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Acetal-initiated Prins bicyclization for the synthesis of hexahydrofuro-[3,4-*c*]furan lignans and octahydropyrano[3,4-*c*]pyran derivatives†

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An acetal-initiated Prins bicyclization approach has been developed for the stereoselective synthesis of hexahydrofuro[3,4-*c*]furan lignans. This also provides a direct way to generate a new series of octahydropyrano[3,4-*c*]pyran derivatives in a single-step process.

Introduction

The tetrahydrofuran core is frequently found in various biologically active natural products.[1,2] In particular, furofuran lignans have attracted considerable interest over the years due to their promising biological activity.[3] Sesamin, a furofuran lignan, was isolated from *Fagara* plants and from sesame oil (Fig. 1).[4]

Sesamin is used as a dietary supplement for fat-reduction and is also known to induce apoptosis in human lymphoid leukemia Molt 4B cells.[5] It contains a substituted 3,7-dioxabicyclooctane core, the synthesis of which is a challenging task.[6] Among various approaches, Prins cyclization is a powerful method for the stereoselective construction of oxygen-containing heterocycles[7] and has been employed successfully for the synthesis of several natural products.[8] In particular, intramolecular Prins cyclization is an attractive strategy for the stereoselective construction of fused heterobicycles and tricycles.[9] However, few methods are reported for the synthesis of tetrahydrofuran derivatives through a Prins cyclization[10] wherein a five-membered oxocarbenium ion is trapped with an external nucleophile.[11] Furthermore, Prins cascade cyclization has not yet been explored for the stereoselective synthesis of furo[3,4-*c*]-furan scaffolds.

In continuation of our interest in Prins cyclization and its application in the total synthesis of natural products,[12] we herein report a versatile method for the synthesis of 1,6-diarylhexahydrofuro[3,4-*c*]furan and 1,8-diaryloctahydropyrano-[3,4-*c*]-pyran derivatives through a Prins bicyclization strategy.

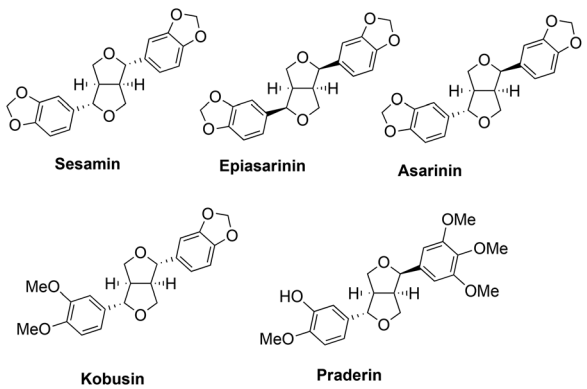

Fig. 1 Biologically active furo[3,4-*c*]furan lignans.

Results and discussion

Initially, we performed a reaction of (*E*)-2-styrylpropane-1,3-diol (**1**) with 2-bromobenzaldehyde in the presence of 10 mol% *p*-TSA. To our surprise, no cyclization was observed under these conditions (Table 1, entry a).

Therefore, the next reaction was performed using 10 mol% $Sc(OTf)_3$. Though the reaction proceeded under these conditions, the desired product was obtained in only a 40% yield after a long reaction time (Table 1, entry b). Similarly, 10 mol% $In(OTf)_3$ also gave the product in poor yield (Table 1, entry c). In fact, no significant improvement either in yield or in reaction time was observed even when increasing the amount of $Sc(OTf)_3$ from 10 mol% to 30 mol% (Table 1, entry d). Remarkably, a combination of $Sc(OTf)_3$ and *p*-TSA gave the product in a high yield in a short reaction time (Table 1, entry e).

