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**PAPER**

# The stereoselective synthesis of *cis*-/*trans*-fused hexahydropyrano[4,3-*b*]-chromenes *via* Prins cyclization trapping by a tethered nucleophile†

**B. V. Subba Reddy,*[a] Sayed Jalal,[a] Prashant Borkar,[a] J. S. Yadav,[a] P. P. Reddy,[b] A. C. Kunwar[b] and B. Sridhar[c]**

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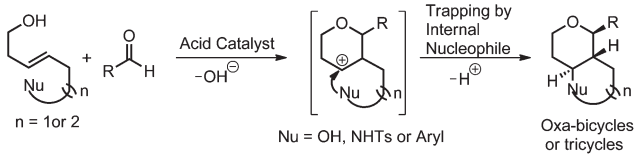
A novel intramolecular Prins cyclization of (*Z*)-2-(5-hydroxypent-2-enyl)phenol with various aldehydes has been achieved using 10 mol% $In(OTf)_3$ and 30 mol% TsOH to produce the *cis*-fused hexahydropyrano[4,3-*b*]chromene derivatives in good yields, while the coupling of (*E*)-2-(5-hydroxypent-2-enyl)phenol with aldehydes under similar conditions affords the corresponding *trans*-fused hexahydropyrano[4,3-*b*]chromene derivatives.

## Introduction

The Prins cyclization is a powerful method for the stereoselective synthesis of a wide range of tetrahydropyran scaffolds.[1,2] In particular, intramolecular Prins cyclization is an important tool for the stereoselective construction of fused heterobicycles and tricycles.[3] Recently, we have successfully explored the intramolecular version of the Prins cyclization by trapping of the resulting carbenium ion with tethered nucleophiles like hydroxyl, *N*-tosylamide and aryl groups to afford the corresponding heterobicycles and tricycles respectively (Scheme 1).[4] However, to the best of our knowledge, there are no reports on the intramolecular version of Prins cyclization with a tethered phenolic group.

Furthermore, oxygen containing heterocycles are often found in various natural products such as flavonoids, catechins and pterocarpans.[5,6] In particular, the hexahydropyrano[4,3-*b*]chromene moiety is a core structure in some natural flavonoids such as dependensin 1 (Fig. 1). It is a dimeric flavonoid isolated as a racemate from the root bark of the Tanzanian medicinal plant *Uvaria dependens*.[7] Although the biological activity of pure dependensin has not been investigated due to its scarcity, the crude extract shows potent antimalarial activity.[7] Some dependensin analogues are known to exhibit antimalarial activity against *Plasmodium falciparum*.[8]




**Scheme 1** Representative examples of intramolecular Prins cyclization.

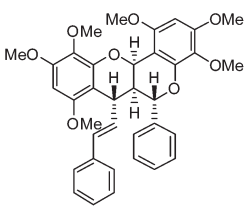



**Fig. 1** Structure of dependensin **1**.

In continuation of our research on Prins type cyclizations and their application to the total synthesis of natural products,[4,9] we herein report a facile method for the stereoselective synthesis of *cis*- and *trans*-fused hexahydropyrano[4,3-*b*]chromenes *via* an intramolecular Prins cyclization.

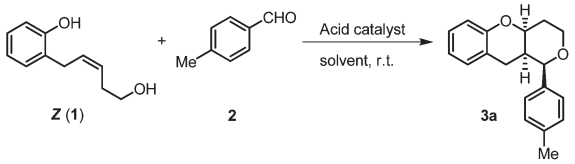
## Results and discussion

As a preliminary experiment, we first attempted the cross coupling of *p*-tolualdehyde (**2a**) with (*Z*)-2-(5-hydroxypent-2-enyl)-phenol (**1**) in the presence of 10 mol% $In(OTf)_3$ and 30 mol% TsOH in 1,2-dichloroethane. Interestingly, the reaction proceeded smoothly at room temperature to furnish the corresponding

[a]*Natural Product Chemistry, Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad 500607, India. E-mail: basireddy@iict.res.in; Fax: (+)91 40 27160512*
[b]*Centre for Nuclear Magnetic Resonance, Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad 500607, India*
[c]*Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad 500607, India*

†Electronic supplementary information (ESI) available: Copies of $^1H$ and $^{13}C$ NMR spectra of products. CCDC 862191. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25771h

**Table 1** Intramolecular Prins cyclization of (*Z*)-2-(5-hydroxypent-2-enyl)phenol (**1**) with *p*-tolualdehyde using various acid catalysts[a]




| Entry | Acid catalyst | mol% | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| a | CSA | 20 | $CH_2Cl_2$ | 24 | 0 |
| b | Ts-OH | 20 | $CH_2Cl_2$ | 24 | 10 |
| c | $In(OTf)_3$ | 10 | $CH_2Cl_2$ | 14 | 75 |
| d | $In(OTf)_3$ | 10 | $ClCH_2CH_2Cl$ | 14 | 80 |
| e | $In(OTf)_3$ + Ts-OH | 10 + 20 | $ClCH_2CH_2Cl$ | 08 | 88 |
| f | $In(OTf)_3$ + Ts-OH | 10 + 30 | $ClCH_2CH_2Cl$ | 07 | 92 |
| g | $Sc(OTf)_3$ | 10 | $ClCH_2CH_2Cl$ | 24 | 40 |
| h | $Sc(OTf)_3$ + Ts-OH | 10 + 30 | $ClCH_2CH_2Cl$ | 12 | 65 |
| i | $InCl_3$ | 10 | $ClCH_2CH_2Cl$ | 24 | 60 |

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



product **3a** in 92% yield with complete *cis*-selectivity (entry f, Table 1). Among various Lewis and Brønsted acids tested, the combination of $In(OTf)_3$ and TsOH (1 : 3) works more effectively than either $In(OTf)_3$ or TsOH alone in terms of reaction time and yields (Table 1). The high catalytic performance of the above reagent system may be attributed to cooperative catalysis[4d,10] between the Lewis acid $In(OTf)_3$ and Brønsted acid TsOH. Of various Lewis and Brønsted acids studied for this reaction (Table 1), the combination of $In(OTf)_3$ and TsOH (1 : 3) was found to give the best results in terms of conversion. Next, we examined the effect of various solvents such as dichloromethane, 1,2-dichloroethane and toluene. Of these, 1,2-dichloroethane appeared to give the best results.

