Viso, A. Sulfur-Directed Enantioselective Synthesis of Functionalized Dihydropyrans. *J. Org. Chem*. **2008**, *73*, 6716−6727.

(10) Huang, H.; Panek, J. S. Stereoselective Synthesis of Functionalized Dihydropyrans via a Formal [4+2]-Annulation of Chiral Crotylsilanes. *J. Am. Chem. Soc*. **2000**, *122*, 9836−9837.

(11) (a) Gockel, B.; Krause, N. Synthesis of bicyclic ethers by a gold/palladium/gold-catalyzed cyclization/cross coupling sequence. *Eur. J. Org. Chem*. **2010**, 311-316. (b) Raghvan, S.; Nyalata, S. Convergent Synthesis of the Dihydropyran Core Containing the C1-C15 Subunit of Sorangicin A Employing Gold(I)-Catalyzed Cyclization of an Allenic Alcohol. *J. Org. Chem*. **2016**, *81*, 10698-10706. (c) Dong, B.; Peng, H.; Motika, S. E.; Shi, X. Gold Redox Catalysis through Base-Initiated Diazonium Decomposition toward Alkene, Alkyne, and Allene Activation. *Chem. Eur. J*. **2017**, *23*, 11093-11099.

(12) (a) Arundale, E.; Mikeska, L. A. The Olefin-Aldehyde Condensation-The Prins Reaction. *Chem. Rev*. **1952**, *52*, 505−555. (b) Adams, D. R.; Bhatnagar, S. P. The Prins reaction. *Synthesis* **1977**, 661−672. (c) Snider, B. B. In The Prins Reaction and Carbonyl Ene Reactions; Trost, B. M.; Fleming, I.; Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527−561. (d) Overman, L. E.; Pennington, L. D. Strategic Use of Pinacol-Terminated Prins Cyclizations in Target-Oriented Total Synthesis. *J. Org. Chem.* **2003**, *68*, 7143−7157. (e) Yadav, V. K.; Kumar, N. V. Highly stereoselective Prins

cyclization of silylmethyl-substituted cyclopropyl carbinols to 2,4,6-trisubstituted tetrahydropyrans. *J. Am. Chem. Soc*. **2004**, *126*, 8652−8653. (f) Yadav, J. S.; Thrimurtulu, N.; Lakshmi, K. A.; Prasad, A. R.; Reddy, B. V. S. The silylalkyne-Prins cyclization. A novel synthesis of 4-iododihydropyrans. *Tetrahedron Lett*. **2010**, *51*, 661−663. (g) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. Oxonia-Cope Rearrangement and Side-Chain Exchange in the Prins Cyclization. *Org. Lett*. **2002**, *4*, 577−580.

(13) (a) Pastor, I. M.; Yus, M. Focused update on the Prins reaction and the Prins cyclization. *Curr. Org. Chem*. **2012**, *16*, 1277−1312. (b) Dobbs, A. P.; Martinović, S. The silyl-Prins reaction: a novel method for the synthesis of dihydropyrans. *Tetrahedron Lett*. **2002**, *43*, 7055−7057. (c) Lian, Y.; Hinkle, R. J. $BiBr_3$-Initiated Tandem Addition/Silyl-Prins Reactions to 2,6-Disubstituted Dihydropyrans. *J. Org. Chem*. **2006**, *71*, 7071−7074. (d) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. Stereoselective Synthesis of Dihydropyrans via Vinylsilane-Terminated Cyclizations of Ester-Substituted Oxycarbenium Ion Intermediates. *J. Org. Chem*. **1997**, *62*, 3426−3427. (e) Meilert, K.; Brimble, M. A. Synthesis of the bis-spiroacetal moiety of the shellfish toxins spirolides B and D using an iterative oxidative radical cyclization strategy. *Org. Biomol. Chem*. **2006**, *4*, 2184−2192. (f) Li, J.; Zheng, H.; Su, Y.; Xie, X.; She, X. Protecting-group-free total synthesis of goniothalesdiol A. *Synlett* **2010**, 2283−2284.

