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Modulating Prins cyclization *versus* tandem Prins processes for the synthesis of hexahydro-1*H*-pyrano[3,4-*c*]chromene skeleton

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Abstract: We propose the synthesis of biologically relevant hexahydro-1*H*-pyrano[3,4-*c*]chromenes, *via* a tandem Prins/Friedels-Crafts process, catalysed by BF₃·Et₂O, starting from (*E*)- and (*Z*)-5-phenoxy-pent-3-en-1-ol. The diastereoselectivity of the process is controlled by the geometry of the homoallylic alcohol. We also point out that the Prins product can be obtained in high yields and good diastereoselectivity when the reaction is promoted by AlCl₃ as Lewis acid in the presence of an external nucleophile.

Introduction

Compounds containing pyran units in their skeletons play a potential role in drug research and discovery because they are in general biologically relevant molecules, and/or building blocks for the synthesis of complex natural products.¹ Among the routes for the construction of tetrahydropyrans, the Prins cyclization, the condensation of homoallylic alcohols and carbonyls, seems quite appealing because of the simultaneous formation of C-C and C-O bonds.² This process is promoted by a variety of Lewis and Brønsted acids and needs an external or appended nucleophile to terminate the reaction sequence. In the first case often the effective Lewis acid plays the double role of promoter and nucleophile source, giving access to 2,4-disubstituted tetrahydropyrans.³ On the other hand, the use of homoallylic alcohols with a tethered nucleophile allows reaching further molecular complexity, with the formation of polycycles via Prins cascade sequences,⁴ even in an enantioselective fashion.^{4d} We have already reported the synthesis of hexahydro-1*H*-pyrano[3,4-*c*]quinolones *via* a tandem Prins/Friedel-Crafts process starting from 5-arylamino-pentenols in the presence of BF₃·Et₂O,⁵ and a FeCl₃-catalysed tandem Prins/Friedel-Crafts has also been reported starting from 6-phenyl-hexenols to deliver hexahydro-1*H*-benzo[*f*]isochromenes.⁶ An elegant method has been reported for the synthesis of chromenes using In(OTf)₃ with ionic liquids.^{7a} We wondered if it was possible to obtain hexahydro-1*H*-pyrano[3,4-*c*]chromenes from 5-phenoxy-pent-3-en-1-ols.^{7b} Indeed this tricyclic core is found in

Calyxin I (Figure 1), a natural product isolated from the seeds of *Alpinia blepharocalyx*, a plant used for the treatment of stomach disorders in China.⁸ Moreover several biologically active molecules contain this structural motif (Figure 1), which is obtained mainly by domino Knoevenagel/hetero Diels-Alder, domino aldol/hetero Diels-Alder reactions or by ring closure of substituted chromanes.⁹

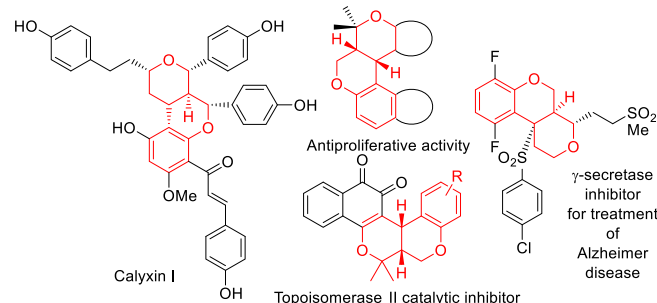


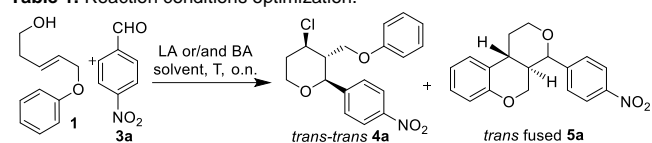
Figure 1. Natural product and biologically active compounds containing hexahydro-1*H*-pyrano[3,4-*c*]chromene skeleton.

Results and Discussion

We wish here to disclose our findings while investigating the reactivity of (*E*)- and (*Z*)-5-phenoxy-pent-3-en-1-ol (**1**) and (**2**) towards aldehydes. We started by screening different Lewis and Brønsted acids on the model reaction involving **1** and *p*-NO₂ benzaldehyde (**3a**) (Table 1). Surprisingly the use of classical Lewis acids such as FeCl₃ or InCl₃ (3 mol%) in CH₂Cl₂ at room temperature didn't give the tricyclic product coming from the tandem Prins/Friedel-Crafts process. The Prins product **4a** was observed instead in the crude reaction mixture in 30% and 40% yield respectively after 24 hours (entries 1 and 2). We thought that the formation of this unexpected product was probably due to the nucleophilicity of the counter ion of the Lewis acid. Therefore, we decided to add TMSCl as external halide ion source in order to promote the Prins pathway and indeed we obtained, with the same Lewis acids, the desired product in 70%

and 80% yield respectively (entries 3 and 4). Thus, we screened different Lewis acids in combination with TMSCl: ZnCl₂ and CuCl₂ were not effective and **4a** was obtained in up to 40% yield (entries 5 and 6). The combination of 3 equiv. of TMSCl and 3 mol% of AlCl₃ gave the desired product with the best yield of 95% in only 3 hours (entry 7). On other hand the use of a strong Lewis acid such as TiCl₄ led to the degradation of the starting materials (entry 8). Next, we attempted the reaction with different Brønsted acids such *p*-TsOH.H₂O and camphorsulfonic acid (30 mol%), and we observed the formation of **4a** in high yields of 85% and 70% respectively, as shown in Table 1, entries 9 and 10. Finally we didn't observe any reaction in absence of Lewis or Brønsted acid, as depicted in entry 11.

Table 1. Reaction conditions optimization.^[a]