The structure and stereochemistry of product **3a** were characterized by extensive NMR experiments including 2-D double quantum filtered correlation spectroscopy (DQFCOSY) and nuclear Overhauser effect spectroscopy (NOESY). The assignments were made with the help of DQFCOSY experiments. From proton NMR spectra $^3J_{4a\text{-}H\text{–}4\text{-}H'}$ = 4.8, $^3J_{4a\text{-}H\text{–}4\text{-}H}$ = 11.9, $^3J_{4a\text{-}H\text{–}10a\text{-}H}$ = 4.8, $^3J_{4\text{-}H'\text{–}3\text{-}H'}$ = 3.6, $^3J_{4\text{-}H'\text{–}3\text{-}H}$ = 5.1, $^3J_{4\text{-}H\text{–}3\text{-}H'}$ = 5.3, $^3J_{4\text{-}H\text{–}3\text{-}H}$ = 11.9, $^3J_{10a\text{-}H\text{–}10\text{-}H'}$ = 5.7 and $^3J_{10a\text{-}H\text{–}10\text{-}H}$ = 12.4 Hz were obtained for **3a**. The nOe correlations 4a-H/3-H, 4a-H/1-H, 3-H/1-H and 4-H/10-H provide emphatic support for the energy minimized structure shown in Fig. 2. The structure clearly brings out the *cis* fusion of the two six membered rings (*cis* disposition of protons 4a-H and 10a-H). Large diaxial couplings and the presence of 1,3-nOe interactions in the six-membered ring containing the *p*-tolyl group confirm its $^4C_1$ chair conformation. The structure is additionally supported by the correlations arising from the ω-couplings between 4-H′–10a-H and 4a-H–10-H′ in the DQFCOSY experiment.

Inspired by the above results, we next extended this process for other aldehydes. The scope of the reaction is illustrated with respect to various aldehydes and the results are summarized in Table 2. Interestingly, 3,4-dimethoxybenzaldehyde (**2d**) underwent a smooth cyclization with (*Z*)-2-(5-hydroxypent-2-enyl)-phenol (**1**) under similar conditions to afford the corresponding

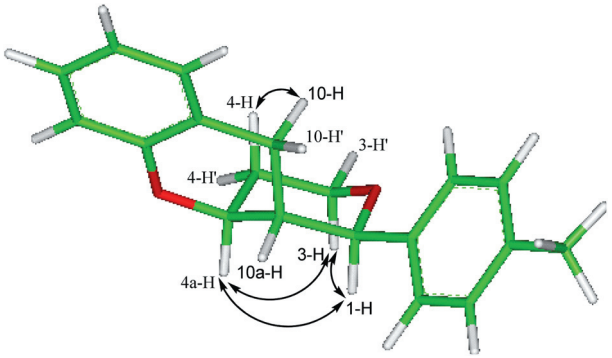



**Fig. 2** Characteristic nOe's and energy minimized structure of **3a**.

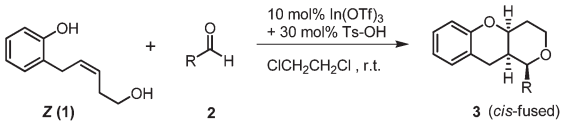
*cis*-fused hexahydropyrano[4,3-*b*]chromene **3d** in 90% yield (entry d, Table 2). The structure of **3d** was confirmed by X-ray crystallography (Fig. 3).[11]

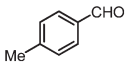
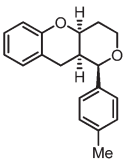
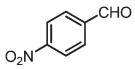
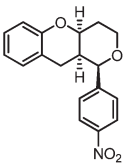
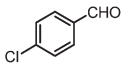
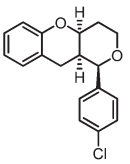
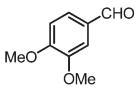
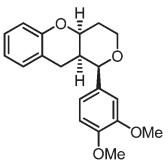
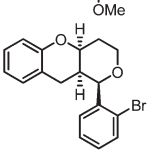
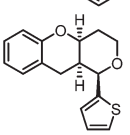
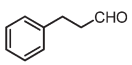
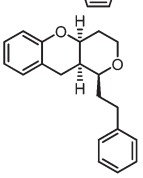
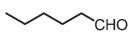
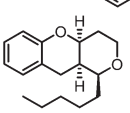
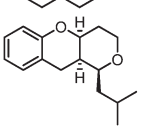
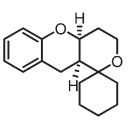
Similarly, other aromatic aldehydes such as 4-nitrobenzaldehyde, 4-chlorobenzaldehyde, 2-bromobenzaldehyde, thiophene-2-carbaldehyde and 3-phenylpropionaldehyde reacted well with (*Z*)-homoallylic alcohol **1** to furnish the respective *cis*-fused hexahydropyrano[4,3-*b*]chromene scaffolds in good yields (entries b, c, e–g, Table 2). The reaction works not only with aromatic aldehydes but also with aliphatic aldehydes such as *n*-hexanal and 3-methylbutanal. In the case of aliphatic aldehydes, the corresponding alkyl substituted *cis*-fused hexahydropyrano[4,3-*b*]-chromene derivatives were obtained in good yields (entries h and i, Table 2). The method is successful not only with aldehydes but also with ketones. For instance, cyclohexanone gave the corresponding *cis*-fused spiro-dioxatricycle under the reaction conditions (entry j, Table 2).

