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PAPER

Oxidative Prins and Prins/Friedel–Crafts cyclizations for the stereoselective synthesis of dioxabicycles and hexahydro-1*H*-benzo[*f*]isochromenes *via* the benzylic C–H activation†

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1-Benzyl ethers of (*E*)- and (*Z*)-hex-3-en-1,6-diols and hept-3-en-1,7-diols undergo a smooth oxidative cyclization with DDQ in the presence of $In(OTf)_3$ through a sequential C–H bond activation and an intramolecular Prins cyclization to afford the corresponding *trans*- and *cis*-fused hexahydro-2*H*-furo[3,2-*c*]pyrans and octahydropyrano[4,3-*b*]pyrans respectively in good yields with an excellent stereoselectivity. Aryl tethered homoallylbenzyl ethers such as benzyl ethers of (*E*)- and (*Z*)-6-arylhex-3-enyl alcohols undergo a tandem Prins/Friedel–Crafts cyclization in the presence of stoichiometric amounts of DDQ and $SnCl_4$ *via* the benzylic C–H bond activation to furnish the corresponding *trans*- and *cis*-fused hexahydro-1*H*-benzo[*f*]isochromenes in good yields with complete stereoselectivity.

Introduction

The Prins cyclization has emerged as a powerful synthetic tool for the synthesis of substituted tetrahydropyran scaffolds,[1,2] whereas its intramolecular version is very useful for the stereoselective synthesis of angularly fused oxa-bicycles and tricycles through an internal attack of tethered nucleophile to the resulting oxocarbenium ion.[3] The selective functionalization of sp^3 C–H bond of ethers by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) has received considerable attention in organic synthesis.[4] It was reported that DDQ can oxidize benzyl ethers to generate oxocarbenium ions.[5] In particular, DDQ-mediated oxidative cyclizations reported by Floreancig's group are attractive for the construction of macrocycles *via* the chemo- and regioselective activation of benzylic as well as allylic sp^3 C–H bonds.[5] Mechanistically, the reaction was proposed to proceed through an oxidative cleavage of a carbon–hydrogen bond in benzylic ether to generate an oxocarbenium ion which in turn reacts with an appended nucleophile.[5h] However, the activation of a C–H bond of the oxygen in ethers is a more challenging task than the activation of a C–H bond of nitrogen in amines due to the former's higher oxidation potential.

In some instances, the use of a Lewis acid is necessary to further increase the oxidative potential of DDQ.[6] However, to the best of our knowledge, there have been no reports on intramolecular Prins and Prins/Friedel–Crafts cyclizations *via* C–H bond activation of benzyl ethers.

The furo[3,2-*c*]pyran skeleton is frequently found in various natural products such as flavonoids, catechins and pterocarpans (Fig. 1, **a**).[7,8] In addition, the pyrano[4,3-*b*]pyran moiety is also a core structure in some biologically active natural products such as Blepharocalyxin D (Fig. 1, **b**).[9] Blepharocalyxin D is a unique member of dimeric diarylheptanoid natural products isolated from the seeds of *Alpinia blepharocalyx*. It acts as an antiproliferative agent (ED_{50} 3.61 μM) against murine colon 26-L5 carcinoma cells.

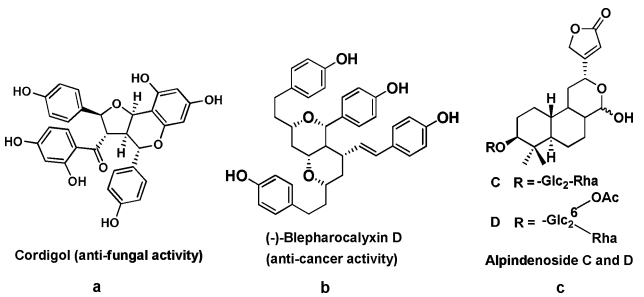

Fig. 1 Examples of some natural products bearing furo[3,2-*c*]pyran, pyrano[4,3-*b*]pyran and the saturated form of hexahydro-1*H*-benzo[*f*]isochromene motifs.

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† Electronic supplementary information (ESI) available: Preparation of starting materials and copies of ^1H and ^{13}C NMR spectrum of products.. CCDC reference number 833511. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06489d

The saturated form of hexahydro-1*H*-benzo[*f*]isochromene motif is present in labdane diterpene glycosides such as alpindenosides C, D and curcumanggoside (Fig. 1, **c**).[10] Alpindenosides C and D are isolated from the stems of *Alpinia densespicata* and are known to exhibit NO inhibitory activities. However, they are non-cytotoxic at 20 μM concentrations against several human tumor cell lines.

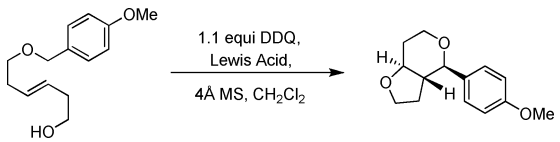
In continuation of our research on Prins type cyclizations and its application to the total synthesis of natural products,[11] we herein report a novel and versatile method for the stereoselective synthesis of bicyclic and tricyclic tetrahydropyran derivatives through a sequential benzylic C–H bond activation and an intramolecular Prins cyclization using a combination of DDQ and Lewis acid.

Results and discussion

We first attempted an intramolecular Prins type cyclization of (*E*)-6-(4-methoxybenzyloxy)hex-3-en-1-ol (**1a**) using DDQ through a benzylic C–H activation. To our surprise, no cyclization was observed in the absence of a Lewis acid. The Prins cyclization was successful in the presence of both DDQ and a Lewis acid. Therefore, to optimize the reaction conditions, several Lewis acids were screened using an equimolar amount of DDQ and the results are presented in Table 1. Of various Lewis acids probed, 1.1 equiv. of $In(OTf)_3$ was found to be most effective for the intramolecular Prins type cyclization. Under optimized conditions, the reaction requires 1.1 equivalents of both DDQ and $In(OTf)_3$ in CH_2Cl_2 at room temperature. Under the above conditions, the desired product **2a** was obtained in 75% yield with *trans* stereoselectivity (Table 1, entry d). Other Lewis acids such as $InBr_3$ and $SnCl_4$ also induced the cyclization of **1a** in the presence of DDQ to give the desired product **2a** in 40% and 56% yields respectively (Table 1, entries f and g). The use of 4 Å molecular sieves was necessary to avoid the hydrolysis of oxocarbenium ion which was assumed to be an active intermediate in the Prins cyclization.

The structure and stereochemistry of product **2a** were characterized by double quantum filtered correlation spectroscopy (DQFCOSY). The proton 4-H shows a large coupling of 9.4 Hz with 3a-H indicating axial orientation of 4-H. 3a-H also shows a large coupling (J = 10.0 Hz) with 7a-H which in turn shows a large coupling (J = 12.0 Hz) with 7-H indicates that 3a-H and 7a-H

Table 1 Effect of various Lewis acids in the Prins cyclization of (*E*)-6-(4-methoxybenzyloxy)hex-3-en-1-ol[a]



(*E*) **1a** **2a**

Entry	Lewis Acid	Equiv.	*T* (°C)	Time (h)	Yield (%)[b]
a	no acid	—	rt	24	0
b	$Sc(OTf)_3$	1.1	rt	24	trace
c	ln(0Tf)3	0.1	0 to rt	10	10
d	$In(OTf)_3$	1.1	rt	18	75
e	$In(OTf)_3$	1.5	rt	18	75
f	$InBr_3$	1.1	0 to rt	24	40
g	$SnCl_4$	1.1	−10 to rt	18	56

[a] The reaction was performed on a 0.5 mmol scale. [b] Isolated yield.

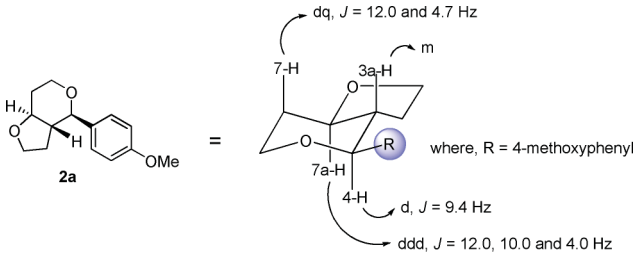
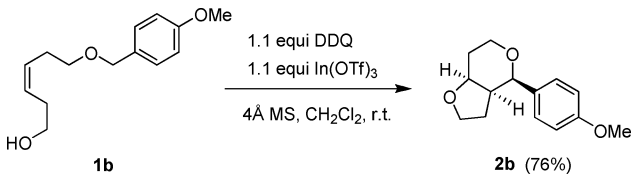


Fig. 2 Diagnostic coupling constants and chemical structure of **2a**.

are in axial orientations. Thus the fusion between the two rings is *trans* as shown in Fig. 2.

However, the cyclization of (*Z*)-6-(4-methoxybenzyloxy)hex-3-en-1-ol in the presence of DDQ and $In(OTf)_3$ in dichloromethane at room temperature gave the product **2b** in 76% yield with *cis*-selectivity (Scheme 1, Table 2, entry b).