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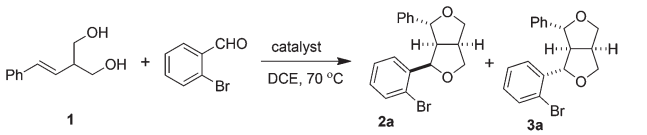
†Electronic supplementary information (ESI) available: Experimental procedures, spectral data, nOe experiments, X-ray crystal co-ordinates and CIF file formats of **2a** and **7a**. CCDC 943366 and 943367. For ESI and crystallographic data in CIF or other electronic formats see DOI: 10.1039/c4ob00305e

Table 1 Screening of acid catalysts in the formation of **2a**/**3a**[a]



Entry	Catalyst	Time (h)	Yield[b] (%)	**2a** : **3a** ratio[c]
a	10 mol% *p*-TSA	4	0	0
b	10 mol% $Sc(OTf)_3$	6	40	6 : 4
c	10 mol% $In(OTf)_3$	6	30	6 : 4
d	30 mol% $Sc(OTf)_3$	6	55	6 : 4
e	10 mol% $Sc(OTf)_3$/*p*-TSA	2	86	6 : 4

[a] The reaction was performed on a 0.5 mmol scale. [b] Isolated yield. [c] The ratios were determined from ^{1}H NMR spectra of the crude products.

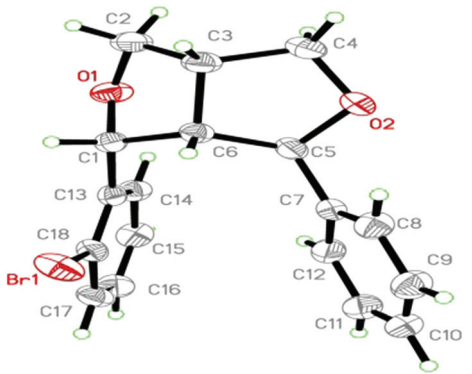


Fig. 2 ORTEP diagram of **2a**.

From the above results, it was obvious that binary acid ($Sc(OTf)_3$/*p*-TSA) is essential for performing the reaction successfully. These results are consistent with our earlier observation that binary acid exhibits remarkable synergistic effects.[13] Therefore, the cooperative effect between the $Sc(OTf)_3$ and the *p*-TSA provides high conversions and enhanced rates in a tandem process. Under optimized conditions, the expected product **2a**/**3a** was obtained in an 86% yield with 6 : 4 diastereoselectivity (Table 1, entry e). The ratio of the products (**2** : **3**) was confirmed from the ^{1}H NMR spectrum of the crude mixture. The diastereomers were easily separated by flash chromatography. The structure and stereochemistry of 1-(2-bromophenyl)-6-phenylhexahydrofuro[3,4-*c*]furan (**2a**) were established by detailed 1D and 2D NMR experiments (see ESI†). Furthermore, the stereochemistries of **2a** and **3a** were confirmed by X-ray crystallography (Fig. 2).

The scope of this process is further illustrated with respect to various aldehydes (Table 2). Both electron-rich and electron-deficient aromatic aldehydes, such as 4-methoxy-, 3,4-methylenedioxy-, 4-chloro-, 4-bromo-, 4-cyano-, and 4-nitro-benzaldehydes, reacted well with (*E*)-homoallylic diol (**1**) to furnish the corresponding *cis*-fused 1,6-diarylhexahydrofuro[3,4-*c*]-furan derivatives in good yields (Table 2, entries b–g). The reaction worked not only with aromatic aldehydes but also with aliphatic aldehydes. In the case of *n*-propionaldehyde, the respective ethyl-substituted *cis*-fused hexahydrofuro[3,4-*c*]furan was obtained in a slightly lower yield than its aromatic counterparts (Table 2, entry h). On the other hand, the α,β-unsaturated aldehyde afforded styryl substituted furo[3,2-*c*]furan in an excellent yield (Table 2, entry i). In addition, the reaction was also successful with heterocyclic aldehydes. For example, furfural gave the corresponding bicyclic ethers **2** and **3** in a 76% yield with 7 : 3 selectivity (Table 2, entry j). This is an entirely new process for the direct conversion of homoallylic diol, **1**, into *cis*-fused furo[3,2-*c*]furan derivatives.