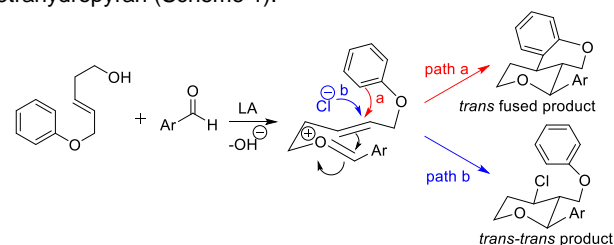


Entry	Lewis Acid (mol%)	Brønsted Acid (mol%)	Halide source	solvent	T(°C)	4a/5a	Yield (%)
1	FeCl ₃ (3)	-	-	CH ₂ Cl ₂	25	>99:1	30
2	InCl ₃ (3)	-	-	CH ₂ Cl ₂	25	>99:1	40
3	FeCl ₃ (3)	-	TMSCl	CH ₂ Cl ₂	25	>99:1	70
4	InCl ₃ (3)	-	TMSCl	CH ₂ Cl ₂	25	>99:1	80
5	ZnCl ₂ (3)	-	TMSCl	CH ₂ Cl ₂	25	>99:1	30
6	CuCl ₂ (3)	-	TMSCl	CH ₂ Cl ₂	25	>99:1	40
7	AlCl₃ (3)	-	TMSCl	CH₂Cl₂	25	>99:1	95^[d]
8	TiCl ₄ (3)	-	TMSCl	CH ₂ Cl ₂	25	-	-
9	-	<i>p</i> -TsOH.H ₂ O (30)	TMSCl	CH ₂ Cl ₂	25	>99:1	85
10	-	CSA (30)	TMSCl	CH ₂ Cl ₂	25	>99:1	70
11	-	-	TMSCl	CH ₂ Cl ₂	25	-	n.r. ^[d]
12	Cu(OTf) ₂ (10)	-	-	DCE	80	>1:99	45
13	In(OTf) ₃ (10)	-	-	DCE	80	>1:99	60
14	BF₃.OEt₂ (10)	-	-	DCE	80	>1:99	92^[e]
15	-	<i>p</i> -TsOH.H ₂ O (30)	-	DCE	80	-	n.r. ^[d]
16	-	CSA (30)	-	DCE	80	-	n.r. ^[d]
17	BF ₃ .OEt ₂ (10)	-	-	CH ₂ Cl ₂	25	>1:99	70
18	BF ₃ .OEt ₂ (10)	-	-	THF	80	>1:99	30
19	BF ₃ .OEt ₂	-	-	toluene	80	>1:99	35

(10)							
20	BF ₃ .OEt ₂ (10)	-	-	CH ₃ CN	80	-	n.r. ^[d]

[a] General conditions: **1** (1 equiv.), **3a** (1.05 equiv.), solvent (0.3 M), o.n. [b] Yields refer to isolated products [c] Reaction runs during 3 h. [d] n.r.: no reaction [e] Reaction runs during 2h.

Once observed this unusual reactivity of homoallylic alcohols bearing a tethered nucleophile toward the formation of halotetrahydropyrans, we wanted to establish reaction conditions for the formation of hexahydro-1*H*-pyrano[3,4-*c*]chromenes. To this end we attempted Lewis and Brønsted acid with a less nucleophilic counter ion on the same model reaction. We started by evaluating triflate metal salts such as Cu(OTf)₂ and In(OTf)₃ (10 mol%) in dichloroethane at 80 °C and indeed we obtained the desired **5a** in 45% and 60% yield respectively (Table 1, entries 12 and 13). When the reaction was carried out using 10 mol% BF₃.OEt₂, the Friedel-Crafts cyclization was observed, due to a non-nucleophilic character of this Lewis acid. However, in few cases, the fluoride ion can attack the tetrahydropyranyl cation to produce 4-fluorotetrahydropyrans.^{2d} The title compound was obtained in 92% yield in only 2 hours (entry 14). When Brønsted acids such as *p*-TsOH.H₂O and camphorsulfonic acid (30 mol%) were employed the reaction didn't take place as the starting materials were recovered after one night (entries 15 and 16). The use of different solvents such as CH₂Cl₂, THF and toluene didn't improve the results, since **5a** was obtained in up to 70% yield (entries 17-19). Finally, the use of acetonitrile was detrimental for the reactivity and **5a** was not observed in the crude reaction mixture (entry 20). It has to be pointed out that the products were obtained in excellent diastereoselectivity, **4a** as single *trans-trans*, and **5a** as single *trans*-fused diastereomer. In a mechanistic point of view, it's clear that the geometry of olefin controls the stereoselectivity of the reaction, as we already observed in previous works.^{4b-h} Thus once the oxocarbenium ion formed, the reaction can undergo two different pathways, depending on the nature of the nucleophile present in the reaction medium.¹⁰ In the presence of Lewis acids bringing a non-nucleophilic counter ion, the path a involving an intramolecular Friedel-Crafts lead to the formation of the pyrano-chromene as single *trans* fused diastereomer. On the other hand, the use of external nucleophile source, such as TMSCl, the path b is faster, the chlorine atom attacks the carbocation in the equatorial position providing the *trans-trans* chloro substituted tetrahydropyran (Scheme 1).¹¹

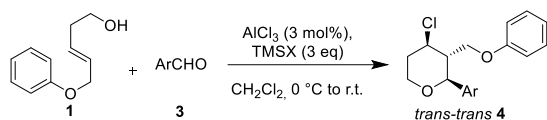


Scheme 1. Possible reaction pathways.

With the optimized conditions in hands for both pathways we examined the scope of the reactions with different aldehydes (Table 2). Concerning the formation of halotetrahydropyrans the best conditions are AlCl₃ (3 mol%), TMSCl (3 equiv.) in CH₂Cl₂, at 0 °C to room temperature. Gratifyingly benzaldehyde **3b**

(entry 1) smoothly participated to the reaction leading to the desired product in 78% yield, and the same *trans-trans* selectivity. The aromatic ring substitution in the *para* position with halogens (entries 2 and 3) is well tolerated as in all the cases the tetrahydropyrans **4c** and **4d** were obtained in 85 and 80% yields respectively. The reaction proved to be less efficient for aromatic aldehydes substituted with an electron-donating group in the *meta* and *para* position (entry 4) leading to **4e** in 65% yield. In the presence of a *meta* electron-donating (entry 5) or -withdrawing group (entry 6) the products were obtained in good yields of 85% and 80% respectively. Tetrahydropyrans **4h** (85% yield, entry 7) substituted with a bromine atom as well as **4i** (80% yield, entry 8) containing an iodine atom can also be obtained by using as halide source 3 equiv. of TMSBr or TMSI respectively.

Table 2. Scope of the Prins cyclization with the (*E*)-5-phenoxy-pent-3-en-1-ol (**1**).^a



Entry	Ar	Product 4	Time (h)	Yield (%) ^[b]
1	C ₆ H ₅ 3b		3	78
2	<i>p</i> -Br-C ₆ H ₄ 3c		1.5	85
3	<i>p</i> -F-C ₆ H ₄ 3d		2.5	80
4	<i>m,p</i> -(OCH ₃) ₂ -C ₆ H ₃ 3e		3	65
5	<i>m</i> -CH ₃ -C ₆ H ₄ 3f		2	85
6	<i>m</i> -CN-C ₆ H ₄ 3g		1	80

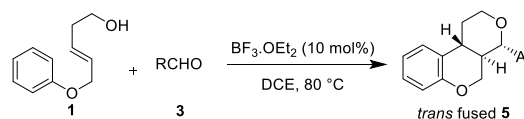
7	<i>p</i> -NO ₂ -C ₆ H ₄ 3a		2	85 ^[c]
8	<i>p</i> -NO ₂ -C ₆ H ₄ 3a		2	80 ^[d]

[a] General conditions: **1** (1 equiv.), **3a** (1.05 equiv.), CH₂Cl₂ (0.3 M) at 0 °C to r.t. [b] Yields refer to isolated products. [c] Performed with 3 equiv. of TMSBr. [d] Performed with 3 equiv. of TMSI.

We then tried to evaluate the influence of the geometry of the double bond of the homoallylic alcohol. The reaction of (*Z*)-5-phenoxy-pent-3-en-1-ol (**2**) with few different aromatic aldehydes in the presence of AlCl₃ (3 mol%), TMSCl (3 equiv.) in CH₂Cl₂, at 0 °C to room temperature led, unfortunately, to the formation of an inseparable mixture of the diastereomers where the *cis-cis* compound is the major.