1b **2b** (76%)

Scheme 1 Oxidative cyclization of (*Z*)-6-(4-methoxybenzyloxy)hex-3-en-1-ol with DDQ/$In(OTf)_3$.

Similarly, (*Z*)-6-(3-methoxybenzyloxy)hex-3-en-1-ol (**1g**) also gave the corresponding furo[3,2-*c*]pyran **2g** in 72% yield with a complete *cis*-selectivity (Table 2, entry **g**). The structure and stereochemistry of product **2g** were characterized by double quantum filtered correlation spectroscopy (DQFCOSY). The coupling between 4-H and 3a-H protons is 3.1 Hz, which indicates that 3a-H is in an equatorial position. This is further confirmed by a small coupling between 3a-H and 7a-H (J = 6.6 Hz). 7a-H is in an axial position as it shows a large coupling (J = 10.0 Hz) with 7-H. From these observations it was confirmed that the fusion between the two rings is *cis* as shown in Fig. 3.

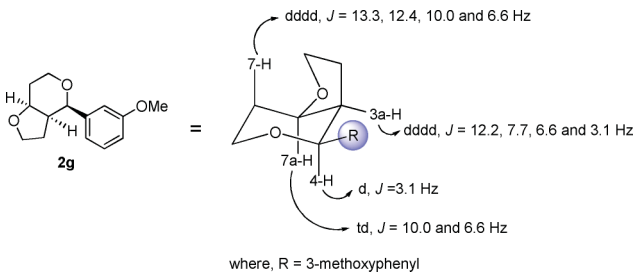
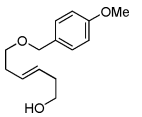
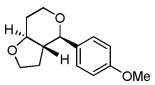
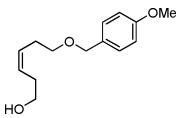
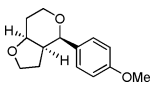
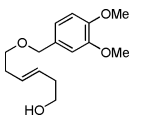
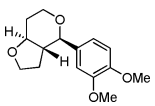
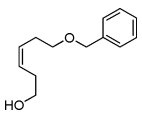
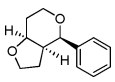
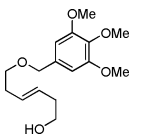
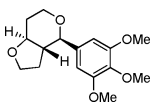
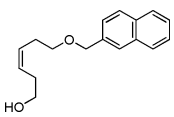
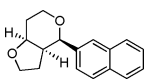
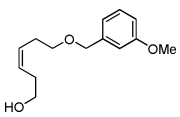
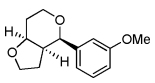
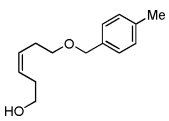
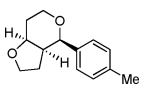
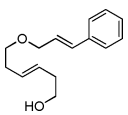
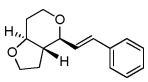


Fig. 3 Diagnostic coupling constants and chemical structure of **2g**.

The scope of the reaction is illustrated in Table 2. A variety of other substrates such as (*E*)-6-(3,4-dimethoxybenzyloxy)hex-3-en-1-ol (**1c**), (*Z*)-6-(benzyloxy)hex-3-en-1-ol (**1d**), (*E*)-6-(3,4,5-trimethoxybenzyloxy)hex-3-en-1-ol (**1e**), (*E*)-6-(naphthalen-2yl-methoxy)hex-3-en-1-ol (**1f**) and (*Z*)-6-(4-methylbenzyloxy)hex-3-en-1-ol (**1h**) participated well to furnish the corresponding *trans*- or *cis*-fused hexahydro-2*H*-furo[3,2-*c*]pyrans in moderate to good yields (entries c, d, e, f and h, Table 2). As seen from Table 2, the electronic factors of the benzyl ring did show some effect on the conversion. In general, electron-rich benzyl ethers gave

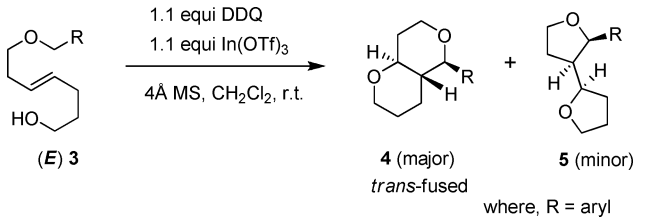
Table 2 Synthesis of *trans*- and *cis*-fused hexahydro-2*H*-furo[3,2-*c*]pyran scaffolds[a]

Entry	Substrate (**1**)	Product (**2**)[b]	Time (h)	Yield (%)[c]
a			18	75
b			18	76
c			16	78
d			24	65
e			16	80
f			22	70
g			19	72
h			22	68
i			24	65

[a] The reactions were performed on a 0.5 mmol scale. [b] All the products were characterized by ^{1}H and ^{13}C NMR, IR and mass spectroscopy. [c] Yield refers to pure products after column chromatography.

higher yields in shorter reaction times compared to simple benzyl ethers. This may be attributed to the lower oxidation potential and the greater stabilizing ability of oxocarbenium ions derived from electron-rich benzyl ethers. Notably, (*E*)-6-(cinnamyloxy)hex-3-en-1-ol (**1i**) also participated well in this reaction to furnish the desired product **2i** in good yield. However, the cyclization was sluggish with the mono-allyl ether of hex-3-en-1-diol and also the desired product was obtained in a low yield. The geometry of the olefin controls the stereoselectivity of the reaction. It is known that *cis*-olefins give the *cis*-fused product whereas *trans*-olefins provide the *trans*-fused product exclusively.[3d–3f]

Next, we studied the reactivity of 1-benzylhept-3-en-1,7-diol in intramolecular Prins cyclization. Thus, treatment of (*E*)-7-(benzyloxy)hept-4-en-1-ol (**3a**) with stoichiometric amounts of DDQ and $In(OTf)_3$ in the presence of molecular sieves in dichloromethane gave the corresponding *trans*-fused octahydropyrano[4,3-*b*]pyran **4a** as a major product along with **5a** in a 9 : 1 ratio with 75% overall yield (Scheme 2; R = phenyl), Table 3, entry **a**). These two isomeric products were inseparable by silica gel column chromatography therefore the ratio of products **4a** : **5a** was determined by HPLC.



Scheme 2 Oxidative Prins cyclization of olefin (***E***)-**3**.

Likewise, the reaction of (*E*)-7-(4-methylbenzyloxy)hept-4-en-1-ol (**3c**) with DDQ under identical conditions afforded the corresponding products **4c** and **5c** in a 9 : 1 ratio with 80% overall yield (Scheme 2; R = *p*-tolyl; Table 3, entry c). The structure and stereochemistry of product **4c** were characterized by extensive NMR experiments including 2-D Nuclear Overhauser Effect spectroscopy (NOESY) and double quantum filtered correlation spectroscopy (DQFCOSY). The assignments were made with the help of a DQFCOSY experiment using a doublet assigned to 5-H at about 4.00 ppm. The NOE correlations, 5-H/8a-H, 5-H/7-H, 8a-H/7-H, 8a-H/4-H, 8a-H/2-H, 4-H/2-H, 5-H/4-H, 4a-H/3-H and 4a-H/8-H provide emphatic support for the energy minimized structure shown in Fig. 4. The structure clearly brings out the *trans* (disposition of 4a-H and 8a-H) fusion of the two six membered rings which take $^{5}C_{8}$ and $^{2}C_{4a}$ chair conformations. The assigned structure is very well supported by di-axial vicinal coupling constants, $^{3}J_{5\text{-H}/4a\text{-H}} = 9.8$, $^{3}J_{4a\text{-H}/8a\text{-H}} = 9.8$, $^{3}J_{4\text{-H}/3\text{-H}} = 12.5$, $^{3}J_{3\text{-H}/2\text{-H}} = 12.5$ and $^{3}J_{8\text{-H}/7\text{-H}} = 11.6$ Hz as well as axial/equatorial and equatorial/equatorial vicinal coupling constants, $^{3}J_{4\text{-H}/3\text{-H}'} = 4.4$, $^{3}J_{3\text{-H}'/2\text{-H}'} = 2.6$, $^{3}J_{8a\text{-H}/8\text{-H}'} = 5.6$, $^{3}J_{8\text{-H}'/7\text{-H}} = 3.3$, $^{3}J_{8\text{-H}/7\text{-H}'} = 4.4$ and $^{3}J_{8\text{-H}'/7\text{-H}'} = 1.9$ Hz.