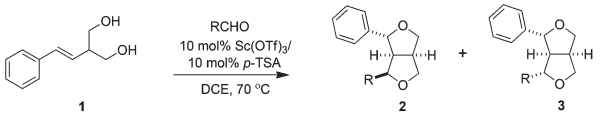
The reaction proceeds *via* the formation of an oxocarbenium ion generated from the acetal. This is formed *in situ* from the aldehyde and the homoallylic diol, most likely after activation with *p*-TSA. The oxocarbenium ion is then attacked by an internal olefin, resulting in the formation of a more stable benzylic carbocation which is simultaneously trapped by a tethered hydroxyl group, leading to the formation of **2** and **3**. The intermediate has flexibility in terms of C–C bond rotation, which can result in the formation of **2** and **3**. However, the thermodynamically more stable diastereomer **2** is predominantly formed. The formation of **4** due to the elimination of the proton was not observed (Scheme 1).[14]

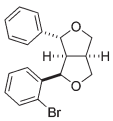
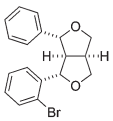
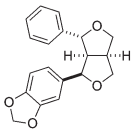
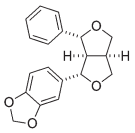
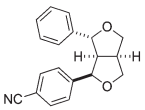
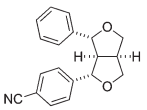
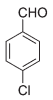
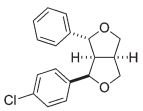
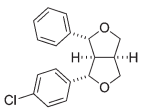
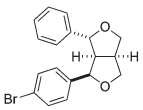
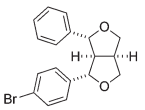
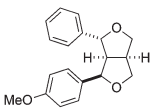
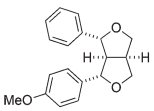
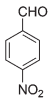
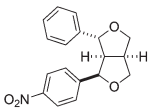
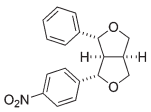
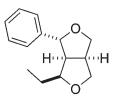
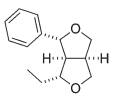
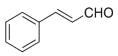
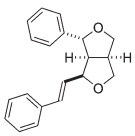
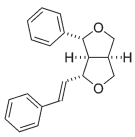
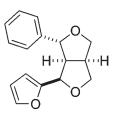
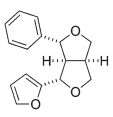
To confirm the reaction mechanism, we carried out the cyclization of (*E*)-2-(4-methoxyphenyl)-5-styryl-1,3-dioxane (**1a**) in the presence of 10 mol% $Sc(OTf)_3$ in DCE at 70 °C. Under the above conditions, the corresponding 1-(4-methoxyphenyl)-6-phenylhexahydrofuro[3,4-*c*]furan was obtained in a 95% yield with 6 : 4 diastereoselectivity. This indicates that acetal formation is a highly likely mechanism for this reaction (Scheme 2).

Inspired by the results obtained with homoallylic diol (**1**), we extended this process to γ,δ-unsaturated alcohols. Accordingly, treatment of (*E*)-3-styrylpentane-1,5-diol (**5**) with 2-bromobenzaldehyde in the presence of 10 mol% $Sc(OTf)_3$ in dichloroethane at room temperature afforded the respective *trans*-fused octahydropyrano[3,4-*c*]pyran **7a** as the sole product, in a 90% yield (Table 3). The structure and stereochemistry of 1-(2-bromophenyl)-8-phenyloctahydropyrano[3,4-*c*]pyran (**7a**) were assigned based on single crystal X-ray analysis (Fig. 3).