Next, we studied the effect of the geometry of the starting olefin on the stereoselectivity of the reaction. Accordingly, treatment of (*E*)-2-(5-hydroxypent-2-enyl)phenol (**4**) with *p*-tolualdehyde (**2a**) in the presence of 10 mol% $In(OTf)_3$ and 30 mol% TsOH in 1,2-dichloroethane gave the respective *trans*-fused hexahydropyrano[4,3-*b*]chromene **5a** as sole product in 90% yield (entry a, Table 3). The structure and stereochemistry of **5a** were characterized by extensive NMR experiments including DQFCOSY and NOESY. The assignments were made with the help of DQFCOSY experiments. From proton NMR spectra, the coupling constants, $^3J_{4a\text{-}H\text{–}4\text{-}H'}$ = 5.0, $^3J_{4a\text{-}H\text{–}4\text{-}H}$ = 10.4, $^3J_{4a\text{-}H\text{–}10a\text{-}H}$ = 11.0, $^3J_{4\text{-}H'\text{–}3\text{-}H'}$ = 1.4, $^3J_{4\text{-}H'\text{–}3\text{-}H}$ = 2.2, $^3J_{4\text{-}H\text{–}3\text{-}H'}$ = 4.8, $^3J_{4\text{-}H\text{–}3\text{-}H}$ = 12.2, $^3J_{1\text{-}H\text{–}10a\text{-}H}$ = 10.0, $^3J_{10a\text{-}H\text{–}10\text{-}H}$ = 12.2 and $^3J_{10a\text{-}H\text{–}10\text{-}H'}$ = 5.1 Hz, were derived for **5a**. The nOe correlations 4a-H/1-H, 4a-H/10-H, 4-H/10a-H, 3-H/1-H and 1-H/10-H amply support the energy minimized structure shown in Fig. 4. The structure clearly brings out the *trans* disposition of protons 4a-H and 10a-H, which indicates the *trans* fusion of the two six-membered rings. Like **3a**, for **5a** also the six membered ring bearing the tolyl group takes a $^4C_1$ chair conformation.

The scope of the stereoselectivity with respect to the *E*-olefin is illustrated with respect to various aldehydes and the results are summarized in Table 3. Interestingly, several aromatic aldehydes such as 4-nitrobenzaldehyde, 3,4-dimethoxybenzaldehyde, 4-chlorobenzaldehyde, 2-bromobenzaldehyde, thiophene-2-carbaldehyde and 3-phenylpropionaldehyde underwent a smooth intramolecular Prins cyclization with (*E*)-homoallylic alcohol **1** to

**Table 2** Synthesis of *cis*-fused hexahydropyrano[4,3-*b*]chromene scaffolds[a]




| Entry | Aldehyde (**2**) | Product (**3**)[b] | Time (h) | % Yield[c] |
|---|---|---|---|---|
| a |  |  | 7 | 92 |
| b |  |  | 9 | 89 |
| c |  |  | 8 | 85 |
| d |  |  | 7 | 90 |
| e |  |  | 9 | 84 |
| f |  |  | 8 | 80 |
| g |  |  | 8 | 78 |
| h |  |  | 7 | 75 |
| i |  |  | 7 | 78 |
| j |  |  | 12 | 70 |

[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.

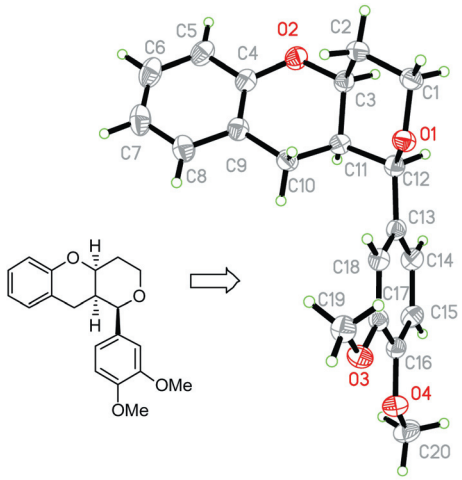



**Fig. 3** ORTEP diagram of **3d**.

furnish the respective *trans*-fused hexahydropyrano[4,3-*b*]chromene scaffolds in good to excellent yields (entries b–g, Table 3). Aliphatic aldehydes such as *n*-hexanal and 3-methylbutanal also gave the corresponding alkyl substituted *trans*-fused hexahydropyrano[4,3-*b*]chromene derivatives in good yields (entries h and i, Table 3). Cyclic ketones such as cyclohexanone also gave the corresponding spiro-dioxatricycles under similar conditions (entry j, Table 3). From the above study, it is evident that the geometry of the olefin controls the stereoselectivity of the reaction *i.e.* a *cis*-olefin gives the *cis*-fused product whereas a *trans*-olefin provides the *trans*-fused product exclusively.

This method provides a wide range of octahydropyrano[4,3-*b*]-chromene derivatives in good yields with excellent stereoselectivity. Mechanistically, the reaction is expected to proceed *via* the formation of an oxocarbenium ion from the hemi-acetal which is formed *in situ* from an aldehyde and a homoallylic alcohol, likely after activation through In(III). This is followed by attack of an internal olefin resulting in the formation of a carbocation which is simultaneously trapped by a tethered phenolic group leading to the formation of the octahydropyrano[4,3-*b*]pyran as depicted in Scheme 2.

## Conclusions

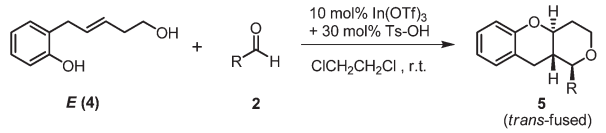
In summary, we have demonstrated a novel intramolecular Prins cyclization for the stereoselective synthesis of a novel class of dioxatricycles with the formation of three stereocenters in a single step. This is the first report on a Prins cyclization in which a tethered phenolic group terminates the cyclization. This method provides an easy access to *cis*- and *trans*-fused hexahydropyrano[4,3-*b*]chromene scaffolds in a single step process.

## Experimental

### General

1,2-Dichloroethane and dichloromethane were dried according to a standard literature procedure. The reactions were performed in oven-dried round bottom flasks under nitrogen atmosphere.

**Table 3** Synthesis of *trans*-fused hexahydropyrano[4,3-*b*]chromene scaffolds[a]



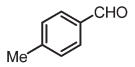
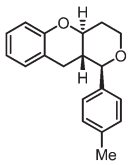
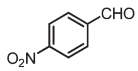
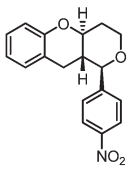
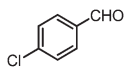
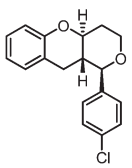
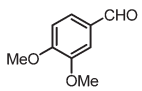
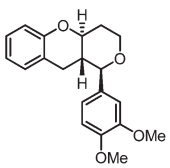
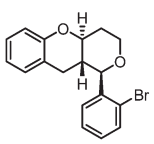
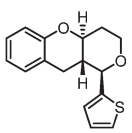
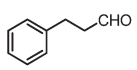
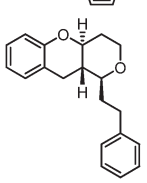
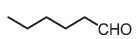
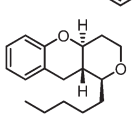
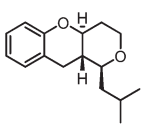
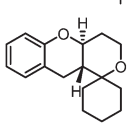
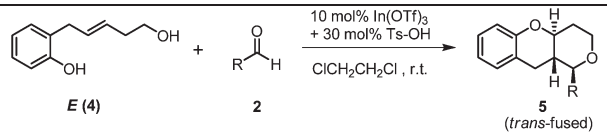

| Entry | Aldehyde (**2**) | Product (**5**)[b] | Time (h) | % Yield[c] |
|---|---|---|---|---|
| a |  |  | 7 | 90 |
| b |  |  | 9 | 85 |
| c |  |  | 8 | 86 |
| d |  |  | 7 | 88 |
| e |  |  | 9 | 82 |
| f |  |  | 8 | 84 |
| g |  |  | 8 | 80 |
| h |  |  | 7 | 84 |
| i |  |  | 7 | 78 |
| j |  |  | 12 | 72 |