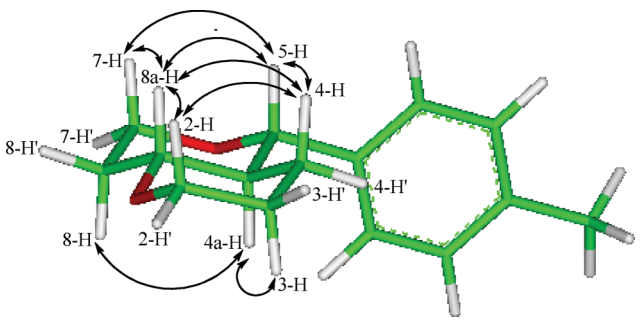
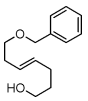
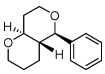
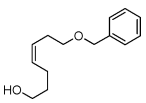
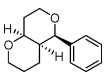
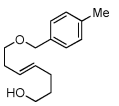
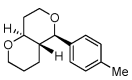
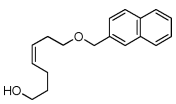
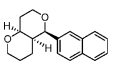
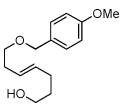
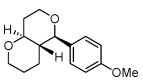
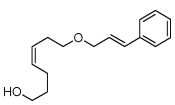
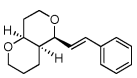
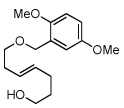
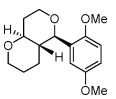


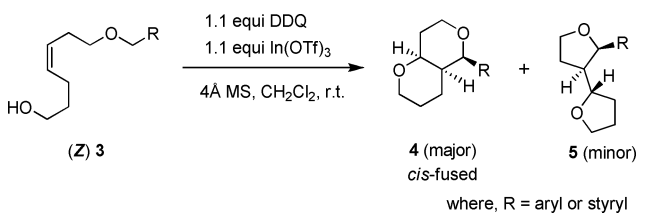
Fig. 4 Characteristic NOE's and energy minimized structure of **4c**.

As expected, the cyclization of (*Z*)-7-(benzyloxy)hept-4-en-1-ol (**3b**) under similar conditions gave the *cis*-fused octahydropyrano[4,3-b]pyran **4b** in 65% yield as a major product (Scheme 3; R = phenyl; Table 3, entry b). The minor product **5b**

Table 3 Synthesis of *trans*- and *cis*-fused octahydropyrano[4,3-*b*]pyran scaffolds[a]

Entry	Substrate (**3**)	Product (**4**)[b]	Time (h)	Yield (%)[c]	**4** : **5** ratio (%)[d]
a			18	75[e]	90 : 10
b			18	65	85 : 15
c			17	80[e]	90 : 10
d			16	60	75 : 25
e			15	84[e]	85 : 15
f			18	65	80 : 20
g			15	66	75 : 25

[a] The reactions were performed on a 0.5 mmol scale. [b] All the products were characterized by ^{1}H and ^{13}C NMR, IR and mass spectroscopy. [c] Yield refers to pure products after column chromatography. [d] Ratio of **4** : **5** was determined by ^{1}H NMR spectra of the crude product. [e] The two isomers were inseparable by silica gel column chromatography and the ratio was determined by HPLC.



Scheme 3 Oxidative Prins cyclization of olefin (***Z***)-**3**.

was obtained in 12% yield. These two isomeric products could be easily separated by silica gel column chromatography.

Similarly, the reaction of (*Z*)-7-(naphthalen-2yl-methoxy)hept-4-en-1-ol (**3d**) afforded the respective *cis*-fused octahydropyrano[4,3-b]pyran **4d** in 60% yield as a major product. The minor product, *i.e.* 2-(2-(naphthalen-2-yl)-tetrahydrofuran-3-yl)-tetrahydrofuran **5d** was obtained in 20% yield (Scheme 3; *R* = 2-naphthyl; Table 3, entry **d**). The structures and stereochemistry of products **4d** and **5d** were characterized by extensive NMR experiments including 2-D nuclear Overhauser effect spectroscopy (NOESY) and double quantum filtered correlation spectroscopy (DQFCOSY). For product **4d**, a small value of 2.8 Hz for $^3J_{5\text{-H}/4a\text{-H}}$ reflects a distinct change to the *cis* fusion of the two six membered rings. The NOE correlations, 5-H/8a-H, 5-H/7-H, 8a-H/7-H, 4a-H/3-H, 4-H/2-H and 4-H/8-H are consistent with energy minimized structure shown in the Fig. 2 which has $^5C_8$ and $^{4a}C_2$ chair conformation of the two six membered rings. The large di-axial vicinal coupling constants, $^3J_{4a\text{-H}/4\text{-H}} = 12.4$, $^3J_{4\text{-H}/3\text{-H}} = 12.4$, $^3J_{3\text{-H}/2\text{-H}} = 11.6$, $^3J_{8a\text{-H}/8\text{-H}} = 12.7$ and $^3J_{8\text{-H}/7\text{-H}} = 12.7$ Hz as well as other couplings (small couplings, $^3J_{4a\text{-H}/8a\text{-H}} = 5.1$, $^3J_{4a\text{-H}/4\text{-H}'} = 4.1$, $^3J_{3\text{-H}/2\text{-H}'} = 4.0$, $^3J_{8a\text{-H}/8\text{-H}'} = 5.1$, $^3J_{8\text{-H}/7\text{-H}'} = 5.4$, $^3J_{8\text{-H}'/7\text{-H}} = 2.0$, $^3J_{8\text{-H}'/7\text{-H}'} = 1.2$ Hz) strongly support the structure as shown in Fig. 5.

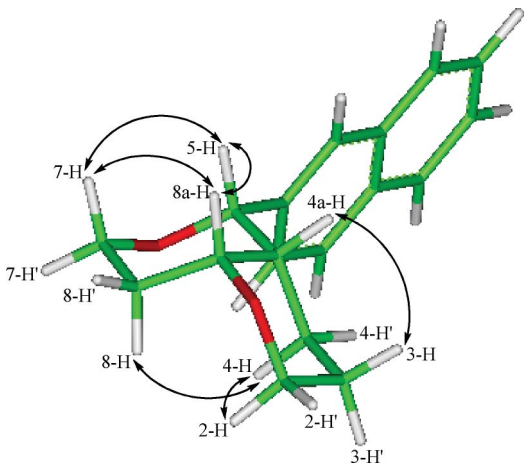


Fig. 5 Characteristic NOE's and energy minimized structure of **4d**.

In the case of **5d**, the *trans* orientation of 2-H with respect to 5-H and 3-H is supported by $^3J_{2\text{-H}/5\text{-H}} = 8.8$ and $^3J_{2\text{-H}/3\text{-H}} = 10.9$ Hz. This implies that 5-H and 3-H will be proximal. Indeed the NOE correlation, 5-H/3-H bears testimony to this. The NOE correlations, 2-H/6-H′, 2-H/4-H′, 6-H′/3-H′, 6-H/3-H and 5-H/7-H are consistent with the energy minimized structure shown in Fig. 6.

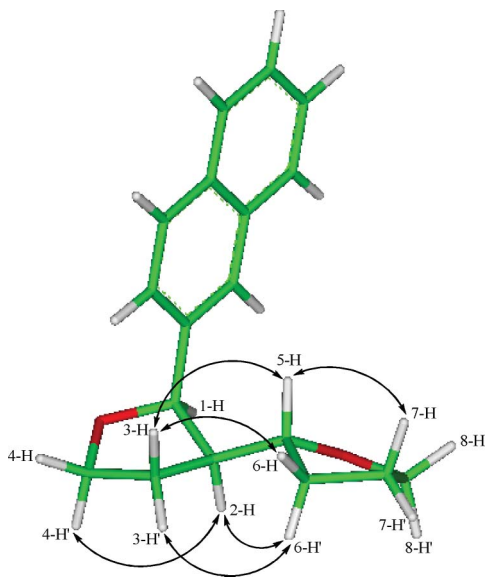
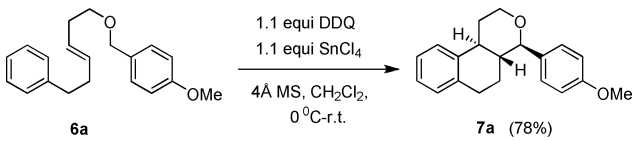


Fig. 6 Characteristic NOE's and energy minimized structure of **5d**.

The scope of the reaction with other 1-benzylhept-3-en-1,7-diols is illustrated in Table 3. Other substrates like (*E*)-7-(4-methoxybenzyloxy)hept-4-en-1-ol (**3e**), (*Z*)-7-(cinnamyloxy)hept-4-en-1-ol (**3f**) and (*E*)-7-(2,5-dimethoxybenzyloxy)hept-4-en-1-ol (**3g**) participated well to furnish the corresponding *trans*- or *cis*-fused pyrano[4,3-*b*]pyrans as major products along with 3-(tetrahydrofuran-2-yl)tetrahydrofurans as minor products in moderate to good yields (entries e–g, Table 3). The electronic effect of the benzyl ring shows some effect on the conversion as discussed earlier.

Encouraged by the results obtained from mono-benzyl ethers of hex-3-en-1,6-diol (**1**) and hept-3-en-1,7-diol (**3**), we extended our efforts to study the Prins/Friedel–Crafts cyclization with aryl tethered homoallyl benzyl ethers. Accordingly, we attempted the oxidative cyclization of (*E*)-1-(6-(4-methoxybenzyloxy)hex-3-enyl)benzene (**6a**) using stoichiometric amounts of DDQ and $SnCl_4$ in the presence of molecular sieves in dichloromethane. Interestingly, the cyclization proceeded smoothly at room temperature to afford the corresponding *trans*-fused hexahydro-1*H*-benzo[*f*]isochromene **7a** as the sole product in 78% yield (Scheme 4, Table 4, entry a). However, the Prins/Friedel–Crafts cyclization was very sluggish when $In(OTf)_3$ was used.