The scope of the formation of hexahydro-1*H*-pyrano[3,4-*c*]chromenes was then investigated in the presence of different aromatic aldehydes (Table 3 and 4). It has to be noted that in general the (*Z*)-5-phenoxy-pent-3-en-1-ol (**2**) is less reactive than the corresponding (*E*)-homoallylic alcohol **1**, therefore the reaction time needed to observe the formation of the *cis* fused products is up to 24 h. Nevertheless, the desired pyranochromenes are obtained in very good yields in a range of 75–90% from **1** and **2**, irrespective of whether the aldehydes bore electron-withdrawing or -donating groups on the *para* (Table 3, entries 2 and 6; Table 4 entries 1 and 3) or *meta* positions of the aromatic ring (Table 3, entries 3–5; Table 4, entry 4). The scope of the reaction is also illustrated with respect to the heteroaromatic 5-bromo-2-thiophenecarboxaldehyde that gives the *trans* fused **5i** in 75% yield after 2 hours (Table 4, entry 7). Finally, for the (*Z*)-5-phenoxy-pent-3-en-1-ol (**2**) the influence of electron-donating groups on the *ortho* position of the aromatic ring of the aldehyde is also taken into account and the reaction with **3m** gave the *cis* fused **6o** in 78% yield after 12 hours (Table 4, entry 5). This protocol was also successful with aliphatic aldehydes to furnish the products as an inseparable mixture of diastereomers (Table 3, entries 8 and 9).

Table 3. Scope of the tandem Prins/Friedel-Crafts cyclization with the (*E*)-5-phenoxy-pent-3-en-1-ol (**1**).^a

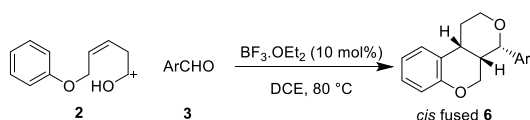


Entry	R	Product 5	Time (h)	Yield (%) ^[b]
1	C ₆ H ₅ 3b		2	80

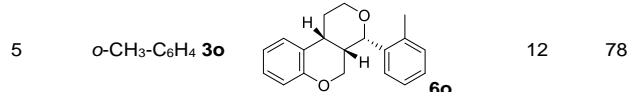
2	<i>p</i> -Br-C ₆ H ₄ 3c		1	88
3	<i>m</i> -CH ₃ -C ₆ H ₄ 3f		2	78
4	<i>m</i> -CN-C ₆ H ₄ 3g		1	85
5	<i>m</i> -NO ₂ -C ₆ H ₄ 3j		1	90
6	<i>p</i> - <i>t</i> Bu-C ₆ H ₄ 3k		1.5	80
7			2	75
8	(CH ₃) ₂ CH 3m		2.5	72
9	CH ₃ (CH ₂) ₃ 3n		2.5	67

[a] General conditions: **1** (1 equiv.), **3a** (1.05 equiv.), in DCE (0.3 M) at 80 °C to r.t. [b] Yields refer to isolated products.

Table 4. Scope of the tandem Prins/Friedel-Crafts cyclization with the (*Z*)-5-phenoxy-pent-3-en-1-ol (**2**).^a



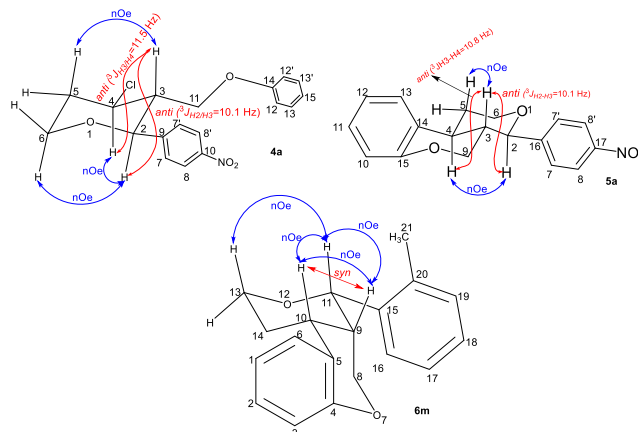
Entry	Ar	Product 6	Time (h)	Yield (%) ^[b]
1	<i>p</i> -NO ₂ -C ₆ H ₄ 3a		12	90
2	C ₆ H ₅ 3b		24	75
3	<i>p</i> -Br-C ₆ H ₄ 3c		24	80
4	<i>m</i> -Br-C ₆ H ₄ 3h		16	78



[a] General conditions: **1** (1 equiv.), **3a** (1.05 equiv.), in DCE (0.3 M) at 80 °C to r.t. [b] Yields refer to isolated products.

To confirm the relative configuration of the products we obtained, a fully characterization by NMR techniques of compounds **4a**, **5a** and **6o** was undertaken. For **4a**, the large coupling constants $^3J_{H2/H3} = 10.1$, $^3J_{H3/H4} = 11.5$ Hz, imply the di-axial disposition of the participating protons moreover, the characteristic nOe correlations between H2/H4, H2/H6 and H3/H5 provide emphatic support for the proposed structure with six membered ring taking chair conformation as shown in **Figure 2**. For compound **5a**, the large di-axial coupling constants, $^3J_{H2/H3} = 9.8$ Hz, $^3J_{H3/H4} = 10.8$ Hz indicate that H2, H3 and H4 are axially disposed in the fused six membered ring. Additional nOe correlations between H2/H4 and H3/H5 strongly support the *anti*-orientation of H2 and H3; H3 and H4 protons (**Figure 2**). Finally, the relative stereochemistry of **6o** was established by the strong nOe correlations H9/H10, H10/H11, H9/H11 and H11/H13 suggesting that H9, H10 and H11 are on the same side of the six membered ring with the *syn*-orientation of H9 and H10 protons (**Figure 2**).

Figure 2. Structure of **4a**, **5a** and **6o** along with the characteristic NOE correlations.



Conclusion

We have shown that when using 5-phenoxy-pent-3-en-1-ol as homoallylic alcohol, and playing on the reaction conditions, we can control the formation of exclusively the Prins tetrahydropyran product or the more interesting hexahydro-1*H*-pyrano[3,4-*c*]chromene skeleton, in high yields and diastereoselectivities. Indeed with (*E*)-5-phenoxy-pent-3-en-1-ol in the presence of catalytic amounts of AlCl₃ as Lewis acid and TMSCl as external nucleophilic source, only the *trans-trans* tetrahydropyrans **4** are obtained. Instead starting from (*E*)- and (*Z*)-5-phenoxy-pent-3-en-1-ol in the presence of BF₃·Et₂O as

catalyst, only the *trans*- and *cis*-fused hexahydro-1*H*-pyrano[3,4-*c*]chromenes respectively are obtained.