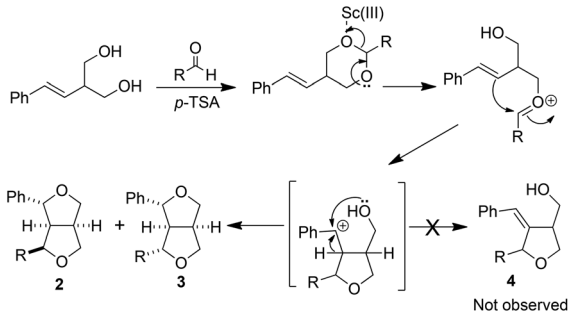
The above results provide a gateway to extend this process to other substrates such as (*E*)-3(2-bromostyryl)pentane-1,5-diol (**6**). The scope of the reaction was investigated with various aldehydes, and the results are presented in Table 3. A variety of aromatic, heteroaromatic and aliphatic aldehydes were treated with (*E*)-3-styrylpentane-1,5-diol to give octahydropyrano[3,4-*c*]pyrans in good to high yields (80–92%). Similarly, α,β-unsaturated aldehydes also worked well in this reaction to produce styryl substituted pyrano[3,4-*c*]pyran (**8f**) in an excellent yield. The structure and stereochemistry of **8d** were established by detailed 1D and 2D NMR experiments (see ESI†). In all cases, the corresponding *trans*-fused octahydropyrano[3,4-*c*]-pyrans were obtained in good yields with a high selectivity (Table 3). Therefore, this method provides a direct approach for the conversion of γ,δ-unsaturated diols into *trans*-fused pyranopyrans.

Table 2 Synthesis of hexahydrofuro[3,4-*c*]furan derivatives[a]

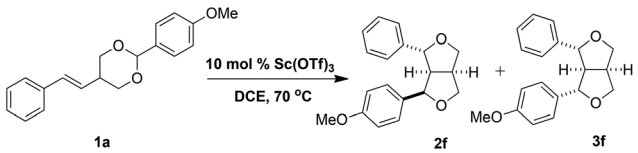


Entry	Aldehyde	Products 2	Products 3	Time (h)	Yield[b] (%)	2 : 3 ratio[c]
a				4	86	60 : 40
b				4	75	60 : 40
c				3	90	56 : 44
d				3	80	55 : 45
e				4	82	62 : 38
f				4	78	60 : 40
g				3	90	58 : 42
h				4	70	60 : 40
i				3	85	65 : 35
j				2	76	70 : 30

[a] The reactions were performed on a 0.5 mmol scale. [b] Yield refers to pure products after column chromatography. [c] Diastereomeric ratios were determined from the ^{1}H NMR spectra of the crude products.

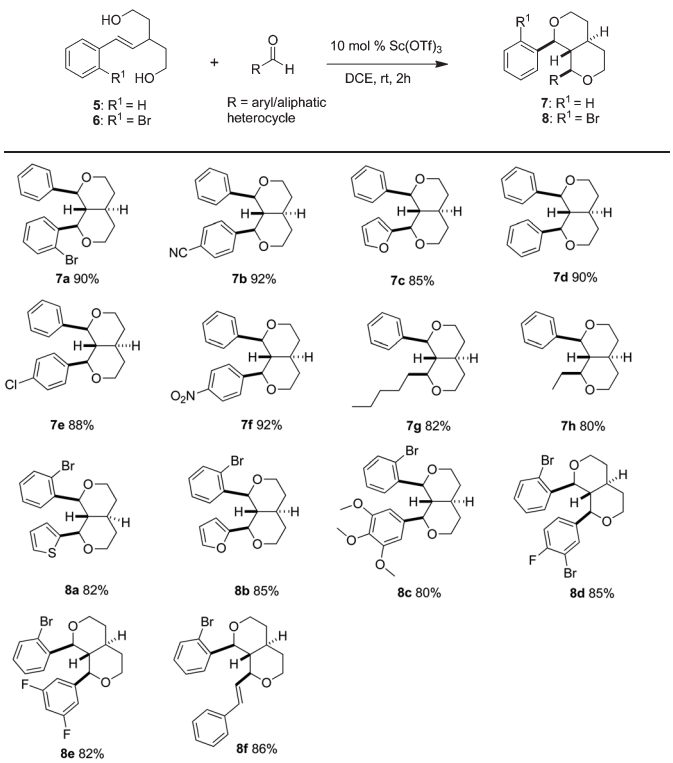


Scheme 1 A plausible reaction pathway.



Scheme 2 Acetal-initiated cyclization of **1a**.

Table 3 Synthesis of octahydropyrano[3,4-*c*]pyran derivatives[ab]



[a] The reactions were performed on a 0.5 mmol scale. [b] Yield refers to pure products after column chromatography.