Scheme 4 Oxidative cyclization of (*E*)-1-(6-(4-methoxybenzyloxy)hex-3-enyl)benzene (**6a**).

The structure and stereochemistry of product **7a** were established by DQFCOSY. A large coupling (J = 12.6 Hz) between 4a-H and 10b-H confirms that 4a-H is in an axial position and also a large coupling (J = 12.5 Hz) between 10b-H and 1-H further confirms that the 10b-H is in an axial position and hence the fusion is in *trans* orientation. Similarly, a large coupling (J = 9.7 Hz) between 4-H and 4a-H confirms the axial orientation of 4-H (Fig. 7).

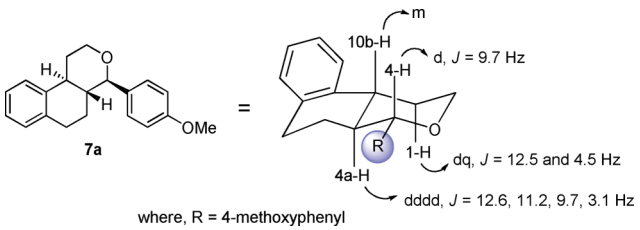
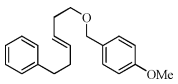
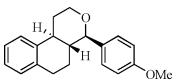
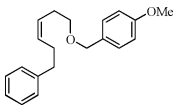
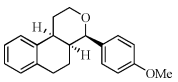
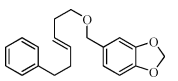
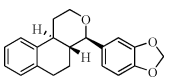
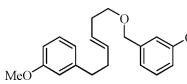
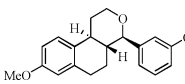
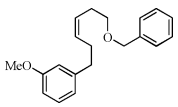
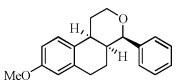
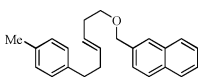
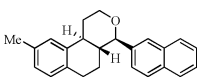
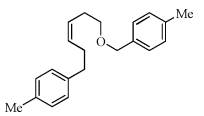
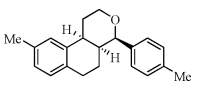
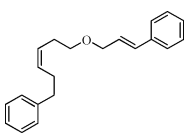
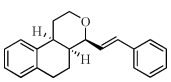


Fig. 7 Characteristic coupling constants and chemical structure of **7a**.

However, an oxidative cyclization of (*Z*)-1-(6-(4-methoxybenzyloxy)hex-3-enyl)benzene (**6b**) under similar conditions afforded the *cis*-fused hexahydro-1*H*-benzo[*f*]isochromene **7b** exclusively in 80% yield (Scheme 5, Table 4, entry b).

The structure and the stereochemistry of product **7b** were also established by DQFCOSY. The coupling between 4-H and 4a-H protons is 2.8 Hz indicating that 4-H and 4a-H are in equatorial positions. This is further confirmed by a small coupling between 4a-H and 10b-H (J = 4.7 Hz). Therefore, 10b-H is in an axial position since it shows a large coupling (J = 12.8 Hz) with 1-H.

Table 4 Synthesis of *trans*- and *cis*-fused hexahydro-1*H*-benzo[*f*]isochromene scaffolds *via* the Prins/Friedel–Crafts cyclization[a]

Entry	Substrate (**6**)	Product (**7**)[b]	Time (h)	Yield (%)[c]
a			14	78
b			14	80
c			11	82
d			12	58[d]
e			14	55[d]
f			14	75
g			14	74
h			15	70

[a] The reactions were performed on a 0.5 mmol scale. [b] All the products were characterized by ^1H and ^{13}C NMR, IR and mass spectroscopy. [c] Yield refers to pure products after column chromatography. [d] Yield of the major regioisomer (regioisomeric ratio = 3 : 1).

Scheme 5 Oxidative cyclization of (*Z*)-1-(6-(4-methoxybenzyloxy)hex-3-enyl)benzene (**6b**).

From these observations, it was confirmed that the fusion between the two rings is *cis* as shown in Fig. 8.

Furthermore, the structure of **7b** was confirmed by X-ray crystallography (Fig. 9).[12]

The scope of the methodology is illustrated in Table 4 with respect to other benzyl ethers of *E*/*Z*-6-arylhex-3-en-1-ol (entries c–g). Various benzyl ethers such as simple benzyl ether (**6e**), methylenedioxybenzyl-, methoxy- and methyl-substituted benzyl ethers (**6c**, **6b**, **6d** and **6g**) and also 1-naphthylmethyl ether (**6f**) underwent smooth cyclization to provide the corresponding *trans*- or *cis*-fused hexahydro-1*H*-benzo[*f*]isochromenes in moderate to

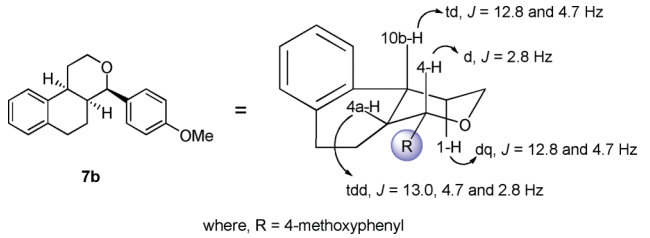


Fig. 8 Characteristic coupling constants and chemical structure of **7b**.

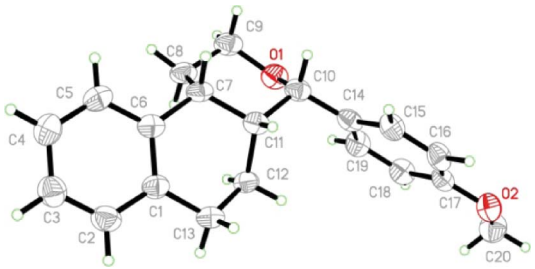
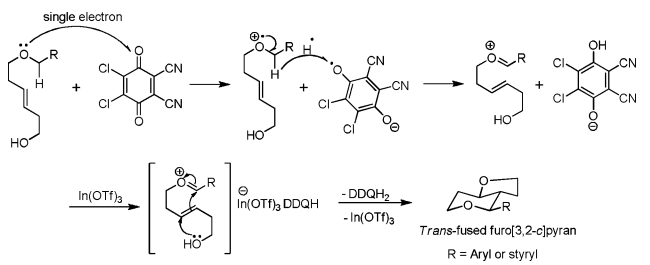


Fig. 9 ORTEP diagram of **7b**.

good yields. These results clearly indicate that the electronic effect of benzyl ring shows some effect on the conversion. In addition to benzyl ethers, 1-((*Z*)-6-(cinnamyloxy)hex-3-enyl)benzene (**6h**) also participated well in this cyclization to afford product **7h** in 70% yield. In the case of *meta*-substituted aryl groups, for example, the benzyl ether of 6-(3-methoxyphenyl)hex-3-en-1-ol, the products were obtained as a 3 : 1 mixture of *para*-/*ortho*-substituted products (entries d–e, Table 4). The ratio of the *para*-/*ortho*-substituted products was determined by ^{1}H NMR spectra of the crude product. The two regioisomers could be easily separated by silica gel column chromatography.

Of the various Lewis acids studied for this conversion (Table 1), $In(OTf)_3$ was found to give the best results in Prins cyclization (Table 1), whereas $SnCl_4$ gave excellent results in Prins/Friedel–Crafts cyclization in terms of conversion. Next, we examined the effect of various solvents, such as dichloromethane, 1,2-dichloroethane and toluene. Of these, dichloromethane appeared to give the best results. This method is simple and convenient and also provides the desired products in good yields with an excellent stereoselectivity.

A plausible mechanism for the coupling is proposed in Scheme 6. The reaction was assumed to proceed *via* a single-electron transfer from the benzyl ether to DDQ which generates a radical cation and a DDQ radical anion. The radical oxygen of the DDQ radical anion then abstracts the H-atom from the radical cation and generates a benzoxy cation. Finally, nucleophilic attack of



Scheme 6 A plausible reaction pathway for intramolecular Prins cyclization.

the olefin on the benzoxy cation generates the carbocation, which could be trapped with a tethered nucleophile to give the desired dioxa-bicycles and oxa-tricycles. The role of $In(OTf)_3$ or $SnCl_4$ is most likely to activate the DDQ to further increase its oxidative potential.

Conclusions

In summary, we have demonstrated a versatile approach for the stereoselective synthesis of a novel class of dioxa-bicycles and oxa-tricycles in a single step operation. This transformation proceeds through benzylic C–H bond activation *via* DDQ oxidation followed by the intramolecular Prins cyclization. This is the first report on intramolecular Prins cyclization through C–H activation by DDQ. Our approach is highly stereoselective to provide *cis*- and *trans*-fused bicyclic and tricyclic tetrahydropyran scaffolds.