**Table 3** *(Contd.)*




| Entry | Aldehyde (**2**) | Product (**5**)[b] | Time (h) | % Yield[c] |
|---|---|---|---|---|

[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.

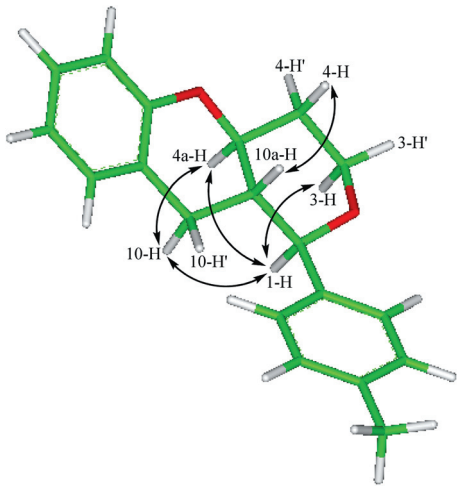
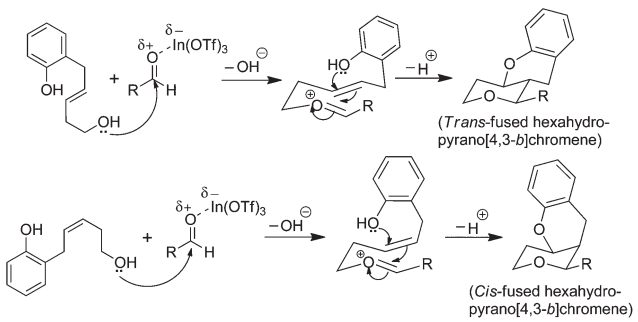



**Fig. 4** Characteristic nOe's and energy minimized structure of **5a**.

Glass syringes were used to transfer the solvent. The products were purified by column chromatography on silica gel of 60–120 mesh. Thin layer chromatography plates were visualized by ultraviolet light and/or by exposure to iodine vapour and/or by exposure to an acidic methanolic 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 an FT-IR spectrometer. $^{1}H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ using 300 or 500 MHz NMR spectrometers. The chemical shifts ($\delta$) were reported in parts per million (ppm) with respect to TMS as an internal standard. The coupling constants ($J$) are quoted in hertz (Hz). Mass spectra were recorded on a mass spectrometer by electrospray ionization (ESI) technique.

### Typical procedure for the intramolecular Prins cyclization

To a stirred solution of (*Z*)- or (*E*)-2-(5-hydroxypent-2-enyl)-phenol (**1** or **3**; 0.50 mmol) and aldehyde (**2**, 0.60 mmol) in dry 1,2-dichloroethane (5 mL) were added $In(OTf)_3$ (10 mol%) and TsOH (30 mol%). The resulting mixture was stirred at room temperature under nitrogen atmosphere for the specified time (Table 2 or Table 3). After completion of the reaction as indicated by TLC, the mixture was quenched with saturated aqueous $NaHCO_3$ solution (0.5 mL) and extracted with dichloromethane




**Scheme 2** A plausible reaction pathway.



(2 × 10 mL). The organic phases were combined, washed with brine (3 × 2 mL), dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo*. The resulting crude product was purified by silica gel column chromatography (60–120 mesh) using ethyl acetate/hexane as eluent to afford pure product **3** or **5** (Table 2 or Table 3).

**(1*R**,4a*S**,10a*S**)-1-*p*-Tolyl-1,3,4,4a,10,10a-hexahydropyrano-[4,3-*b*]chromene (3a; Table 2; entry a).** Yield, 92%; Solid, mp 112–114 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.27–7.14 (m, 4H), 7.10–7.01 (m, 1H), 6.94–6.87 (m, 1H), 6.83–6.73 (m, 2H), 4.64 (broad s, 1H), 4.61 (td, $J$ = 11.9 and 4.8 Hz, 1H), 4.25 (ddd, $J$ = 11.9, 5.1 and 1.1 Hz, 1H), 3.67 (dt, $J$ = 11.9 and 2.3 Hz, 1H), 2.88 (dd, $J$ = 16.6 and 12.4 Hz, 1H), 2.58–2.46 (m, 1H), 2.36 (s, 3H), 2.08 (dd, $J$ = 16.6 and 5.5 Hz, 1H), 1.98 (dq, $J$ = 12.1 and 5.3 Hz, 1H), 1.83–1.71 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 152.4, 136.8, 136.6, 130.0, 128.9, 127.2, 125.2, 120.4, 120.1, 116.6, 79.4, 73.9, 66.4, 37.2, 27.1, 21.1, 20.0; IR (KBr): $\nu$ 2923, 2858, 1488, 1453, 1231, 1082, 1051, 807, 756 cm$^{-1}$; ESI-MS: $m/z$ 281 $(M + H)^+$; HRMS (ESI) calculated for $C_{19}H_{21}O_2$: 281.1538 $(M + H)^+$, Found 281.1565.