Experimental Section

General procedure for synthesis of compounds 4. To a stirred solution of 5-phenoxy-pent-3-en-1-ol (**1**) (0.561 mmol) and aldehydes (0.589 mmol) in dry dichloromethane (2 mL) under nitrogen atmosphere were added AlCl₃ (3 mol%) and TMSCl (3 equiv, 1.68 mmol) at 0 °C. The reaction mixture was stirred at room temperature for specified time and then quenched with saturated aqueous NaHCO₃ solution (4-5 mL), washed with brine solution (2 x 5 mL), extracted with dichloromethane (2 x 10 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel column using a gradient mixture of *n*-hexane and ethyl acetate to give the desired compounds.

(2*S*,3*R*,4*R*)-4-chloro-2-(4-nitrophenyl)-3-(phenoxy-methyl) tetrahydro-2*H*-pyran (4a**)** Yield, 0.185g (95%); pale yellow solid m.p. 120-122 °C; IR (KBr, cm⁻¹) 3446, 3068, 2958, 2865, 1514, 1486, 1349, 1249, 1225, 1091, 855, 769; ¹H NMR (500 MHz, CDCl₃) δ: 8.15 (d, *J* = 6.9 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.27 (dt, *J* = 12.6, 6.3 Hz, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.73 (d, *J* = 10.0 Hz, 1H), 4.56 (td, *J* = 11.4, 4.8 Hz, 1H), 4.33 (d, *J* = 2.2 Hz, 1H), 4.18 (ddd, *J* = 12.0, 4.9, 1.6 Hz, 1H), 3.71 (td, *J* = 12.3, 2.2 Hz, 1H), 3.42 (dd, *J* = 9.9, 2.2 Hz, 1H), 2.43 – 2.35 (m, 1H), 2.26 (ddd, *J* = 25.4, 12.6, 5.0 Hz, 1H), 1.98 (t, *J* = 10.4 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ: 158.5, 147.8, 147.0, 129.8, 128.0, 124.1, 121.5, 114.6, 80.5, 67.3, 63.7, 57.2, 51.5, 37.5; HRMS (EI) calculated for C₁₈H₁₉ClNO₄, 347.09244 Found 347.09305.

(2*S*,3*R*,4*R*)-4-Chloro-3-(phenoxy-methyl)-2-phenyltetrahydro-2*H*-pyran (4b**)** Yield 0.132g, (78%); Semi solid; IR (KBr, cm⁻¹): 3447, 3058, 3027, 2924, 2854, 1598, 1463, 1242, 1084, 756, 697; ¹H NMR (400 MHz, CDCl₃) δ: 7.38 – 7.22 (m, 7H), 6.94 (dd, *J* = 8.5, 3.1 Hz, 1H), 6.89 – 6.79 (m, 2H), 4.67 – 4.52 (m, 2H), 4.34 – 4.22 (m, 1H), 4.18 – 4.05 (m, 1H), 3.78 – 3.57 (m, 1H), 3.47 (dd, *J* = 9.6, 2.0 Hz, 1H), 2.42 – 2.17 (m, 2H), 2.12 – 1.95 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 154.1, 140.1, 129.0, 128.4, 127.7, 127.2, 126.3, 125.0, 120.2, 116.7, 79.3, 68.4, 61.9, 37.3, 35.3, 31.2; ESI-MS *m/z*: 303 [M+H]⁺.

(2*S*,3*R*,4*R*)-2-(4-Bromophenyl)-4-chloro-3-(phenoxy-methyl) tetrahydro-2*H*-pyran (4c**)** Yield 0.181g, (85%); White solid, m.p. 120-122 °C; IR (KBr, cm⁻¹): 3040, 2969, 2932, 2893, 1593, 1239, 1174, 1084, 955, 819, 751, 640; ¹H NMR (400 MHz, CDCl₃) δ: 7.45 – 7.38 (m, 2H), 7.30 – 7.23 (m, 2H), 7.22 – 7.17 (m, 2H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.83 (dd, *J* = 8.6, 1.8 Hz, 2H), 4.66 – 4.46 (m, 2H), 4.28 (dd, *J* = 9.7, 2.2 Hz, 1H), 4.14 (ddd, *J* = 11.9, 4.8, 1.6 Hz, 1H), 3.67 (td, *J* = 12.2, 2.3 Hz, 1H), 3.45 (dd, *J* = 9.7, 2.1 Hz, 1H), 2.42 – 2.17 (m, 2H), 2.05 – 1.86 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 158.8, 138.6, 131.7, 129.5, 128.7, 122.2, 121.2, 114.5, 80.4, 67.2, 64.1, 57.0, 51.9, 37.4; HRMS (EI) calculated for C₁₈H₁₈BrClO₂, 380.01787 Found 380.01765.

(2*S*,3*R*,4*R*)-4-Chloro-2-(4-fluorophenyl)-3-(phenoxy-methyl) tetrahydro-2*H*-pyran (4d**)** Yield 0.143g, (80%); white solid, m.p. 128-130 °C; IR (KBr, cm⁻¹): 3067, 2966, 2941, 2895, 2856, 2728, 1599, 1503, 1463, 1241, 1134, 848, 823, 754, 542; ¹H NMR (500 MHz, CDCl₃) δ: 7.33 – 7.24 (m, 4H), 7.01 – 6.93 (m, 3H), 6.86 – 6.79 (m, 2H), 4.65 – 4.48 (m, 2H), 4.28 (dd, *J* = 9.6, 2.2 Hz, 1H), 4.14 (ddd, *J* = 11.9, 4.9, 1.6 Hz, 1H), 3.68 (td, *J* = 12.3, 2.2 Hz, 1H), 3.44 (dd, *J* = 9.6, 2.1 Hz, 1H), 2.39 – 2.32 (m, 1H), 2.24 (ddd, *J* = 13.1, 5.1, 2.6 Hz, 1H), 2.04 – 1.91 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 163.5, 161.5, 158.5, 135.5, (d, *J*_{CF} = 2.7 Hz), 129.5, 128.7, (d, *J*_{CF} = 8 Hz), 121.1, 115.5 (d, *J*_{CF} = 21 Hz), 114.5, 80.6, 67.2, 64.2, 57.0, 52.0, 37.4; HRMS (EI) calculated for C₁₈H₁₈ClFO₂ 320.09794 Found 320.09826.

(2*S*,3*R*,4*R*)-4-Chloro-2-(3,4-dimethoxyphenyl)-3-(phenoxy-methyl)tetrahydro-2*H*-pyran (4e**)** Yield 0.162g, (65%); White solid, m.p. 104-106 °C; IR (KBr, cm⁻¹): 3447, 2996, 2958, 2858, 1596, 1516, 1462, 1236, 1164, 1073, 1024, 754, 693, 507; ¹H NMR (500 MHz, CDCl₃) δ: 7.28 – 7.23 (m, 2H), 6.96 – 6.92 (m, 1H), 6.88 – 6.82 (m, 3H), 6.78 (dd, *J* = 8.0, 3.1 Hz, 2H), 4.62 – 4.53 (m, 2H), 4.29 (dd, *J* = 9.5, 2.1 Hz, 1H), 4.15 (ddd, *J* = 11.9, 4.8, 1.6 Hz, 1H), 3.83 (s, 3H), 3.73 – 3.68 (m, 1H), 3.66 – 3.52 (m, 3H), 3.49 (dd, *J* = 9.5, 2.1 Hz, 1H), 2.34 (ddd, *J* = 6.6, 4.8, 2.4 Hz, 1H), 2.25 (ddd, *J* = 14.5, 12.5, 4.9 Hz, 1H), 2.03 – 1.96 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 159.0, 148.8, 132.3, 129.5, 121.3, 119.5, 114.5, 111.0, 109.7, 81.2, 67.2, 64.2, 57.3, 55.9, 55.6, 52.2, 37.6; HRMS (EI) calculated for C₂₀H₂₃ClO₄, 362.12849 Found 362.12811.