To demonstrate the synthetic utility of this method, we applied the protocol to the generation of allocolchicine analogues. Accordingly, compound **7a** was transformed into a polycyclic compound, **9a**, in a 76% yield *via* aryl–aryl bond formation[15] using $Pd(OAc)_2$ (10 mol%), triphenylphosphine

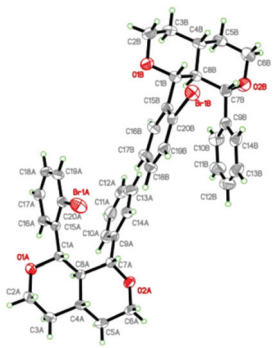
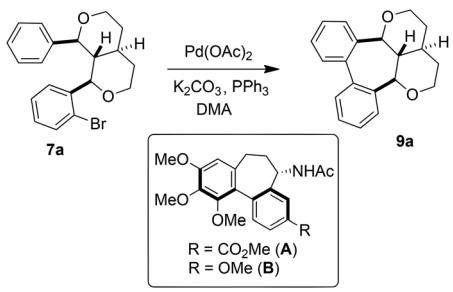


Fig. 3 ORTEP diagram of **7a**.



Scheme 3 Heck reaction of **7a** for the construction of the biaryl derivative **9a**.

(10 mol%), and K_2CO_3 (2 equiv.), in DMA at 130 °C (Scheme 3). The 6-7-6-carbocyclic framework is a common structural core in allocolchicine (**A**) and *N*-acetyl colchinol-*O*-methyl ether (NCME) (**B**). The allocolchicines are seven-membered biaryl derivatives of naturally occurring colchicines, which are potent tubulin inhibitors.[16]

Conclusions

In summary, we have developed an acetal-initiated Prins cascade reaction for the synthesis of *cis*-fused hexahydrofuro-[3,4-*c*]furan derivatives. This reaction provides direct access to furofuran lignan analogues, which are reported to be potent antitumor, antimitotic, and antiviral agents. The method generates two heterocyclic rings with four new stereogenic centers, in a one-pot operation.

Experimental

General remarks

IR spectra were recorded on an FT-IR spectrometer (KBr) and are reported in reciprocal centimeters (cm^{-1}). ^1H NMR spectra were recorded at 500 MHz and 300 MHz, and ^{13}C NMR at 125 MHz and 75 MHz. For ^1H NMR, tetramethylsilane (TMS) was used as the internal standard (δ = 0) and values are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet,

br = broad), and the coupling constants in Hz. For ^{13}C NMR, $CDCl_3$ (δ = 77.27) was used as the internal standard and spectra were obtained with complete proton decoupling. Low-resolution MS and HRMS data were obtained using ESI and EI ionization. Melting points were measured on micro melting point apparatus. Commercially available salicylaldehyde, acetophenone, and TMSOTf were used without further purification. DCE was distilled from CaH under a N_2 atmosphere.

Typical procedure for Prins cascade cyclization. To a stirred solution of alcohol (**1** or **5** or **6**) (0.5 mmol) and aldehyde (0.6 mmol) in dry dichloromethane (5 mL) at 0 °C was added the catalyst, as specified in Tables 2 and 3. The resulting mixture was stirred at the temperature specified in Tables 2 and 3 under a nitrogen atmosphere. After completion, as indicated by thin-layer chromatography (TLC), the reaction mixture was quenched with saturated $NaHCO_3$ solution (1.0 mL) and extracted with dichloromethane (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude product was purified by silica gel column chromatography, using ethyl acetate–hexane as the eluent, to afford the pure product.

(3a*S*,3a^1*S*,11b*R*,14a*S*)-1,2,3a,3a^1,11b,13,14,14a-Octahydro-3,12-dioxadibenzo[4,5:6,7]cyclohepta[1,2,3-*de*]naphthalene (9a). To a stirred solution of compound (**7a**) (372 mg, 1 mmol) in DMA (3 mL) were added triphenylphosphine (26 mg, 10 mmol), $Pd(OAc)_2$ (22 mg, 10 mmol) and K_2CO_3 (276 mg, 2 equiv.) at room temperature under a nitrogen atmosphere. The resulting mixture was heated at 140 °C under vigorous stirring for 48 h. After completion, the reaction was diluted with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by silica gel chromatography to give the compound **9a** in a 75% yield as a solid.