Experimental

General

The solvent dichloromethane was dried according to a standard literature procedure. The reactions were performed in oven-dried two necked round bottom flasks under an argon atmosphere. Glass syringes were used to transfer the solvent. The products were purified by column chromatography on silica gel of 60–120 or 100–200 mesh. Thin layer chromatography plates were visualized by ultraviolet light and/or by exposure to iodine vapours and/or by exposure to methanolic acidic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on a rotary evaporator at 35–40 °C. IR spectra were recorded on FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using 300, 400, 500 or 600 MHz NMR spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (J) are quoted in hertz (Hz). Mass spectra were recorded on a mass spectrometer by Electrospray ionization (ESI) or Atmospheric pressure chemical ionization (APCI) technique.

Typical procedure for the Prins cyclization of substrate 1 *via* C–H activation

To a 25 mL two neck round bottom flask containing dried 4 Å molecular sieves (300 mg) was added a solution of homoallylic ether **1** (0.5 mmol) in dry dichloromethane (10 mL) under an argon atmosphere. Then DDQ (1.1 equiv.) and $In(OTf)_3$ (1.1 equiv.) were added sequentially at 0 °C. The resulting mixture was stirred at room temperature for the specified time (Table 2). After completion of the reaction as indicated by TLC, the mixture was quenched with saturated aqueous $NaHCO_3$ solution and then extracted with Et_2O (2 × 20 mL). The organic extracts were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (silica gel, 60–120 mesh) using a gradient mixture of ethyl acetate/hexane to afford the pure product **2** (Table 2).

(3a*R,4*R**,7a*S**)-4-(4-Methoxyphenyl)-hexahydro-2*H*-furo[3,2-*c*]pyran (2a; Table 2; Entry a).** Yield, 88 mg, 75%; Liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.27 (m, 2H), 6.90–6.87 (m,

2H), 4.23 (ddd, J = 12.0, 4.7 and 2.0 Hz, 1H), 4.15 (d, J = 9.4 Hz, 1H), 3.92 (ddd, J = 9.7, 8.5 and 2.7 Hz, 1H), 3.86 (ddd, J = 9.7, 8.5 and 7.5 Hz, 1H), 3.55 (dt, J = 12.0 and 2.0 Hz, 1H), 3.35 (ddd, J = 12.0, 10.0 and 4.0 Hz, 1H), 2.12 (tdd, J = 12.0, 4.0 and 2.0 Hz, 1H), 1.82 (dq, J = 12.0 and 4.7 Hz, 1H), 1.75–1.56 (m, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 132.6, 127.5, 113.7, 82.8, 80.9, 66.3, 65.8, 55.1, 50.2, 32.6, 27.3; IR (neat): ν 2928, 2849, 1513, 1247, 1169, 1057, 826 cm^{-1}; MS (*APCI*): m/z 235 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{14}H_{19}O_3$ (M + H)$^+$: 235.1334, found 235.1342.

(3a*S,4*R**,7a*S**)-4-(4-Methoxyphenyl)-hexahydro-2*H*-furo[3,2-*c*]pyran (2b; Table 2; Entry b).** Yield, 89 mg, 76%; Liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.27 (m, 2H), 6.89–6.84 (m, 2H), 4.72 (d, J = 3.1 Hz, 1H), 4.32–4.25 (m, 1H), 4.12 (ddd, J = 12.0, 5.0 and 2.0 Hz, 1H), 4.00–3.95 (m, 1H), 3.80 (s, 3H), 3.79–3.73 (m, 1H), 3.50 (dt, J = 12.0 and 2.0 Hz, 1H), 2.53–2.44 (m, 1H), 1.99–1.91 (m, 1H), 1.80–1.67 (m, 2H), 1.43–1.35 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 133.7, 126.2, 113.5, 77.0, 74.9, 66.4, 65.7, 55.2, 44.6, 28.4, 23.9; IR (neat): ν 2935, 2837, 1500, 1253, 1152, 1036, 823 cm^{-1}; MS (*APCI*): m/z 235 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{14}H_{19}O_3$ (M + H)$^+$: 235.1334, found 235.1345.

(3a*R,4*R**,7a*S**)-4-(3,4-Dimethoxyphenyl)-hexahydro-2*H*-furo-[3,2-*c*]pyran (2c; Table 2; Entry c).** Yield, 103 mg, 78%; Liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97–6.80 (m, 3H), 4.29–4.20 (m, 1H), 4.15 (d, J = 8.8 Hz, 1H), 3.98–3.80 (m, 8H), 3.61–3.52 (m, 1H), 3.40–3.31 (m, 1H), 2.18–2.09 (m, 1H), 1.90–1.78 (m, 1H), 1.77–1.51 (m, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0, 148.7, 133.2, 118.6, 110.9, 109.4, 83.1, 80.9, 66.3, 65.9, 55.8, 50.4, 32.7, 27.4; IR (neat): ν 2928, 2850, 1514, 1262, 1156, 1028, 806 cm^{-1}; ESI-MS: m/z 265 (M + H)$^+$; HRMS (ESI) calculated for $C_{15}H_{21}O_4$ (M + H)$^+$: 265.1440, found 265.1451.

(3a*S,4*R**,7a*S**)-4-Phenylhexahydro-2*H*-furo[3,2-*c*]pyran (2d; Table 2; Entry d).** Yield, 66 mg, 65%; Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.15 (m, 5H), 4.72 (d, J = 3.0 Hz, 1H), 4.30–4.19 (m, 1H), 4.12 (ddd, J = 12.1, 4.5 and 2.3 Hz, 1H), 3.98–3.88 (m, 1H), 3.78–3.66 (m, 1H), 3.48 (dt, J = 12.1 and 3.0 Hz, 1H), 2.56–2.44 (m, 1H), 2.00–1.82 (m, 1H), 1.80–1.59 (m, 2H), 1.39–1.26 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4, 128.2, 126.9, 125.0, 77.3, 74.9, 66.4, 65.6, 44.4, 28.4, 23.9; IR (neat): ν 2926, 2847, 1061, 771 cm^{-1}; MS (*APCI*): m/z 205 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{13}H_{17}O_2$ (M + H)$^+$: 205.1229, found 205.1232.

(3a*R,4*R**,7a*S**)-4-(3,4,5-Trimethoxyphenyl)-hexahydro-2*H*-furo[3,2-*c*]pyran (2e; Table 2; Entry e).** Yield, 118 mg, 80%; Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.58 (s, 2H), 4.31–4.21 (m, 1H), 4.14 (d, J = 8.9 Hz, 1H), 4.01–3.85 (m, 8H), 3.83 (s, 3H), 3.57 (dt, J = 12.1 and 2.3 Hz, 1H), 3.42–3.30 (m, 1H), 2.19–2.09 (m, 1H), 1.93–1.56 (m, 4H);^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1, 137.4, 136.1, 103.1, 83.3, 80.8, 66.3, 65.8, 60.7, 56.0, 50.3, 32.6, 27.3; IR (neat): ν 2934, 2849, 1591, 1459, 1234, 1124, 1067 cm^{-1}; ESI-MS: m/z 295 (M + H)$^+$; HRMS (ESI) calculated for $C_{16}H_{23}O_5$ (M + H)$^+$: 295.1545, found 295.1554.

(3a*S, 4*R**, 7a*S**)-4-(Naphthalene-2-yl)hexahydro-2*H*-furo[3,2-*c*]pyran (2f; Table 2; Entry f).** Yield, 90 mg, 70%; Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82–7.73 (m, 4H), 7.47–7.33 (m, 3H), 4.89 (d, J = 3.0 Hz, 1H), 4.35–4.25 (m, 1H), 4.23–4.14 (m, 1H), 3.93 (dt, J = 9.8 and 3.0 Hz, 1H), 3.77–3.66 (m, 1H), 3.55 (dt, J = 12.0 and 3.0 Hz, 1H), 2.69–2.55 (m, 1H), 2.04–1.86 (m, 1H), 1.85–1.63 (m, 2H), 1.38–1.21 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 133.2, 132.5, 127.9, 127.8, 127.5, 125.9, 125.5, 123.4, 123.3, 77.1, 74.8, 66.3, 65.6, 44.2, 28.3, 23.9; IR (neat): ν 2924, 2852, 1061, 754 cm^{-1}; MS (*APCI*): m/z 255 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{17}H_{19}O_2$ (M + H)$^+$: 255.1385, found 255.1385.