(2*S*,3*R*,4*R*)-4-Chloro-3-(phenoxy-methyl)-2-(*m*-tolyl) tetrahydro-2*H*-pyran (4f**)** Yield 0.150g, (85%); white solid, m.p. 127-129 °C IR (KBr, cm⁻¹): 3447, 3068, 2925, 2850, 1635, 1556, 1521, 1460, 1391, 1260, 1135, 1043, 857, 760; ¹H NMR (400 MHz, CDCl₃) δ: 7.30 – 7.22 (m, 2H), 7.15 (dd, *J* = 8.3, 3.1 Hz, 2H), 7.08 (d, *J* = 7.3 Hz, 2H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.83 (dd, *J* = 8.6, 0.8 Hz, 2H), 4.64 – 4.52 (m, 2H), 4.27 (dd, *J* = 9.6, 2.2 Hz, 1H), 4.14 (ddd, *J* = 11.9, 4.8, 1.7 Hz, 1H), 3.68 (td, *J* = 12.1, 2.4 Hz, 1H), 3.48 (dd, *J* = 9.6, 2.0 Hz, 1H), 2.40 – 2.16 (m, 5H), 2.10 – 1.98 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 158.9, 139.6, 138.3, 129.4, 129.0, 128.4, 127.6, 124.3, 121.0, 114.7, 81.4, 67.2, 64.4, 57.3, 51.8, 37.5, 21.4; HRMS (EI) calculated for C₁₉H₂₁ClNO₂, 316.12301 Found 316.12201.

4-(2*S*,3*R*,4*R*)-4-Chloro-3-(phenoxy-methyl)tetrahydro-2*H*-pyran-2-yl)benzonitrile (4g**)** Yield 0.146g, (80%); Colourless liquid; IR (KBr, cm⁻¹): 3040, 2969, 2932, 2893, 1593, 1239, 1174, 1084, 955, 819, 751, 640; ¹H NMR (500 MHz, CDCl₃) δ: 7.68 (d, *J* = 8.6 Hz, 1H), 7.57 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.02 – 6.95 (m, 1H), 6.83 (dd, *J* = 8.7, 1.9 Hz, 2H), 4.65 (d, *J* = 10.0 Hz, 1H), 4.54 (td, *J* = 11.5, 4.8 Hz, 1H), 4.32 (dd, *J* = 9.9, 2.2 Hz, 1H), 4.19 – 4.11 (m, 1H), 3.69 (td, *J* = 12.3, 2.2 Hz, 1H), 3.43 (dd, *J* = 9.9, 2.2 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.31 – 2.15 (m, 1H), 1.99 (tt, *J* = 10.6, 2.2 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 158.3, 141.2, 132.0, 131.7, 130.7, 129.6, 129.3, 121.5, 118.5, 114.5, 112.9, 80.3, 67.3, 64.1, 52.0, 37.4; ESI-MS *m/z*: 350 [M+Na]⁺.

(2*S*,3*R*,4*R*)-4-Bromo-2-(4-nitrophenyl)-3-(phenoxy-methyl) tetrahydro-2*H*-pyran (4h**)** Yield 0.186g, (85%); Yellow Semi solid; IR (KBr, cm⁻¹): 3450, 3071, 2926, 2854, 1598, 1521, 1346, 1238, 1087, 851, 753, 694; ¹H NMR (500 MHz, CDCl₃) δ: 8.15 (d, *J* = 8.7 Hz, 2H), 7.52 (dd, *J* = 7.7, 2.6 Hz, 2H), 7.28 (dd, *J* = 8.1, 3.0 Hz, 2H), 6.98 (td, *J* = 7.4, 1.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 4.79 – 4.66 (m, 2H), 4.56 (tt, *J* = 11.4, 5.8 Hz, 1H), 4.32 (ddd, *J* = 9.9, 4.2, 2.2 Hz, 1H), 3.78 – 3.63 (m, 1H), 3.44 (ddd, *J* = 12.6, 5.1, 2.2 Hz, 1H), 2.56 – 2.44 (m, 1H), 2.42 – 2.20 (m, 1H), 2.15 – 1.94 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 158.2, 147.8, 146.8, 129.6, 127.9, 123.7, 121.2, 114.4, 80.6, 80.2, 68.2, 67.3, 65.5, 63.9, 56.6, 52.0, 51.8, 49.1, 38.4, 37.3; ESI-MS *m/z*: 392 [M+H]⁺.

(2*S*,3*R*,4*R*)-4-Iodo-2-(4-nitrophenyl)-3-(phenoxy-methyl) tetrahydro-2*H*-pyran (4i**)** Yield 0.197g, (80%); Pale brown Semi solid; IR (KBr, cm⁻¹): 3449, 3121, 3063, 2927, 2865, 1600, 1521, 1353, 1233, 1076, 854, 750; ¹H NMR (400 MHz, CDCl₃) δ: 8.27 – 8.10 (m, 2H), 7.60 – 7.42 (m, 2H), 7.34 – 7.19 (m, 2H), 7.07 – 6.89 (m, 1H), 6.89 – 6.74 (m, 2H), 4.82 (ddd, *J* = 12.6, 5.3, 2.1 Hz, 2H), 4.21 (dd, *J* = 10.0, 2.3 Hz, 1H), 4.07 – 3.88 (m, 1H), 3.77 – 3.60 (m, 1H), 3.51 (dt, *J* = 13.2, 6.6 Hz, 1H), 2.82 – 2.55 (m, 2H), 2.18 – 2.13 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 158.2, 147.7, 147.0, 129.6, 127.9, 123.7, 121.5, 114.5, 80.5, 69.6, 68.4, 52.4, 40.9, 27.4; ESI-MS *m/z*: 440 [M+H]⁺.

General procedure for synthesis of compounds 5 and 6. To a stirred solution of (*E*)-5-phenoxy-pent-3-en-1-ol (**1**) or (**2**) and aldehyde (0.589 mmol) in dry 1,2-dichloroethane (2 mL) under nitrogen atmosphere was added BF₃·OEt₂ (10 mol%) at 0 °C and then heated to 80 °C. The reaction mixture was stirred at the same temperature for the specified time and then quenched with sat. NaHCO₃ solution (4-5 mL),

extracted with dichloromethane (2x10 mL), washed with brine solution (2x5 mL) and dried over anhydrous Na₂SO₄. Removal of the solvent followed by purification on silica gel column using a gradient mixture of *n*-hexane and ethyl acetate gave the desired compounds.