(1*R*,4a*S*,8*S*,8a*S*)-1-(2-Bromophenyl)-8-phenyloctahydropyrano[3,4-*c*]pyran (7a). White solid, m.p. 110–112 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.06–6.96 (m, 4H), 6.90–6.80 (m, 4H), 6.71–6.63 (m, 1H), 4.71 (d, J = 9.6 Hz, 1H), 4.19–4.05 (m, 3H), 3.81–3.67 (m, 2H), 2.18 (q, J = 9.8 Hz, 1H), 2.05–1.89 (m, 1H), 1.82–1.63 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.1, 138.8, 131.3, 129.1, 128.1, 127.1, 127.0, 126.9, 126.6, 123.6, 81.7, 80.2, 68.8, 68.4, 50.8, 40.4, 33.5, 33.3 ppm; IR (KBr): ν 3034, 2835, 2717, 1731, 1455, 1149, 1081, 818, 766 cm^{-1}; MS (EI): m/z ([M]$^+$): 372; HRMS (EI): m/z calcd for $C_{20}H_{21}BrO_2$: 372.0725; found: 372.0732.

4-((1*R*,4a*S*,8*S*,8a*S*)-8-Phenyloctahydropyrano[3,4-*c*]pyran-1-yl)-benzonitrile (7b). White solid, m.p. 186–188 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, J = 8.3 Hz, 2H), 6.98–6.77 (m, 7H), 4.15–4.03 (m, 4H), 3.77–3.65 (m, 2H), 2.13 (q, J = 9.8 Hz, 1H), 1.97–1.66 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 138.8, 130.6, 128.0, 127.4, 127.2, 127.0, 118.3, 110.1, 82.5, 81.7, 68.6, 68.5, 50.9, 40.6, 33.5, 33.4 ppm; IR (KBr): ν 2925, 2890, 2851, 2221, 1453, 1092, 983, 833, 764 cm^{-1}; MS (EI): m/z ([M]$^+$): 319; HRMS (EI): m/z calcd for $C_{21}H_{21}NO_2$: 319.1572; found: 319.1577.

(1*R*,4a*S*,8*S*,8a*S*)-1-(Furan-2-yl)-8-phenyloctahydropyrano[3,4-*c*]-pyran (7c). White solid, m.p. 85–87 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.10–6.95 (m, 5H), 6.86 (brs, 1H), 5.74–5.69 (m, 1H), 5.61 (d, J = 3.7 Hz, 1H), 4.20–3.99 (m, 4H), 3.76–3.62 (m, 2H), 2.29 (q, J = 9.8 Hz, 1H), 1.89–1.53 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.5, 140.6, 139.1, 127.1, 126.8, 126.4, 109.4, 108.3, 82.9, 74.2, 68.6, 68.4, 48.6, 40.6, 33.4, 31.2 ppm; IR (KBr): ν 3034, 2835, 2717, 1731, 1455, 1149, 1081, 818, 766 cm^{-1}; MS (EI): m/z ([M]$^+$): 284; HRMS (EI): m/z calcd for $C_{18}H_{20}O_3$: 284.1412; found: 284.1425.

(1*R*,4a*S*,8*S*,8a*S*)-1,8-Diphenyloctahydropyrano[3,4-*c*]pyran (7d). White solid, m.p. 104–106 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 6.86–6.79 (m, 10H), 4.15–4.04 (m, 4H), 3.77–3.66 (m, 2H), 2.21 (q, J = 9.8 Hz, 1H), 1.97–1.64 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 127.3, 126.9, 126.4, 82.9, 68.5, 50.6, 40.9, 33.6 ppm; IR (KBr): ν 3033, 2924, 2852, 1729, 1454, 1147, 1088, 979, 754 cm^{-1}; MS (EI): m/z ([M]$^+$): 294; HRMS (EI): m/z calcd for $C_{20}H_{22}O_2$: 294.1619; found: 294.1623.