(3a*S,4*R**,7a*S**)-4-(3-Methoxyphenyl)-hexahydro-2*H*-furo[3,2-*c*]pyran (2g; Table 2; Entry g).** Yield, 84 mg, 72%; Liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (t, J = 7.9 Hz, 1H), 6.92–6.87 (m, 2H), 6.79 (dd, J = 8.3 and 2.4 Hz, 1H), 4.74 (d, J = 3.1 Hz, 1H), 4.30 (td, J = 10.0 and 6.6 Hz, 1H), 4.13 (ddd, J = 12.4, 5.0 and 2.2 Hz, 1H), 3.97 (ddd, J = 9.6, 8.5 and 2.4 Hz, 1H), 3.81 (s, 3H), 3.76 (ddd, J = 9.6, 8.5 and 7.7 Hz, 1H), 3.50 (dt, J = 12.4 and 2.2 Hz, 1H), 2.52 (dddd, J = 12.2, 7.7, 6.6 and 3.1 Hz, 1H), 1.96 (tt, J = 12.2 and 9.6 Hz, 1H), 1.77 (tdd, J = 13.3, 6.6 and 2.2 Hz, 1H), 1.70 (dddd, J = 13.3, 12.4, 10.0 and 6.6 Hz, 1H), 1.37 (dtd, J = 12.2, 7.7 and 2.4 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 143.1, 129.1, 117.3, 112.3, 110.6, 77.0, 74.8, 66.3, 65.5, 55.0, 44.3, 28.3, 23.8; IR (neat): ν 2953, 2843, 1600, 1458, 1259, 1151, 1056, 855, 727 cm^{-1}; MS (*APCI*): m/z 235 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{14}H_{19}O_3$ (M + H)$^+$: 235.1334, found 235.1328.

(3a*S,4*R**,7a*S**)-4-*p*-Tolyl-hexahydro-2*H*-furo[3,2-*c*]pyran (2h; Table 2; Entry h).** Yield, 74 mg, 68%; Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20–7.02 (m,4H), 4.66 (broad s, 1H), 4.27–4.14 (m, 1H), 4.13–4.02 (m, 1H), 3.95–3.85 (m, 1H), 3.76–3.63 (m, 1H), 3.51–3.37 (m, 1H), 2.54–2.38 (m, 1H), 2.31 (s, 3H), 1.98–1.79 (m, 1H), 1.78–1.51 (m, 2H), 1.38–1.23 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 136.3, 128.7, 124.8, 77.1, 74.8, 66.3, 65.5, 44.4, 28.3, 23.8, 21.0; IR (neat): ν 2953, 2877, 1362, 1148, 1094, 1062, 732 cm^{-1}; MS (*APCI*): m/z 219 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{14}H_{19}O_2$ (M + H)$^+$: 219.1385, found 219.1378.

(3a*R,4*S**,7a*S**,*E*)-4-Styryl-hexahydro-2*H*-furo[3,2-*c*]pyran (2i; Table 2; Entry i).** Yield, 75 mg, 65%; Liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51–7.16 (m, 5H), 6.64 (d, J = 15.6 Hz, 1H), 6.22 (dd, J = 15.6 and 6.8 Hz, 1H), 4.26–4.14 (m, 1H), 4.00–3.82 (m, 3H), 3.55–3.44 (m, 1H), 3.32–3.22 (m, 1H), 2.14–1.93 (m, 2H), 1.83–1.70 (m, 1H), 1.69–1.43 (m, 2H);^{13}C NMR (75 MHz, $CDCl_3$): δ 136.6, 131.4, 128.5, 128.1, 127.8, 126.5, 81.7, 80.8, 66.5, 65.5, 49.3, 32.6, 27.2; IR (neat): ν 2928, 2853, 1162, 1072, 967, 749, 695 cm^{-1}; MS (*APCI*): m/z 231 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{15}H_{19}O_2$ (M + H)$^+$: 231.1385, found 231.1378.

Typical procedure for the Prins cyclization of substrate 3 *via* C–H activation

To a 25 mL two neck round bottom flask containing dried 4 Å molecular sieves (300 mg) was added a solution of homoallylic ether **3** (0.5 mmol) in anhydrous dichloromethane (10 mL) under an argon atmosphere. Then DDQ (1.1 equiv.) and $In(OTf)_3$ (1.1 equiv.) were added sequentially at 0 °C. The resulting mixture was stirred at room temperature for the specified time (Table 3). After completion of the reaction as indicated by TLC, the mixture was quenched with saturated aqueous $NaHCO_3$ solution and then extracted with Et_2O (2 × 20 mL). The organic extracts were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (silica gel, 100–200 mesh) using ethyl acetate/hexane mixture to afford products **4**/**5** (Table 3).

(4a*R,5*R**,8a*S**)-5-Phenyl-octahydropyrano[4,3-*b*]pyran (4a; Table 3; Entry a).** The reaction afforded a 9 : 1 mixture of two products **4a** and **5a**. The two regioisomers were inseparable by silica gel column chromatography and **4a**:**5a** ratio was determined by HPLC. Yield, 82 mg, 75%; Liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.22 (m, 5H), 4.20–4.15 (m, 1H), 4.01–3.95 (m, 1H), 3.92 (d, J = 10.0 Hz, 1H), 3.73–3.65 (m, 1H), 3.52–3.45 (m, 1H), 3.34–3.25 (m, 1H), 1.92–1.84 (m, 2H), 1.67–1.49 (m, 3H), 1.27–1.20 (m, 1H), 1.12–1.02 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 128.3, 127.9, 127.1, 83.6, 79.5, 68.2, 66.7, 47.3, 32.8, 26.1, 25.1; IR (neat): ν 2934, 2849, 1094, 758, 701 cm^{-1}; MS (*APCI*): m/z 219 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{14}H_{19}O_2$ (M + H)$^+$: 219.1385, found 219.1388.

(4a*S,5*R**,8a*S**)-5-Phenyl-octahydropyrano[4,3-*b*]pyran (4b; Table 3; Entry b).** The reaction afforded a 85 : 15 mixture of two products **4b** and **5b**. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major isomer, 71 mg, 65%; Liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.23 (m, 2H), 7.22–7.14 (m, 3H), 4.42 (d, J = 1.9 Hz, 1H), 4.24–4.17 (m, 1H), 4.16–4.08 (m, 1H), 3.67–3.57 (m, 2H), 3.53 (dt, J = 12.1 and 1.9 Hz, 1H), 2.49–2.38 (m, 1H), 2.11–2.03 (m, 1H), 1.61–1.43 (m, 4H), 1.05–0.97 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 140.1, 128.0, 126.8, 125.4, 81.0, 72.8, 66.7, 60.5, 41.4, 25.8, 23.9, 17.2; IR (neat): ν 2925, 2852, 1098, 772, 702 cm^{-1}; MS (*APCI*): m/z 219 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{14}H_{19}O_2$ (M + H)$^+$: 219.1385, found 219.1376.

(4a*R,5*R**,8a*S**)-5-*p*-Tolyl-octahydropyrano[4,3-*b*]pyran (4c; Table 3; Entry c).** The reaction afforded a 90 : 10 mixture of two products **4c** and **5c**. The two regioisomers were inseparable by silica gel column chromatography and **4c** : **5c** ratio was determined by HPLC. Yield, 124 mg, 80%; Liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20–7.12 (m,4H), 4.15 (ddd, J = 11.6, 4.4 and 1.9 Hz, 1H), 3.97 (tdd, J = 11.6, 4.4 and 1.6 Hz, 1H), 3.88 (d, J = 9.8 Hz, 1H), 3.67 (dt, J = 11.6 and 3.3 Hz, 1H), 3.47 (dt, J = 11.6 and 2.6 Hz, 1H), 3.28 (dt, J = 9.8 and 5.6 Hz, 1H), 2.33 (s, 3H), 1.90–1.82 (m, 2H), 1.64–1.49 (m, 3H), 1.27–1.22 (m, 1H), 1.04 (dq, J = 12.5 and 4.4 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4, 136.5, 128.9, 127.0, 83.4, 79.6, 68.1, 66.6, 47.2, 32.8, 26.1, 25.1, 21.1; IR (neat): ν 2924, 2852, 1095, 811 cm^{-1}; MS (*APCI*): m/z 233 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{15}H_{21}O_2$ (M + H)$^+$: 233.1542, found 233.1532.

(4a*S,5*R**,8a*S**)-5-(Naphthalen-2-yl)-octahydropyrano[4,3-*b*]-pyran (4d; Table 3; Entry d).** The reaction afforded a 75 : 25 mixture of two products **4d** and **5d**. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major isomer, 81 mg, 60%; Semi-solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84–7.79 (m, 3H), 7.75 (s, 1H), 7.48–7.42 (m, 2H), 7.34 (dd, J = 8.4 and 1.1 Hz, 1H), 4.64 (d, J = 2.8, 1H), 4.30 (ddd, J = 11.7, 5.4, and 1.2 Hz, 1H), 4.24 (td, J = 12.7 and 5.1 Hz, 1H), 3.72–3.61 (m, 3H), 2.52 (dq, J = 12.7 and 5.4 Hz, 1H), 2.22 (dddd, = 12.4, 5.1, 4.1 and 2.8 Hz, 1H), 1.66–1.44 (m, 4H), 1.00 (qd, J = 12.6 and 4.1 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 133.1, 132.5, 127.9, 127.6, 127.5, 126.0, 125.5, 124.0, 123.6, 81.0, 72.9, 66.8, 60.6, 41.3, 25.8, 24.0, 17.3; IR (neat): ν 2937, 2851, 1094, 741 cm^{-1}; MS (*APCI*): m/z 269 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{18}H_{21}O_2$ (M + H)$^+$: 269.3581, found 269.3585.