**(1*R**,4a*S**,10a*S**)-1-(4-Nitrophenyl)-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (3b; Table 2; entry b).** Yield, 89%; Solid, mp 154–156 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.31–8.18 (m, 2H), 7.58–7.46 (m, 2H), 7.07–6.97 (m, 1H), 6.86–6.77 (m, 1H), 6.76–6.69 (m, 2H), 4.72 (broad s, 1H), 4.59 (td, $J$ = 11.7 and 4.9 Hz, 1H), 4.27 (ddd, $J$ = 11.7, 4.9 and 1.1 Hz, 1H), 3.68 (dt, $J$ = 11.7 and 2.0 Hz, 1H), 2.81 (dd, $J$ = 16.6 and 12.7 Hz, 1H), 2.64–2.52 (m, 1H), 1.98 (dq, $J$ = 12.7 and 4.9 Hz, 1H), 1.91 (dd, $J$ = 16.6 and 5.9 Hz, 1H), 1.83–1.75 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 152.1, 147.6, 147.1, 129.9, 127.5, 126.1, 123.5, 120.7, 120.3, 116.7, 78.6, 73.4, 66.5, 36.9, 26.8, 19.9; IR (KBr): $\nu$ 2924, 2855, 1520, 1343, 1082, 1055, 804, 753 cm$^{-1}$; ESI-MS: $m/z$ 312 $(M + H)^+$; HRMS (ESI) calculated for $C_{18}H_{18}NO_4$: 312.1236 $(M + H)^+$, Found 312.1244.

**(1*R**,4a*S**,10a*S**)-1-(4-Chlorophenyl)-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (3c; Table 2; entry c).** Yield, 85%; Solid, mp 152–154 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.52–7.41 (m, 2H), 7.23–7.15 (m, 2H), 7.05–6.95 (m, 1H), 6.88–6.79 (m, 1H), 6.78–6.66 (m, 2H), 4.59 (broad s, 1H), 4.55 (td, $J$ = 11.7 and 4.5 Hz, 1H), 4.23 (ddd, $J$ = 11.9, 4.5 and 1.3 Hz, 1H), 3.65 (dt, $J$ = 12.0 and 2.1 Hz, 1H), 2.88–2.71 (m, 1H), 2.56–2.43 (m, 1H), 2.08–1.86 (m, 2H), 1.82–1.69 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 152.3, 138.8, 131.3, 130.0, 127.3, 127.0, 120.9, 120.2, 120.0, 116.6, 78.8, 73.6, 66.4, 36.9, 26.9, 19.9; IR (KBr): $\nu$ 2925, 2855, 1486, 1457, 1243, 1049, 757 cm$^{-1}$; ESI-MS: $m/z$ 301 $(M + H)^+$; HRMS (ESI) calculated for $C_{18}H_{18}ClO_2$: 301.0995 $(M + H)^+$, Found 301.1012.

**(1*R**,4a*S**,10a*S**)-1-(3,4-Dimethoxyphenyl)-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (3d; Table 2; entry d).** Crystals for XRD were obtained by dissolving compound in 4–5 mL methanol, followed by slow evaporation of solvent over 4 days. Yield, 90%; Solid, mp 128–130 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.04–6.95 (m, 1H), 6.91–6.66 (m, 6H), 4.64 (broad s, 1H), 4.62 (td, $J$ = 12.0 and 4.7 Hz, 1H), 4.25 (ddd, $J$ = 12.0, 5.1 and 1.2 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.66 (dt, $J$ = 12.0 and 2.0 Hz, 1H), 2.84 (dd, $J$ = 16.8 and 12.3 Hz, 1H), 2.58–2.46 (m, 1H), 2.09 (dd, $J$ = 16.8 and 5.7 Hz, 1H), 1.97 (dq, $J$ = 12.0 and 5.2 Hz, 1H), 1.82–1.69 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 152.3, 148.7, 147.8, 132.4, 130.0, 127.2, 120.3, 120.1, 117.2, 116.6, 110.9, 108.5, 79.0, 73.8, 66.4, 55.8, 37.3, 27.0, 20.0; IR (KBr): $\nu$ 2925, 2854, 1514, 1455, 1230, 1026, 753 cm$^{-1}$; ESI-MS: $m/z$ 327 $(M + H)^+$; HRMS (ESI) calculated for $C_{20}H_{23}O_4$: 327.1596 $(M + H)^+$, Found 327.1586.

**(1*R**,4a*S**,10a*S**)-1-(2-Bromophenyl)-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (3e; Table 2; entry e).** Yield, 84%; Solid, mp 107–109 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.58–7.48 (m, 2H), 7.42–7.34 (m, 1H), 7.22–7.13 (m, 1H), 7.11–7.03 (m, 1H), 6.94–6.86 (m, 1H), 6.84–6.74 (m, 2H), 4.88 (broad s, 1H), 4.66 (td, $J$ = 12.1 and 4.5 Hz, 1H), 4.25 (ddd, $J$ = 12.1, 5.3 and 1.0 Hz, 1H), 3.73 (dt, $J$ = 12.1 and 2.3 Hz, 1H), 3.02–2.77 (m, 2H), 2.10–1.89 (m, 2H), 1.85–1.73 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 152.3, 133.8, 132.8, 130.0, 128.8, 128.3, 127.3, 127.1, 122.9, 120.7, 120.1, 116.6, 79.1, 73.3, 66.5, 33.5, 26.9, 20.2; IR (KBr): $\nu$ 2927, 2853, 1489, 1461, 1240, 1103, 1059, 753 cm$^{-1}$; ESI-MS: $m/z$ 345 $(M + H)^+$; HRMS (ESI) calculated for $C_{18}H_{18}BrO_2$: 345.0485 $(M + H)^+$, Found 345.0491.

**(1*R**,4a*S**,10a*S**)-1-(Thiophen-2-yl)-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (3f; Table 2; entry f).** Yield, 80%; Solid, mp 108–110 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.27–7.17 (m, 1H), 7.11–6.68 (m, 6H), 4.86 (d, $J$ = 1.1 Hz, 1H), 4.54 (td, $J$ = 11.9 and 4.5 Hz, 1H), 4.22 (ddd, $J$ = 12.1, 5.1 and 1.9 Hz, 1H), 3.68 (dt, $J$ = 12.1 and 2.0 Hz, 1H), 2.91 (dd, $J$ = 16.8 and 12.3 Hz, 1H), 2.64–2.52 (m, 1H), 2.32 (dd, $J$ = 16.8 and 5.5 Hz, 1H), 1.99 (dq, $J$ = 12.5 and 5.0 Hz, 1H), 1.79–1.68 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 152.3, 142.9, 130.1, 127.3, 126.7, 124.0, 122.4, 120.7, 120.2, 116.7, 77.3, 73.2, 66.8, 37.5, 26.9, 20.2; IR (KBr): $\nu$ 2924, 2855, 1520, 1343, 1082, 1055, 804, 753 cm$^{-1}$; ESI-MS: $m/z$ 273 $(M + H)^+$; HRMS (ESI) calculated for $C_{16}H_{17}O_2S$: 273.0944 $(M + H)^+$, Found 273.0924.