(1*R*,4a*S*,8*S*,8a*S*)-1-(4-Chlorophenyl)-8-phenyloctahydropyrano-[3,4-*c*]pyran (7e). White solid, m.p. 124–126 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.01–6.70 (m, 9H), 4.16–4.01 (m, 4H), 3.77–3.65 (m, 2H), 2.12 (q, J = 9.8 Hz, 1H), 1.94–1.64 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 137.9, 131.9, 128.5, 127.3, 127.1, 126.9, 126.4, 82.7, 81.9, 68.5, 51.1, 40.8, 33.6 ppm; IR (KBr): ν 3064, 2924, 2837, 1731, 1492, 1149, 1091, 980, 756 cm^{-1}; MS (EI): m/z ([M]$^+$): 328; HRMS (EI): m/z calcd for $C_{20}H_{21}ClO_2$: 328.1230; found: 328.1234.

(1*R*,4a*S*,8*S*,8a*S*)-1-(4-Nitrophenyl)-8-phenyloctahydropyrano-[3,4-*c*]pyran (7f). White solid, m.p. 218–220 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–7.61 (d, J = 9.0 Hz, 2H), 7.01 (d, J = 8.3 Hz, 2H), 6.90–6.77 (m, 6H), 4.21–4.04 (m, 4H), 3.77–3.67 (m, 2H), 2.17 (q, J = 9.0 Hz, 1H), 2.01–1.86 (m, 1H), 1.84–1.67 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.7, 145.6, 138.9, 128.1, 127.4, 127.1, 126.8, 121.9, 82.4, 81.3, 68.5, 68.5, 51.2, 40.5, 32.5, 32.5 ppm; IR (KBr): ν 3078, 2925, 2846, 1517, 1346, 1084, 982, 755 cm^{-1}; MS (EI): m/z ([M]$^+$): 339; HRMS (EI): m/z calcd for $C_{20}H_{21}NO_4$: 339.1470; found: 339.1472.

(1*S*,4a*R*,8*S*,8a*R*)-1-Pentyl-8-phenyloctahydropyrano[3,4-*c*]-pyran (7g). Semi solid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.32–7.26 (m, 5H), 4.11–4.07 (m, 1H), 4.02–3.96 (m, 2H), 3.70–3.64 (m, 1H), 3.54–3.48 (m, 1H), 3.09 (dt, J = 3.6, 8.5 Hz, 1H), 1.74–1.55 (m, 5H), 1.16–1.08 (m, 1H), 1.08–0.93 (m, 1H), 0.73 (t, J = 7.3 Hz, 1H), 0.60–0.55 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 128.0, 127.7, 127.3, 83.0, 78.9, 68.5, 67.8, 50.1, 40.4, 34.4, 33.6, 33.5, 31.8, 25.0, 22.7, 14.4 ppm; IR (KBr): ν 3365, 2993, 2795, 1697, 1654, 1056, 872, 755, 732 cm^{-1}; MS (EI): m/z ([M]$^+$): 288; HRMS (EI): m/z calcd for $C_{19}H_{28}O_2$: 288.2089; found: 288.2093.

(1*S*,4a*R*,8*S*,8a*R*)-1-Ethyl-8-phenyloctahydropyrano[3,4-*c*]pyran (7h). Semi solid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.32–7.25 (m, 5H), 4.10–4.06 (m, 1H), 4.03–3.98 (m, 2H), 3.69–3.64 (m, 1H), 3.55–3.49 (m, 1H), 3.05–3.00 (m, 1H), 1.75–1.55 (m, 5H), 0.70–0.64 (m, 1H), 0.56 (t, J = 3.3 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 128.0, 127.7, 127.3, 82.8, 80.1, 68.5, 67.8, 49.8, 40.3, 33.6, 33.4, 27.4, 10.2 ppm; IR (KBr): ν 3088, 2920, 2843, 1717, 1646, 1184, 791, 768 cm^{-1}; MS (EI): m/z

([M]$^+$): 246; HRMS (EI): *m*/*z* calcd for $C_{16}H_{22}O_2$: 246.1620; found: 246.1626.