(2*R,3*R**)-2-(Naphthalen-2-yl)-3-((*S**)-tetrahydrofuran-2-yl)-tetrahydrofuran (minor product 5d; Table 3; Entry d).** Yield, 27 mg, 20%; Liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85–7.80 (m, 2H), 7.79–7.76 (m, 2H), 7.50 (dd, J = 8.4 and 1.2 Hz, 1H), 7.48–7.42 (m, 2H), 5.37 (d, J = 7.5 Hz, 1H), 4.39 (dt, J = 8.4 and 2.1 Hz, 1H), 4.01 (ddd, J = 10.2, 8.4 and 6.8 Hz, 1H), 3.84 (dt, J = 8.2 and 6.0 Hz, 1H), 3.54 (dt, J = 8.2 and 5.5 Hz, 1H), 3.14 (dt, J = 8.8 and 5.4 Hz, 1H), 2.69 (dddd, J = 10.9, 8.8, 7.5 and 6.8 Hz, 1H), 1.94 (dtd, J = 12.3, 6.8 and 2.1 Hz, 1H), 1.90–1.78 (m, 2H), 1.70–1.62 (m, 2H), 1.50–1.41 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 133.1, 132.6, 128.0, 127.5, 127.1, 125.7, 125.4, 125.2, 82.2, 78.5, 68.3, 67.4, 49.1, 30.1, 27.1, 25.5; IR (neat): ν 2928, 2868, 1059, 820, 755 cm^{-1}; MS (*APCI*): m/z 269 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{18}H_{21}O_2$ (M + H)$^+$: 269.3581, found 269.3570.

(4a*R,5*R**,8a*S**)-5-(4-Methoxyphenyl)-octahydropyrano[4,3-*b*]pyran (4e; Table 3; Entry e).** The reaction afforded a 85 : 15 mixture of two products **4e** and **5e**. The two regioisomers were inseparable by silica gel column chromatography and **4e** : **5e** ratio was determined by HPLC. Yield, 104 mg, 84%; Semi-solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.11 (m, 2H), 6.85–6.76 (m, 2H), 4.17–4.07 (m, 1H), 3.98–3.88 (m, 1H), 3.80 (d, J = 10.1 Hz, 1H), 3.78 (s, 3H), 3.69–3.56 (m, 1H), 3.42 (dt, J = 11.5 and 3.0 Hz, 1H), 3.28–3.15 (m, 1H), 1.91–1.72 (m, 2H), 1.68–1.32 (m, 3H), 1.31–1.18 (m, 1H), 1.08–0.90 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 132.0, 128.4, 113.7, 83.3, 79.8, 68.2, 66.7, 55.1, 47.5, 33.0, 26.3, 25.4; IR (neat): ν 2932, 2860, 1497, 1261, 1093, 835, 741 cm^{-1}; MS (*APCI*): m/z 249 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{15}H_{21}O_3$ (M + H)$^+$: 249.1491, found 249.1480.

(4a*S,5*S**,8a*S**,*E*)-5-Styryl-octahydropyrano[4,3-*b*]pyran (4f; Table 3; Entry f).** The reaction afforded a 80 : 20 mixture of two products **4f** and **5f**. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major isomer, 79 mg, 65%; Liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.32 (m, 2H), 7.29–7.25 (m, 2H), 7.22–7.17 (m, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.09 (dd, J = 16.0 and 7.6 Hz, 1H), 4.42–4.36 (m, 1H), 4.09–4.02(m, 1H), 3.85–3.74 (m, 2H), 3.72–3.67 (m, 1H), 3.48 (dt, J = 12.0 and 2.2 Hz, 1H), 1.92–1.82 (m, 2H), 1.81–1.65 (m, 2H), 1.61–1.46 (m, 2H), 1.33–1.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.7, 133.0, 128.8, 128.5, 127.7, 126.5, 75.9, 72.8, 68.8, 62.8, 39.2, 32.5, 25.0, 21.3; IR (neat): ν 2926, 2855, 1455, 1088, 748 cm^{-1}; MS (*APCI*): m/z 245 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{16}H_{21}O_2$, 245.1542 (M + H)$^+$; Found, 245.1532.

(4a*R,5*R**,8a*S**)-5-(2,5-Dimethoxyphenyl)-octahydropyrano[4,3-*b*]pyran (4g; Table 3; Entry g).** The reaction afforded a 75 : 25 mixture of two products **4g** and **5g**. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major isomer, 92 mg, 66%; Liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.00–6.97 (m, 1H), 6.82–.6.75 (m, 2H), 4.52 (d, J = 10.1 Hz, 1H), 4.18–4.12 (m, 1H), 4.00–3.94 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.73–3.66 (m, 1H), 3.49 (dt, J = 12.0 and 3.0 Hz, 1H), 3.38–3.31 (m, 1H), 1.91–1.79 (m, 2H), 1.68–1.45 (m, 4H), 1.24–1.12 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 151.0, 129.4, 113.6, 112.9, 111.7, 79.6, 75.5, 68.3, 66.8, 56.1, 55.7, 47.9, 32.9, 26.3, 24.5; IR (neat): ν 2940, 2849, 1495, 1212, 1054, 810, 748 cm^{-1}; ESI-MS: m/z 279 (M + H)$^+$; HRMS (ESI) calculated for $C_{16}H_{23}O_4$ (M + H)$^+$: 279.3514, found 279.3526.

((2*R,3*R**)-2-(2,5-Dimethoxyphenyl)-3-((*R**)-tetrahydrofuran-2-yl)-tetrahydrofuran (minor product 5g; Table 3; Entry g).** Yield, 30 mg, 22%; Liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04–7.00 (m, 1H), 6.72–6.65 (m, 2H), 5.02 (d, J = 5.9 Hz, 1H), 4.18–4.09 (m, 1H), 3.88–3.79 (m, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.72–3.64 (m, 1H), 3.49–3.40 (m, 1H), 3.34–3.24 (m, 1H), 2.57–2.44 (m, 1H), 2.34–2.21 (m, 1H), 2.20–2.07 (m, 1H), 1.77–1.52 (m, 2H), 1.12–0.95 (m, 2H);^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 150.5, 129.5, 112.9, 112.7, 110.5, 78.5, 77.2, 67.0, 66.8, 55.8, 55.6, 47.1, 30.2, 29.3, 26.0; IR (neat): ν 2944, 2869, 1497, 1217, 1058, 806 cm^{-1}; ESI-MS: m/z 279 (M + H)$^+$; HRMS (ESI) calculated for $C_{16}H_{23}O_4$ (M + H)$^+$: 279.3514, found 279.3507.

Typical procedure for the intramolecular Prins/Friedel–Crafts cyclization *via* C–H activation

To a 25 mL two neck round bottom flask containing dried 4 Å molecular sieves (400 mg) was added a solution of homoallylic ether substrate **6** (0.5 mmol) in anhydrous dichloromethane (10 mL) under an argon atmosphere. Then DDQ (1.1 equiv.) and $SnCl_4$ (1.1 equiv., 1 M in DCM) were added sequentially at −10 °C. The resulting mixture was stirred at room temperature for the specified time (Table 4). After completion of the reaction as indicated by TLC, it was quenched with saturated aqueous $NaHCO_3$ solution and then extracted with Et_2O (2 × 20 mL). The organic extracts were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (silica gel, 100–200 mesh) using a gradient mixture of ethyl acetate/hexane to afford pure product **7** (Table 4).

(4*R,4a*R**,10b*S**)-4-(4-Methoxyphenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (7a; Table 4; Entry a).** Yield, 115 mg, 78%; Semi-solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.26 (m, 3H), 7.20–7.16 (m, 1H), 7.15–7.12 (m, 1H), 7.08–7.04 (m, 1H), 6.91–6.87 (m, 2H), 4.31 (ddd, J = 11.5, 4.5 and 1.5 Hz, 1H), 4.06 (d, J = 9.7 Hz, 1H), 3.85–3.79 (m, 4H), 2.81–2.68 (m, 3H), 2.36 (tdd, J = 12.5, 4.5 and 2.0 Hz, 1H), 1.79 (dq, J = 12.5 and 4.5 Hz, 1H), 1.67 (dddd, J = 12.6, 11.2, 9.7 and 3.1 Hz, 1H), 1.45 (tdd, J = 12.6, 6.7 and 3.1 Hz, 1H), 1.36 (dtd, J = 12.6, 11.2 and 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 139.0, 136.5, 133.0, 128.9, 128.6, 125.9, 125.7, 124.7, 113.7, 85.0, 68.5, 55.2, 44.6, 41.5, 30.7, 28.7, 24.6; IR (KBr): ν 2922, 2840, 1513, 1249, 1092, 828, 743 cm^{-1}; ESI-MS: m/z 295 (M + H); HRMS calculated for $C_{20}H_{23}O_2$ (M + H)$^+$: 295.1698, found 295.1699.