(4aR,10bR)-4-(4-nitrophenyl)-1,4a,5,10b-tetrahydro-2H,4H-

pyrano[3,4-c]chromene: (5a) Yield 0.160g, (92%); yellow semi solid; IR (KBr, cm⁻¹): 3447, 3063, 2924, 2854, 1601, 1521, 1495, 1353, 1234, 1173, 1132, 1078, 998, 855, 750, 691, 565, 507; ¹H NMR (400 MHz, CDCl₃) δ: 8.29 – 8.22 (m, 2H), 7.61 – 7.54 (m, 2H), 7.10 (dd, *J* = 15.5, 8.0 Hz, 1H), 6.88 (t, *J* = 8.9 Hz, 1H), 6.84 – 6.78 (m, 2H), 4.34 – 4.25 (m, 1H), 4.15 (d, *J* = 9.9 Hz, 1H), 4.00 (tt, *J* = 12.1, 6.1 Hz, 1H), 3.86 – 3.73 (m, 1H), 2.50 (dd, *J* = 16.0, 12.2 Hz, 1H), 2.24 (ddt, *J* = 6.6, 4.1, 1.9 Hz, 1H), 2.14 (dd, *J* = 16.4, 5.0 Hz, 1H), 2.10 – 1.91 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 153.9, 147.9, 146.4, 129.7, 128.0, 127.6, 123.8, 120.7, 120.6, 116.5, 82.7, 75.8, 66.4, 42.6, 32.2, 27.3; HRMS (EI) calculated for C₁₈H₁₇NO₄, 311.11576 Found 311.11476.

(4aR,10bR)-4-Phenyl-1,4a,5,10b-tetrahydro-2H,4H-pyrano[3,4-

c]chromene: (5b) Yield 0.119g, (80%); Semi solid; IR (KBr, cm⁻¹): 3449, 3032, 2926, 2855, 1486, 1234, 1079, 759, 694; ¹H NMR (400 MHz, CDCl₃) δ: 7.43 – 7.21 (m, 5H), 7.13 – 6.99 (m, 1H), 6.90 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.85 – 6.75 (m, 2H), 4.26 (ddd, *J* = 11.9, 4.9, 1.7 Hz, 1H), 4.05 – 3.94 (m, 2H), 3.77 (dt, *J* = 12.2, 2.5 Hz, 1H), 2.48 – 2.36 (m, 1H), 2.24 – 2.13 (m, 2H), 2.13 – 1.98 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 154.1, 139.1, 129.8, 128.4, 127.4, 127.3, 121.4, 120.5, 116.4, 83.9, 76.3, 66.4, 42.2, 32.4, 27.4; HRMS (EI) calculated for C₁₈H₁₈O₂, 266.13068 Found. 266.13058.

(4aR,10bR)-4-(4-Bromophenyl)-1,4a,5,10b-tetrahydro-2H,4H-

pyrano[3,4-c]chromene: (5c) Yield 0.170g, (88%); Semi-solid; IR (KBr, cm⁻¹): 3450, 3052, 2973, 2925, 2891, 2852, 1489, 1237, 1081, 756; ¹H NMR (400 MHz, CDCl₃) δ: 7.54 – 7.49 (m, 2H), 7.29 – 7.24 (m, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 7.3 Hz, 1H), 6.84 – 6.77 (m, 2H), 4.26 (ddd, *J* = 11.9, 4.9, 1.6 Hz, 1H), 4.03 – 3.93 (m, 2H), 3.76 (td, *J* = 12.4, 2.2 Hz, 1H), 2.42 (dd, *J* = 12.2, 16.1 Hz, 1H), 2.25 – 2.13 (m, 2H), 2.12 – 1.91 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 154.0, 138.2, 131.7, 129.8, 128.9, 127.5, 122.2, 121.2, 120.6, 116.5, 83.1, 76.1, 66.3, 42.3, 32.5, 27.3; HRMS (EI) calculated for C₁₈H₁₇BrO₂, 344.04119 Found 344.04109.

(4aS,10bR)-4-(*m*-Tolyl)-1,4a,5,10b-tetrahydro-2H,4H-pyrano[3,4-

c]chromene: (5f) Yield 0.141g, (90%); White solid, m.p. 126–128 °C IR (KBr, cm⁻¹): 3449, 2937, 2854, 1488, 1225, 1092, 1041, 753; ¹H NMR (400 MHz, CDCl₃) δ: 7.25 (dd, *J* = 8.0, 3.3 Hz, 2H), 7.15 (d, *J* = 7.2 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.4 Hz, 1H), 6.85 – 6.75 (m, 2H), 4.32 – 4.20 (m, 1H), 4.08 – 3.90 (m, 2H), 3.85 – 3.70 (m, 1H), 2.50 – 2.39 (m, 1H), 2.36 – 2.30 (m, 3H), 2.28 – 2.15 (m, 2H), 2.13 – 1.97 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 154.1, 138.9, 138.4, 129.8, 129.2, 128.4, 127.9, 127.4, 124.5, 121.5, 120.5, 116.4, 83.9, 76.4, 66.4, 42.0, 32.4, 27.4, 21.4; HRMS (EI) calculated for C₁₉H₂₀O₂, 280.14633 Found 280.14611.

3-(4aR,10bR)-1,4a,5,10b-Tetrahydro-2H,4H-pyrano[3,4-c]chromen-4-

yl)benzoxonitrile: (5g) Yield 0.138g, (85%); Semi solid; IR (KBr, cm⁻¹): 3426, 3052, 2961, 2932, 2850, 2224, 1485, 1240, 1083, 1046, 761, 688; ¹H NMR (400 MHz, CDCl₃) δ: 7.69 (t, *J* = 1.5 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.54 – 7.47 (m, 1H), 7.09 (t, *J* = 7.9 Hz, 1H), 6.90 (dt, *J* = 6.3, 3.2 Hz, 1H), 6.81 (dd, *J* = 11.4, 4.3 Hz, 2H), 4.28 (ddd, *J* = 11.9, 4.9, 1.6 Hz, 1H), 4.07 (d, *J* = 9.9 Hz, 1H), 4.04 – 3.96 (m, 1H), 3.77 (td, *J* = 12.4, 2.2 Hz, 1H), 2.48 (dd, *J* = 16.0, 12.2 Hz, 1H), 2.26 – 2.19 (m, 1H), 2.14 (dd, *J* = 16.1, 5.1 Hz, 1H), 2.11 – 1.91 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 154.0, 140.9, 131.5, 129.7, 129.4, 127.6, 120.7, 118.6, 116.5, 112.6, 82.7, 75.8, 66.4, 42.3, 32.3, 27.3; HRMS (EI) calculated for C₁₉H₁₇NO₂, 291.12593 Found 291.12545.