**(1*S**,4a*S**,10a*R**)-1-Phenethyl-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (3g; Table 2; entry g).** Yield, 78%; Solid, mp 72–74 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.35–7.15 (m, 5H), 7.13–7.01 (m, 2H), 6.88–6.75 (m, 2H), 4.36 (td, $J$ = 11.7 and 4.9 Hz, 1H), 4.08 (ddd, $J$ = 11.7, 4.5 and 1.2 Hz, 1H), 3.54–3.39 (m, 2H), 2.98 (dd, $J$ = 16.6 and 12.5 Hz, 1H), 2.88–2.53 (m, 3H), 2.27–2.15 (m, 1H), 2.10–1.63 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 152.6, 141.7, 130.1, 128.4, 128.4,

127.3, 125.9, 120.1, 120.1, 116.7, 77.4, 73.6, 66.2, 34.9, 34.0, 32.1, 27.3, 20.1; IR (KBr): $\nu$ 2926, 2857, 1490, 1455, 1235, 1074, 758, 697 $cm^{-1}$; ESI-MS: *m/z* 295 $(M + H)^+$; HRMS (ESI) calculated for $C_{20}H_{23}O_2$: 295.1698 $(M + H)^+$, Found 295.1712.

**(1*S**,4a*S**,*10*a*R**)-1-Pentyl-1,3,4,4a,10,10a-hexahydropyrano-[4,3-*b*]chromene (3h; Table 2; entry h).** Yield, 75%; Viscous liquid; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.08–6.92 (m, 2H), 6.82–6.67 (m, 2H), 4.31 (td, *J* = 11.9 and 4.7 Hz, 1H), 4.00 (ddd, *J* = 11.7, 4.5 and 1.2 Hz, 1H), 3.49–3.30 (m, 2H), 2.91 (dd, *J* = 16.6 and 12.3 Hz, 1H), 2.52 (dd, *J* = 16.6 and 5.8 Hz, 1H), 2.22–2.09 (m, 1H), 1.84 (dq, *J* = 12.5 and 5.1 Hz, 1H), 1.71–1.54 (m, 2H), 1.51–1.17 (m, 7H), 0.91 (t, *J* = 6.4 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 152.6, 130.1, 127.3, 120.3, 120.1, 116.7, 78.5, 73.8, 66.3, 34.7, 32.1, 31.8, 27.3, 25.5, 22.6, 20.0, 14.0; IR (Neat): $\nu$ 2929, 2854, 1489, 1457, 1239, 1081, 753 $cm^{-1}$; ESI-MS: *m/z* 261 $(M + H)^+$; HRMS (ESI) calculated for $C_{17}H_{25}O_2$: 261.1849 $(M + H)^+$, Found 261.1840.

**(1*S**,4a*S**,10a*R**)-1-Isobutyl-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (3i; Table 2; entry i).** Yield, 78%; Solid, mp 54–56; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.13–7.02 (m, 2H), 6.88–6.76 (m, 2H), 4.40 (td, *J* = 12.1 and 4.5 Hz, 1H), 4.04 (ddd, *J* = 11.3, 5.3 and 1.5 Hz, 1H), 3.57–3.42 (m, 2H), 2.95 (dd, *J* = 16.6 and 12.1 Hz, 1H), 2.58 (dd, *J* = 16.6 and 6.0 Hz, 1H), 2.23–2.11 (m, 1H), 1.87(dq, *J* = 12.8 and 5.3 Hz, 1H), 1.80–1.52 (m, 3H), 1.35–1.15 (m, 1H), 0.99–0.91 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 152.6, 130.1, 127.3, 120.3, 120.1, 116.7, 76.6, 73.9, 66.3, 41.2, 35.1, 27.3, 24.5, 23.1, 22.4, 20.2; IR (Neat): $\nu$ 2928, 2855, 1490, 1457, 1240, 1080, 754 $cm^{-1}$; ESI-MS: *m/z* 247 $(M + H)^+$; HRMS (ESI) calculated for $C_{16}H_{23}O_2$: 247.1683 $(M + H)^+$, Found 247.1678.

**(4a′*S**,10a′*S**)-4′,4a′,10′,10a′-Tetrahydro-3′*H*-spiro[cyclohexane-1,1′-pyrano[4,3-*b*]chromene] (3j; Table 2; entry j).** Yield, 70%; Solid, mp 80–84 °C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.08–6.88 (m, 2H), 6.83–6.64 (m, 2H), 4.60–4.43 (m, 1H), 3.86–3.73 (m, 1H), 3.72–3.57 (m, 1H), 2.90–2.75 (m, 1H), 2.74–2.60 (m, 1H), 2.07–1.94 (m, 1H), 1.93–1.62 (m, 3H), 1.61–1.07 (m, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 153.1, 129.8, 127.1, 120.9, 120.1, 116.6, 75.1, 70.5, 58.3, 32.4, 28.3, 25.8, 22.7, 21.5, 21.4; IR (KBr): $\nu$ 2928, 2855, 1490, 1453, 1236, 1075, 754 $cm^{-1}$; ESI-MS: *m/z* 259 $(M + H)^+$; HRMS (ESI) calculated for $C_{17}H_{23}O_2$: 259.1698 $(M + H)^+$, Found 259.1715.

**(1*R**,4a*S**,10a*R**)-1-*p*-Tolyl-1,3,4,4a,10,10a-hexahydropyrano-[4,3-*b*]chromene (5a; Table 3; entry a).** Yield, 90%; Solid, mp 122–124 °C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.24–7.16 (m, 2H), 7.15–7.07 (m, 2H), 7.05–6.96 (m, 1H), 6.86–6.79 (m, 1H), 6.78–6.67 (m, 2H), 4.23–4.12 (m, 1H), 3.97–3.85 (m, 2H), 3.69 (dt, *J* = 12.1 and 2.3 Hz, 1H), 2.41–2.31 (m, 1H), 2.29 (s, 3H), 2.18–2.07 (m, 2H), 2.06–1.90 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 154.1, 138.1, 136.0, 129.8, 129.2, 127.3, 127.2, 121.5, 120.4, 116.4, 83.7, 76.4, 66.3, 42.1, 32.4, 27.4, 21.2; IR (KBr): $\nu$ 2922, 2849, 1490, 1235, 1083, 810, 761 $cm^{-1}$; ESI-MS: *m/z* 281 $(M + H)^+$; HRMS (ESI) calculated for $C_{19}H_{21}O_2$: 281.1538 $(M + H)^+$, Found 281.1558.