(4*R,4a*S**,10b*S**)-4-(4-Methoxyphenyl)-2,4,4a,5,6,10*b*-hexahydro-1*H*-benzo[*f*]isochromene (7b; Table 4; Entry b).** Crystals for XRD were obtained by dissolving compound in 4–5 mL ethanol, followed by slow evaporation of solvent over 4 days. Yield, 118 mg, 80%; White solid, mp 118–120 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25–7.22 (m, 2H), 7.16–7.09 (m, 3H), 7.08–7.04 (m, 1H), 6.92–6.88 (m, 2H), 4.68 (d, J = 2.8 Hz, 1H), 4.21 (ddd, J = 11.5, 4.7 and 1.2 Hz, 1H), 3.81 (s, 3H), 3.76 (ddd, J = 12.7, 11.5 and 2.3 Hz, 1H), 3.12 (td, J = 12.8 and 4.7 Hz, 1H), 2.78 (ddd, J = 17.0, 5.8 and 1.7 Hz, 1H), 2.62 (ddd, J = 17.0, 12.8 and 6.3 Hz, 1H), 2.06 (tdd, J = 13.0, 4.7 and 2.8 Hz, 1H), 1.92 (dq, J = 12.8 and 4.7 Hz, 1H), 1.81 (dq, J = 13.0 and 5.8 Hz, 1H), 1.73–1.67 (m, 1H), 1.35 (tddd, J = 13.0, 6.3, 2.8 and 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 140.9, 136.1, 133.5, 129.0, 128.6, 126.6, 125.9, 125.6, 113.4, 81.3, 68.8, 55.2, 39.8, 39.5, 31.4, 29.2, 16.7; IR (KBr): ν 2931, 2837, 1509, 1246, 1090, 1023, 742 cm^{-1}; ESI-MS: m/z 317 (M + Na)$^+$; HRMS calculated for $C_{20}H_{23}O_2$ (M + H): 295.1698, found 295.1690.

(4*R,4a*R**,10b*S**)-4-(Benzo[*d*][1,3]dioxol-5-yl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (7c; Table 4; Entry c).** Yield, 126 mg, 82%; Solid, mp 84–86 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.16 (m, 1H), 7.15–6.96 (m, 3H), 6.84–80 (m, 1H), 6.78–6.69 (m, 2H), 5.93 (s, 2H), 4.26 (ddd, J = 11.5, 4.3 and 1.3 Hz, 1H), 3.97 (d, J = 9.6 Hz, 1H), 3.76 (dt, J = 12.3 and 2.3 Hz, 1H), 2.82–2.60 (m, 3H), 2.39–2.26 (m, 1H), 1.83–1.66 (m, 1H), 1.65–1.27 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.7, 147.1, 138.9, 136.4, 134.7, 128.9, 125.9, 125.7, 124.7, 121.1, 107.8, 107.5, 100.9, 85.2, 68.5, 44.6, 41.4, 30.7, 28.7, 24.6; IR (KBr): ν 2919, 2846, 1490, 1443, 1248, 1092, 1038, 744 cm^{-1}; MS (*APCI*): m/z 309 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{20}H_{21}O_3$ (M + H)$^+$: 309.1491, found 309.1502.

(4*R,4a*R**,10b*S**)-8-Methoxy-4-(3-methoxyphenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (7d; Table 4; Entry d).** The reaction afforded a 3 : 1 mixture of *para*-/*ortho*-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 94 mg, 58%; White solid, mp 108–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.17 (m, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.90–6.75 (m, 3H), 6.66 (dd, J = 8.3 and 2.3 Hz, 1H), 6.52 (d, J = 2.3 Hz, 1H), 4.28 (ddd, J = 11.3, 4.5 and 1.5 Hz, 1H), 4.02 (d, J = 9.8 Hz, 1H), 3.83–3.72 (m, 7H), 2.78–2.58 (m, 3H), 2.37–2.26 (m, 1H), 1.84–1.67 (m, 1H), 1.66–1.23 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 157.7, 142.3, 137.8, 131.2, 129.3, 125.8, 120.0, 113.6, 113.5, 112.7, 111.7, 85.4, 68.5, 55.2, 44.9, 41.0, 30.9, 29.0, 24.6; IR (KBr): ν 2942, 2843, 1588, 1455, 1259, 1084, 1040, 786 cm^{-1}; MS (*APCI*): m/z 325 (M + H)$^+$; HRMS (*APCI*) calculated for $C_{21}H_{25}O_3$ (M + H)$^+$: 325.1804, found 325.1806.

(4*R,4a*S**,10b*S**)-8-Methoxy-4-phenyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (7e; Table 4; Entry e).** The reaction afforded a 3 : 1 mixture of *para*-/*ortho*-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 81 mg, 55%; Semi-solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.13 (m, 5H), 6.98–6.89 (m, 1H), 6.69–6.56 (m, 1H), 6.53–6.46 (m, 1H), 4.64 (br s, 1H), 4.22–4.10 (m, 1H), 3.83–3.61 (m, 4H), 3.07–2.95 (m, 1H), 2.78–2.48 (m, 2H), 2.12–1.97 (m, 1H), 1.96–1.53 (m, 3H), 1.32–1.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 141.3, 137.2, 133.2, 129.4, 128.0, 126.6, 125.5, 113.2, 112.2, 81.7, 68.7, 55.1, 39.9, 38.8, 31.5, 29.5, 16.6; IR (KBr): ν 2932, 2845, 1500, 1265, 1097, 703 cm^{-1}; MS (*APCI*): m/z 295 (M + H); HRMS (*APCI*) calculated for $C_{20}H_{23}O_2$ (M + H): 295.1698, found 295.1705.

(4*R,4a*R**,10b*S**)-9-Methyl-4-(naphthalen-2-yl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (7f; Table 4; Entry f).** Yield, 123 mg, 75%; Solid, mp 102–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.72 (m, 4H), 7.50–7.38 (m, 3H), 7.06–7.02 (m, 1H), 6.92–6.84 (m, 2H), 4.34 (ddd, J = 11.3, 4.5 and 1.5 Hz, 1H), 4.23 (d, J = 9.8 Hz, 1H), 3.84 (dt, J = 12.1 and 2.3 Hz, 1H), 2.80–2.59 (m, 3H), 2.45–2.35 (m, 1H), 2.32 (s, 1H), 1.92–1.66 (m, 2H), 1.50–1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.3, 135.1, 133.3, 133.2, 128.9, 128.1, 128.0, 127.6, 126.8, 126.7, 126.0, 125.8, 125.4, 125.2, 85.7, 68.7, 44.8, 41.6, 30.9, 28.4, 24.8, 21.2; IR

(KBr): ν 2943, 2833, 1080, 818, 744 cm^{-1}; MS (*APCI*): *m*/*z* 329 (M + H); HRMS (*APCI*) calculated for $C_{24}H_{25}O$ (M + H): 329.1905, found 329.1912.

(4*R,4a*S**,10b*S**)-9-Methyl-4-*p*-tolyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (7g; Table 4; Entry g).** Yield, 108 mg, 74%; Solid, mp 92–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18–7.06 (m, 4H), 6.92–6.81 (m, 3H), 4.63 (d, J = 1.9 Hz, 1H), 4.24–1.14 (m, 1H), 3.77–3.65 (m, 1H), 3.08–2.97 (m, 1H), 2.77–2.64 (m, 1H), 2.63–2.46 (m, 1H), 2.34 (s, 3H), 2.29 (s, 3H), 2.10–1.98 (m, 1H), 1.97–1.59 (m, 3H), 1.33–1.22 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 138.3, 136.1, 135.0, 133.0, 129.1, 128.9, 128.7, 126.9, 125.4, 81.7, 68.8, 39.8, 39.6, 31.5, 28.9, 21.1, 21.0, 16.8; IR (KBr): ν 2925, 2834, 1088, 820 cm^{-1}; MS (*APCI*): *m*/*z* 293 (M + H); HRMS (*APCI*) calculated for $C_{21}H_{25}O$ (M + H)$^+$: 293.1905, found 293.1898.

(4*S,4a*S**,10b*S**,*E*)-4-Styryl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (7h; Table 4; Entry h).** Yield, 102 mg, 70%; White solid, mp 96–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.33 (m, 2H), 7.32–7.14 (m, 3H), 7.11–6.98 (m, 4H), 6.60 (dd, J = 16.6 and 1.5 Hz, 1H), 6.19 (dd, J = 15.9 and 4.5 Hz, 1H), 4.29–4.22 (m, 1H), 4.17–4.07 (m, 1H), 3.73–3.60 (m, 1H), 3.04–2.68 (m, 3H), 2.03–1.75 (m, 4H), 1.70–1.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 137.0, 136.0, 129.7, 129.1, 129.0, 128.6, 128.5, 127.3, 126.3, 126.0, 125.7, 80.1, 68.4, 39.1, 38.8, 31.4, 29.3, 17.3; IR (KBr): ν 2930, 2832, 1143, 1079, 972, 756, 698 cm^{-1}; MS (*APCI*): *m*/*z* 291 (M + H); HRMS (*APCI*) calculated for $C_{21}H_{23}O$ (M + H)$^+$: 291.1749, found 291.1738.

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Notes and references

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12 CCDC-833511 (**7b**) contains the supplementary crystallographic data for this paper †.