(4aS,10bR)-4-(3-Nitrophenyl)-1,4a,5,10b-tetrahydro-2H,4H-

pyrano[3,4-c]chromene: (5j) Yield, 0.136g, (78%); Yellow semi solid; IR (KBr, cm⁻¹): 3443, 3023, 2955, 2862, 1486, 1235, 1084, 756, 574; ¹H

NMR (400 MHz, CDCl₃) δ: 8.35 – 8.16 (m, 2H), 7.72 (t, *J* = 8.4 Hz, 2H), 7.68 – 7.46 (m, 1H), 7.19 – 6.99 (m, 1H), 6.98 – 6.71 (m, 2H), 4.38 – 4.23 (m, 1H), 4.17 (t, *J* = 11.6 Hz, 1H), 4.09 – 3.91 (m, 1H), 3.75 (dddd, *J* = 17.5, 13.9, 13.4, 10.3 Hz, 1H), 2.51 (dd, *J* = 15.9, 12.3 Hz, 1H), 2.28 – 2.21 (m, 1H), 2.20 – 2.12 (m, 1H), 2.31 – 1.95 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 154.0, 148.3, 141.4, 133.2, 129.7, 129.6, 127.6, 123.3, 122.3, 120.7, 116.5, 82.7, 75.8, 66.1, 42.8, 32.2, 27.1; HRMS (EI) calculated for C₁₈H₁₇NO₄, 311.11576 Found 311.11532.

(4aR,10bR)-4-(4-(tert-Butyl)phenyl)-1,4a,5,10b-tetrahydro-2H,4H-

pyrano[3,4-c]chromene: (5k) Yield 0.144g, (80%); Semi solid; IR (KBr, cm⁻¹): 3443, 3023, 2955, 2862, 1486, 1235, 1084, 756, 574; ¹H NMR (400 MHz, CDCl₃) δ: 7.39 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.84 – 6.73 (m, 2H), 4.29 – 4.18 (m, 1H), 4.05 – 3.93 (m, 2H), 3.83 – 3.69 (m, 1H), 2.42 (dd, *J* = 16.2, 12.2 Hz, 1H), 2.30 – 2.15 (m, 2H), 2.13 – 1.96 (m, 2H), 1.32 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ: 154.1, 151.3, 136.0, 129.8, 127.3, 127.0, 125.5, 121.6, 120.4, 116.4, 83.6, 76.4, 66.3, 41.9, 34.6, 32.4, 31.3, 27.4; HRMS (EI) calculated for C₂₂H₂₆O₂, 322.19328 Found 322.19323.

(4aR,10bR)-4-(5-Bromothiophen-2-yl)-1,4a,5,10b-tetrahydro-2H,4H-

pyrano[3,4-c]chromene: (5l) Yield 0.146g, (75%); Yellow liquid; IR (KBr, cm⁻¹): 2925, 2854, 1459, 1430, 1230, 1080, 755; ¹H NMR (400 MHz, CDCl₃) δ: 7.10 (t, *J* = 7.6 Hz, 1H), 7.00 – 6.92 (m, 2H), 6.83 – 6.81 (m, 3H), 4.24 (ddd, *J* = 6.4, 5.1, 2.6 Hz, 2H), 3.93 (td, *J* = 10.7, 4.7 Hz, 1H), 3.74 (td, *J* = 12.4, 2.1 Hz, 1H), 2.43 (d, *J* = 8.5 Hz, 2H), 2.20 (d, *J* = 4.0 Hz, 1H), 2.11 – 1.91 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 154.1, 139.1, 129.8, 128.6, 128.4, 127.4, 127.3, 121.4, 120.5, 116.4, 83.1, 76.3, 66.4, 42.2, 32.3, 27.4; . ESI-MS *m/z*: 351 [M+H]⁺.

(4R,4aR,10bR)-4-isopropyl-1,4a,5,10b-tetrahydro-2H,4H-pyrano[3,4-

c]chromene: (5m) Yield 0.165g, (72%); White liquid; IR (KBr, cm⁻¹): 3460, 3015, 2967, 1487, 1251, 1165, 1094, 779, 691, 676; ¹H NMR (500 MHz, CDCl₃) δ 7.13 – 7.03 (m, 2H), 6.88 – 6.78 (m, 2H), 4.13 (ddd, *J* = 11.7, 5.0, 1.5 Hz, 1H), 3.80 (td, *J* = 10.9, 4.7 Hz, 1H), 3.53 (td, *J* = 12.6, 2.1 Hz, 1H), 2.94 (dd, *J* = 9.8, 2.1 Hz, 1H), 2.67 (dd, *J* = 16.1, 5.3 Hz, 1H), 2.40 (dd, *J* = 16.0, 12.1 Hz, 1H), 2.11 – 2.03 (m, 1H), 1.95 – 1.88 (m, 1H), 1.87 – 1.79 (m, 2H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 154.3, 129.9, 127.4, 121.5, 120.4, 116.5, 84.2, 76.6, 65.9, 38.2, 32.5, 28.1, 27.0, 20.5, 14.6. HRMS (EI) calculated for C₂₂H₂₆O₂, 233.1541 Found 233.1552.

(4R,4aR,10bR)-4-butyl-1,4a,5,10b-tetrahydro-2H,4H-pyrano[3,4-

c]chromene: (5n) Yield 0.142g, (67%); White liquid; IR (KBr cm⁻¹): 3415, 3085, 2842, 2815, 1425, 1282, 1351, 1168, 1097, 741, 718, 667; ¹H NMR (500 MHz, CDCl₃) δ 7.13 – 7.09 (m, 3H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.89 – 6.85 (m, 2H), 6.82 – 6.78 (m, 2H), 4.32 (dd, *J* = 10.4, 3.9 Hz, 1H), 4.22 – 4.18 (m, 1H), 4.14 – 4.10 (m, 1H), 3.80 (td, *J* = 11.2, 5.1 Hz, 2H), 3.67 – 3.61 (m, 1H), 3.58 – 3.53 (m, 1H), 3.19 – 3.14 (m, 1H), 3.06 (t, *J* = 7.6 Hz, 1H), 2.71 (dd, *J* = 15.9, 5.3 Hz, 2H), 2.44 – 2.39 (m, 1H), 2.24 – 2.21 (m, 1H), 2.08 (dd, *J* = 13.4, 5.4 Hz, 1H), 1.91 – 1.86 (m, 1H), 1.71 (dd, *J* = 13.6, 6.3 Hz, 3H), 1.54 – 1.48 (m, 4H), 1.35 (dd, *J* = 12.7, 7.2 Hz, 6H), 0.92 (d, *J* = 5.2 Hz, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 154.2, 153.7, 129.9, 127.6, 127.4, 125.2, 121.5, 120.4, 120.2, 116.5, 116.2, 80.3, 78.4, 76.3, 67.8, 67.2, 65.8, 40.8, 40.7, 37.4, 32.8, 32.4, 32.1, 29.6, 27.4, 27.1, 22.8, 14.1. HRMS (EI) calculated for C₂₂H₂₆O₂, 247. 1698 Found 247.1709.