**(1*R**,4a*S**,10a*R**)-1-(4-Nitrophenyl)-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (5b; Table 3; entry b).** Yield, 85%; Solid, mp 184–186 °C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.33–8.20 (m, 2H), 7.63–7.50 (m, 2H), 7.16–7.03 (m, 1H), 6.95–6.75 (m, 3H), 4.36–4.24 (m, 1H), 4.15 (d, *J* = 9.8 Hz, 1H), 4.01 (dt, *J* = 10.6 and 4.9 Hz, 1H), 3.79 (dt, *J* = 12.1 and 2.3 Hz, 1H), 2.56–2.43 (m, 1H), 2.37–1.88 (m, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 153.9, 147.8, 146.4, 129.7, 128.0, 127.6, 123.8, 123.4, 120.7, 116.5, 82.7, 75.8, 66.4, 42.6, 31.9, 27.2; IR (KBr): $\nu$ 2925, 2854, 1519, 1461, 1352, 1228, 1081, 755 $cm^{-1}$; MS-ESI: *m/z* 312 $(M + H)^+$; HRMS (ESI) calculated for $C_{18}H_{18}NO_4$: 312.1236 $(M + H)^+$, Found 312.1251.

**(1*R**,4a*S**,10a*R**)-1-(4-Chlorophenyl)-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (5c; Table 3; entry c).** Yield, 86%; Solid, mp 182–184 °C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.42–7.29 (m, 4H), 7.14–7.04 (m, 1H), 6.94–6.87 (m, 1H), 6.86–6.76 (m, 2H), 4.27 (ddd, *J* = 11.7, 4.7 and 1.5 Hz, 1H), 4.01 (d, *J* = 10.0 Hz, 1H), 3.99 (dt, *J* = 10.6 and 4.7 Hz, 1H), 3.77 (dt, *J* = 11.7 and 2.3 Hz, 1H), 2.51–2.36 (m, 1H), 2.27–1.91 (m, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 154.0, 137.6, 134.0, 129.7, 128.7, 128.5, 127.4, 121.1, 120.5, 116.4, 83.0, 76.0, 66.3, 42.3, 32.3, 27.3; IR (KBr): $\nu$ 2925, 2854, 1490, 1238, 1087, 757 $cm^{-1}$; MS-ESI: *m/z* 301 $(M + H)^+$; HRMS (ESI) calculated for $C_{18}H_{18}ClO_2$: 301.0995 $(M + H)^+$, Found 301.1008.

**(1*R**,4a*S**,10a*R**)-1-(3,4-Dimethoxyphenyl)-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (5d; Table 3; entry d).** Yield, 88%; Solid, mp 134–136 °C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.14–7.04 (m, 1H), 6.99–6.76 (m, 6H), 4.31–4.21 (m, 1H), 4.07–3.92 (m, 1H), 3.97 (d, *J* = 9.8 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.77 (dt, *J* = 12.1 and 2.3 Hz, 1H), 2.48–2.33 (m, 1H), 2.29–2.15 (m, 2H), 2.14–1.98 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 154.1, 149.3, 149.1, 131.6, 129.8, 127.3, 121.5, 120.5, 119.9, 116.4, 110.9, 109.9, 83.7, 76.3, 66.3, 55.9, 42.1, 32.4, 27.4; IR (KBr): $\nu$ 2925, 2855, 1516, 1232, 1158, 1088, 1026, 755 $cm^{-1}$; MS-ESI: *m/z* 327 $(M + H)^+$; HRMS (ESI) calculated for $C_{20}H_{23}O_4$: 327.1596 $(M + H)^+$, Found 327.1598.

**(1*R**,4a*S**,10a*R**)-1-(2-Bromophenyl)-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (5e; Table 3; entry e).** Yield, 82%; Solid, mp 118–120 °C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.56–7.41 (m, 2H), 7.33–7.24 (m, 1H), 7.16–7.07 (m, 1H), 7.05–6.95 (m, 1H), 6.90–6.80 (m, 1H), 6.78–6.68 (m, 2H), 4.63 (d, *J* = 9.8 Hz, 1H), 4.19 (ddd, *J* = 12.1, 5.3 and 1.5 Hz, 1H), 4.01 (dt, *J* = 10.6 and 4.5 Hz, 1H), 3.75 (dt, *J* = 12.1 and 2.3 Hz, 1H), 2.70–2.53 (m, 1H) 2.22–2.08 (m, 2H), 2.07–1.88 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 154.0, 138.6, 132.6, 129.7, 129.6, 128.8, 128.0, 127.4, 124.0, 121.4, 120.5, 116.4, 80.6, 76.0, 66.4, 43.1, 32.4, 26.6; IR (KBr): $\nu$ 2924, 2853, 1487, 1460, 1249, 1085, 755 $cm^{-1}$; ESI-MS: *m/z* 345 $(M + H)^+$; HRMS (ESI) calculated for $C_{18}H_{18}BrO_2$: 345.0485 $(M + H)^+$, Found 345.0495.

**(1*R**,4a*S**,10a*R**)-1-(Thiophen-2-yl)-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (5f; Table 3; entry f).** Yield, 84%; Solid, mp 126–128 °C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.31–7.21 (m, 1H), 7.07–6.82 (m, 4H), 6.80–6.69 (m, 2H), 4.29 (d, *J* = 9.8 Hz, 1H), 4.19 (ddd, *J* = 12.1, 5.3 and 1.5 Hz, 1H), 3.90 (dt, *J* = 10.6 and 5.3 Hz, 1H), 3.71 (dt, *J* = 12.1 and 2.3 Hz, 1H), 2.44–2.26 (m, 2H), 2.17–1.90 (m, 3H); $^{13}C$ NMR

(75 MHz, $CDCl_3$): $\delta$ 154.0, 141.9, 129.8, 127.4, 126.3, 125.6, 121.2, 120.5, 116.4, 78.8, 76.0, 66.3, 43.1, 32.1, 27.4; IR (KBr): $\nu$ 2925, 2853, 1228, 1074, 754, 720 $cm^{-1}$; ESI-MS: $m/z$ 273 $(M + H)^+$; HRMS (ESI) calculated for $C_{16}H_{17}O_2S$: 273.0944 $(M + H)^+$, Found 273.0936.