(14) (a) For current review please see Saha, P.; Saikia, Ene cyclization reaction in heterocycle synthesis, *Org. Biomol. Chem*. **2018**, *16*, 2820-2840. (b) Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. Diverse Cyclization Catalyzed by $In(OTf)_3$ for the Convergent Assembly of Substituted Tetrahydrofurans and Tetrahydropyrans, *Org. Lett*., **200**1, *3*, 2669-2672. (c) Chen, S.-L.; Hu, Q.-Y.; Loh, T.-P. Highly Efficient Chemical Kinetic Resolution of Bishomoallylic Alcohols: Synthesis of (R)-Sulcatol, *Org. Lett*., **2004**, *6*, 3365-3367. (d) Bondalapati, S.; Reddy, U. C.; Saha, P.; Saikia, A. K. An efficient

synthesis of dihydro- and tetrahydropyrans via oxonium-ene cyclization reaction, *Org. Biomol. Chem*., **2011**, *9*, 3428-3438. (d) Raju, N. P.; Reddy, B. J. M.; Anjibabu, R.; Muralikrishna, K.; Subba Reddy, B. V. A simple and expeditious synthesis of 2,3,6-trisubstituted tetrahydropyrans through (3,5)-oxonium-ene cyclization using molecular iodine, *Tetrahedron Lett*., **2013**, *54*, 3639-3642. (e) Saha, P.; Ghosh, P.; Sultana, S.; Saikia, A. K. Diastereoselective synthesis of substituted dihydropyrans via an oxonium–ene cyclization reaction. *Org. Biomol. Chem*. **2012**, *10*, 8730−8738.

(15) Han, Y.; Tang, X.; Cheng, J.; Ma, S. Indium(III) Triflate-Catalyzed Efficient Prins-Type Cyclization of *β*-Allenols and Aldehydes. *Adv. Synth. Catal*. **2016**, *358*, 4019-4029.

(16) The crystallographic data for compounds **6m** has been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1488115.

(17) (a) Aydogmus, Z.; Imre, S.; Ersoy, L.; Wray, V. Halogenated secondary metabolites from Laurencia obtuse. *Nat. Prod. Res*. **2004**, *18*, 43-49. (b) Hall, J. G.; Reiss, J. A. Elatenyne - a pyrano[3,2-b]pyranyl vinyl acetylene from the red alga Laurencia elata. *Aust. J. Chem*. **1986**, *39*, 1401-1409. (c) Wright, A. D.; KHnig, G. M.; De Nys, R.; Sticher, O. Seven new metabolites from the marine red alga Laurencia majuscule. *J. Nat. Prod.* **1993**, *56*, 394-401. (d) Gonzalez, I. C.; Forsyth, C. J. Total Synthesis of Thyrsiferyl 23-Acetate, a Specific Inhibitor of Protein Phosphatase 2A and an Anti-Leukemic Inducer of Apoptosis. *J. Am. Chem. Soc*. **2000**, *122*, 9099-9108 (e) Norte, M.; Fernandez, J. J.; Souto, M. L.; Garcia-Gravalos, M. D. Two new antitumoral polyether squalene derivatives *Tetrahedron Lett*. **1996**, *37*, 2671-2674. (f) Evidente, A. M., L.; Spanu, E.; Franceschini, A.; Lazzaroni, S.; Motta, A. Diplopyrone, a new phytotoxic tetrahydropyranpyran-2-one produced by Diplodia mutila, a fungus pathogen of cork oak. *J. Nat. Prod*. **2003**, *66*, 313-315.

(18) Onoue, H.; Marubayashi, R.; Ishikawa, E.; Konoki, K.; Torikai, K.; Ebine, M.; Murata, M.; Oishi, T. Syntheses and Biological Activities of the LMNO, ent-LMNO, and NOPQR(S) Ring Systems of Maitotoxin. *J. Org. Chem*. **2017**, *82*, 9595−9618.

(19) The crystallographic data for compound **8e** and **8k** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1840405 and 1860367 respectively.

(20) Fleming, I. Frontier Orbitals and Organic Chemical Reactions, John Willey & Sons, New York, 1976, pp 121-142.

(21) (a) Xu, D.; Lu, Z.; Lic, Z.; Ma, S. Novozym 435-catalyzed kinetic resolution of *β*-allenols. A facile route for the preparation of optically active *β*-allenols or allenyl acetates *Tetrahedron* **2004**, *60*, 11879–11887. (b) Naapuri, J.; Rolfes, J. D.; Keil, J.; Sapu, C. M.; Deska, J. Enzymatic halocyclization of allenic alcohols and carboxylates: a biocatalytic entry to functionalized *O*-heterocycles *Green Chem*. **2017**, *19*, 447-452. (c) Garcia, P.; Harrak, Y.; Diab, L.; Cordier, P.; Ollivier, C.; Gandon, V.; Malacria, M.; Fensterbank, L.; Aubert, C.; Silver-Catalyzed Cycloisomerization of 1,n-Allenynamides, *Org. Lett*. **2011**, *13*, 2952-2955.

Table of Content