(4aS,10bR)-4-(4-Nitrophenyl)-1,4a,5,10b-tetrahydro-2H,4H-

pyrano[3,4-c]chromene: (6a) Yield 0.157g, (90%); Yellow semi solid; IR (KBr, cm⁻¹): 3095, 2971, 2928, 2889, 1525, 1487, 1350, 130, 1085, 1048, 758, 689; ¹H NMR (400 MHz, CDCl₃) δ 8.40 – 8.03 (m, 2H), 7.52 – 7.49 (m, 2H), 7.12 – 6.90 (m, 2H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 4.90 (d, *J* = 3.0 Hz, 1H), 4.28 (dd, *J* = 11.6, 4.7 Hz, 1H), 4.21 – 4.07 (m, 1H), 3.86 – 3.75 (m, 1H), 3.65 – 3.52 (m, 1H), 3.24 – 3.09 (m, 1H), 2.63 – 2.41 (m, 1H), 2.06 – 1.87 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 153.9, 139.0, 131.5, 128.9, 127.8, 126.8, 126.0, 121.0, 120.2, 116.8,

78.6, 68.4 61.7, 37.1, 35.1, 31.1; HRMS (EI) calculated for C₁₈H₁₇NO₄, 311.11576 Found 311.11494.

(4a*S*,10b*R*)-4-Phenyl-1,4a,5,10b-tetrahydro-2H,4H-pyrano[3,4-

c]chromene: (6b) Yield 0.107g, (72%); Semi solid; IR (KBr, cm⁻¹): 3449, 3032, 2926, 2855, 1486, 1234, 1079, 759, 694; ¹H NMR (400 MHz, CDCl₃) δ: 7.39 – 7.27 (m, 5H), 7.12 – 7.06 (m, 2H), 6.90 – 6.83 (m, 1H), 6.78 (dd, *J* = 8.3, 3.6 Hz, 1H), 4.82 (d, *J* = 3.0 Hz, 1H), 4.30 – 4.22 (m, 1H), 4.21 – 4.11 (m, 1H), 3.83 – 3.70 (m, 2H), 3.16 – 3.08 (m, 1H), 2.46 (ddd, *J* = 11.7, 4.5, 1.9 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.93 – 1.84 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 154.0, 139.9, 129.0, 128.4, 127.7, 127.2, 126.3, 125.3, 125.0, 120.2, 116.7, 79.3, 68.4, 62.0, 37.3, 35.3, 31.1; HRMS (EI) calculated for C₁₈H₁₈O₂, 266.13068 Found 266.13056.

(4a*S*,10b*R*)-4-(4-Bromophenyl)-1,4a,5,10b-tetrahydro-2H,4H-

pyrano[3,4-c]chromene: (6c) Yield 0.154g, (80%); Semi solid; IR (KBr, cm⁻¹): 3450, 3052, 2973, 2925, 2891, 2852, 1489, 1237, 1081, 756; ¹H NMR (400 MHz, CDCl₃) δ: 7.63 – 7.40 (m, 2H), 7.23 – 7.17 (m, 2H), 7.13 – 7.05 (m, 2H), 6.91 – 6.83 (m, 1H), 6.81 – 6.73 (m, 1H), 4.77 (d, *J* = 3.0 Hz, 1H), 4.31 – 4.20 (m, 1H), 4.13 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.77 (dt, *J* = 12.3, 2.4 Hz, 1H), 3.67 (dt, *J* = 11.3, 5.7 Hz, 1H), 3.18 – 3.03 (m, 1H), 2.48 – 2.40 (m, 1H), 2.12 – 1.96 (m, 1H), 1.93 – 1.83 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 154.1, 139.0, 131.5, 129.1, 127.8, 126.8, 126.1, 121.0, 120.29, 116.8, 78.6, 68.5, 61.7, 37.1, 35.1, 31.1; HRMS (EI) calculated for C₁₈H₁₇BrO₂, 344.04119 Found 344.04229.

(4a*S*,10b*R*)-4-(3-Bromophenyl)-1,4a,5,10b-tetrahydro-2H,4H-

pyrano[3,4-c]chromene: (6h) Yield 0.145g, (75%); Semi solid; IR (KBr, cm⁻¹): 3450, 3052, 2973, 2925, 2891, 2852, 1489, 1237, 1081, 756; ¹H NMR (400 MHz, CDCl₃) δ: 7.56 – 7.49 (m, 1H), 7.40 (dd, *J* = 8.3, 3.2 Hz, 1H), 7.23 (t, *J* = 8.3 Hz, 2H), 7.13 – 7.06 (m, 2H), 6.91 – 6.84 (m, 1H), 6.81 – 6.74 (m, 1H), 4.77 (d, *J* = 3.0 Hz, 1H), 4.23 (dd, *J* = 11.3, 4.4 Hz, 1H), 4.14 (t, *J* = 11.5 Hz, 1H), 3.80 – 3.66 (m, 2H), 3.15 – 3.05 (m, 1H), 2.45 (ddd, *J* = 11.6, 4.8, 1.6 Hz, 1H), 2.02 (ddd, *J* = 11.4, 4.6, 1.5 Hz, 1H), 1.90 – 1.81 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 153.9, 142.3, 130.3, 130.0, 129.0, 128.3, 127.8, 126.0, 123.6, 122.7, 120.3, 116.8, 78.4, 68.4, 61.7, 37.1, 35.1, 31.1; HRMS (EI) calculated for C₁₈H₁₇BrO₂, 344.04119 Found 344.04211.

(4a*S*,10b*R*)-4-(*o*-tolyl)-1,4a,5,10b-tetrahydro-2H,4H-pyrano[3,4-

c]chromene: (6o) Yield, 0.122g, (78%); semi-solid; IR (KBr, cm⁻¹): 3449, 3071, 2937, 2854, 1488, 1375, 1225, 1100, 1092, 1041, 753, 656; ¹H NMR (400 MHz, CDCl₃) δ: 7.41 – 7.33 (m, 1H), 7.24 – 7.04 (m, 5H), 6.91 – 6.84 (m, 1H), 6.81 – 6.72 (m, 1H), 4.93 (d, *J* = 2.8 Hz, 1H), 4.33 – 4.19 (m, 2H), 3.87 – 3.67 (m, 2H), 3.18 – 3.08 (m, 1H), 2.49 – 2.35 (m, 1H), 2.31 (s, 3H), 2.12 – 2.01 (m, 1H), 1.93 – 1.84 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 154.0, 137.8, 133.2, 130.5, 129.0, 127.8, 127.1, 125.9, 125.8, 120.1, 116.7, 77.2, 68.6, 62.5, 35.2, 34.6, 31.2, 18.9; HRMS (EI) calculated for C₁₉H₂₀O₂, 280.14633 Found 280. 14525.

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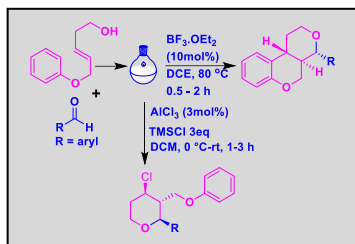
Keywords: Prins cyclization • tandem processes • tetrahydropyran • hexahydro-1*H*-pyrano[3,4-*c*]chromene

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Playing on the reaction conditions, we can control the formation of biologically relevant hexahydro-1H-pyrano[3,4-c]chromenes, via a tandem Prins/Friedels-Crafts cascade, or of the tetrahydropyrane issue of the Prins process. In both cases the the products are obtained in high yields and good diastereoselectivities.