**(1*S**,4a*S**,10a*S**)-1-Phenethyl-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (5g; Table 3; entry g).** Yield, 80%; Solid, mp 93–95 °C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.34–7.15 (m, 5H), 7.13–6.98 (m, 2H), 6.89–6.76 (m, 2H), 4.22–4.13 (m, 1H), 3.79 (dt, $J$ = 10.6 and 4.5 Hz, 1H), 3.58 (dt, $J$ = 12.1 and 2.3 Hz, 1H), 3.06 (dt, $J$ = 9.1 and 2.3 Hz, 1H), 2.96–2.83 (m, 1H), 2.76–2.62 (m, 2H), 2.44–2.26 (m, 2H), 2.15–1.67 (m, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 154.2, 142.1, 129.8, 128.5, 128.4, 127.4, 125.8, 121.3, 120.5, 116.4, 79.2, 76.1, 65.7, 40.7, 34.4, 32.4, 31.5, 27.2; IR (KBr): $\nu$ 2925, 2855, 1488, 1452, 1230, 1085, 760 $cm^{-1}$; MS-ESI: $m/z$ 295 $(M + H)^+$; HRMS (ESI) calculated for $C_{20}H_{23}O_2$: 295.1698 $(M + H)^+$, Found 295.1692.

**(1*S**,4a*S**,10a*S**)-1-Pentyl-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (5h; Table 3; entry h).** Yield, 84%; Viscous liquid; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.16–6.01 (m, 2H), 6.90–6.76 (m, 2H), 4.18–4.08 (m, 1H), 3.80 (dt, $J$ = 10.6 and 4.7 Hz, 1H), 3.57 (dt, $J$ = 12.3 and 2.1 Hz, 1H), 3.12–3.01 (m, 1H), 2.78–2.66 (m, 1H), 2.49–2.35 (m, 1H), 2.14–2.03 (m, 1H), 1.98–1.79 (m, 1H), 1.79–1.37 (m, 9H), 0.91 (t, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 154.2, 129.8, 127.3, 121.4, 120.4, 116.4, 80.3, 76.3, 65.7, 40.6, 32.4, 32.3, 32.0, 27.3, 24.8, 22.6, 14.1; IR (Neat): $\nu$ 2926, 2854, 1488, 1457, 1250, 1231, 1100, 753 $cm^{-1}$; ESI-MS: $m/z$ 261 $(M + H)^+$; HRMS (ESI) calculated for $C_{17}H_{25}O_2$: 261.1849 $(M + H)^+$, Found 261.1855.

**(1*S**,4a*S**,10a*S**)-1-Isobutyl-1,3,4,4a,10,10a-hexahydropyrano[4,3-*b*]chromene (5i; Table 3; entry i).** Yield, 78%; Solid, mp 70–72 °C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.08–6.93 (m, 2H), 6.83–6.69 (m, 2H), 4.04 (ddd, $J$ = 12.1, 5.3 and 1.5 Hz, 1H), 3.73 (dt, $J$ = 10.6 and 5.3 Hz, 1H), 3.48 (dt, $J$ = 12.1 and 2.3 Hz, 1H), 3.03 (dt, $J$ = 9.8 and 2.3 Hz, 1H), 2.70–2.58 (m, 1H), 2.39–2.25 (m, 1H), 2.07–1.96 (m, 1H), 1.92–1.72 (m, 2H), 1.68–1.28 (m, 3H), 0.92–0.80 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 154.2, 129.8, 127.3, 121.5, 120.4, 116.4, 78.4, 76.3, 65.7, 41.7, 41.3, 32.3, 27.4, 24.1, 24.0, 21.4; IR (KBr): $\nu$ 2926, 2856, 1489, 1460, 1374, 1236, 1091, 1053, 755 $cm^{-1}$; ESI-MS: $m/z$ 247 $(M + H)^+$; HRMS (ESI) calculated for $C_{16}H_{23}O_2$: 247.1683 $(M + H)^+$, Found 247.1690.

**(4a′*S**,10a′*R**)-4′,4a′,10′,10a′-Tetrahydro-3′*H*-spiro[cyclohexane-1,1′-pyrano[4,3-*b*]chromene] (5j; Table 3; entry j).** Yield, 72%; Solid, mp 106–108 °C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.16–6.97 (m, 2H), 6.89–6.74 (m, 2H), 4.08 (dt, $J$ = 10.8 and 5.1 Hz, 1H), 3.93–3.80 (m, 1H), 3.75–3.60 (m, 1H), 2.74–2.53 (m, 2H), 2.16–2.03 (m, 1H), 2.02–1.39 (m, 9H), 1.37–1.18 (m, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 153.6, 129.5, 127.2, 122.0, 120.1, 116.2, 75.3, 72.5, 58.2, 45.2, 36.7, 32.8, 26.4, 26.0, 24.8, 21.1, 20.1; IR (KBr): $\nu$ 2927, 2854, 1489, 1452, 1233, 1079, 1018, 806, 752 $cm^{-1}$; ESI-MS: $m/z$ 259 $(M + H)^+$; HRMS (ESI) calculated for $C_{17}H_{23}O_2$: 259.1698 $(M + H)^+$, Found 259.1704.



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## Notes and references

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11 The crystal belongs to the monoclinic crystal system, space group is $P21/c$ with $a$ = 12.8286(7) Å, $b$ = 12. 1802(7) Å, $c$ = 11.4263(6) Å, $\beta$ = 111.313(1), $V$ = 1663.31(16) $Å^3$, $\rho_{calc}$ = 1.303 mg $m^{-3}$, $\lambda$ = 0.71073 Å, $\mu$(Mo Kα) = 0.090 $mm^{-1}$, $F_{000}$ = 696, $T$ = 294(2) K. Data collection yielded 15 572 reflections resulting in 2927 unique, averaged reflection, 2641 with $I > 2(I)$, $\theta$ range: 1.70–25.00°. Full-matrix least-squares refinement led to a final $R$ = 0.0327, w$R$ = 0.0900 and GOF = 1.047. Intensity data were measured on Bruker Smart Apex with CCD area detector. The supplementary crystallographic data (CIF File) for this compound is available as ESI†

 