(1*S*,4a*S*,8*R*,8a*S*)-1-(2-Bromophenyl)-8-(thiophen-2-yl)octahydropyrano[3,4-*c*]pyran (8a). White solid, m.p. 78–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96–6.93 (m, 5H), 6.84 (d, J = 5.2 Hz, 1H), 6.35–6.26 (m, 2H), 4.42 (d, J = 9.8 Hz, 1H), 4.16–4.06 (m, 3H), 3.76–3.66 (m, 2H), 2.14 (q, J = 9.8 Hz, 1H), 1.93–1.57 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.0, 139.6, 127.3 127.1, 126.6, 125.8, 125.4, 124.2, 83.1, 77.1, 68.5, 68.4, 52.0, 40.7, 33.3, 33.1 ppm; IR (KBr): ν 3035, 2838, 2707, 1701, 1475, 1159, 1081, 811, 700 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 378; HRMS (EI): *m*/*z* calcd for $C_{18}H_{19}BrO_2S$: 378.0289; found: 378.0297.

(1*S*,4a*S*,8*R*,8a*S*)-1-(2-Bromophenyl)-8-(furan-2-yl)octa hydropyrano[3,4-*c*]pyran (8b). White solid, m.p. 85–87 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07–6.94 (m, 5H), 6.84 (brs, 1H), 5.72–5.69 (m, 1H), 5.61 (d, J = 3.0 Hz, 1H), 4.18–4.00 (m, 5H), 3.75–3.64 (m, 2H), 2.35 (q, J = 9.8 Hz, 1H), 1.89–1.55 (m, 7H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.5, 140.6, 139.1, 127.1, 126.8, 126.4, 109.5, 108.3, 83.0, 74.2, 68.7, 68.4, 48.7, 40.7, 33.5, 33.1 ppm; IR (KBr): ν 3028, 2924, 2844, 1739, 1436, 1370, 1248, 1147, 1083, 756 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 362; HRMS (EI): *m*/*z* calcd for $C_{18}H_{19}BrO_3$: 362.0518; found: 362.0513.

(1*S*,4a*R*,8*R*,8a*R*)-1-(2-Bromophenyl)-8-(3,4,5-trimethoxy phenyl)-octahydropyrano[3,4-*c*]pyran (8c). White solid, m.p. 102–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97–6.84 (m, 4H), 6.08 (s, 1H), 4.15–3.97 (m, 3H), 3.72 (s, 6H), 3.66 (s, 3H), 2.14 (q, J = 9.8 Hz, 1H), 1.92–1.53 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.4, 139.6, 135.9, 134.9, 127.2, 126.6, 126.5, 105.3, 83.2, 82.5, 68.6, 68.4, 60.3, 55.9, 50.9, 40.8, 33.6, 33.5 ppm; IR (KBr): ν 2924, 2717, 1436, 1370, 1248, 1083, 756, 697 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 462; HRMS (EI): *m*/*z* calcd for $C_{23}H_{27}BrO_5$: 462.1042; found: 462.1051.

(1*R*,4a*R*,8*S*,8a*R*)-1-(3-Bromo-4-fluorophenyl)-8-(2-bromophenyl)-octahydropyrano[3,4-*c*]pyran (8d). White solid, m.p. 128–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97–6.90 (m, 4H), 6.85–6.77 (m, 3H), 6.57 (t, J = 8.3 Hz, 1H), 4.12–3.98 (m, 4H), 3.72–3.65 (m, 2H), 2.07 (q, J = 9.9 Hz, 1H), 1.90–1.81 (m, 1H), 1.78–1.64 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 155.0, 139.0, 136.9, 132.5, 127.7, 127.6, 127.1, 126.9, 126.8, 114.9, 114.6, 82.4, 81.2, 68.5, 68.5, 51.1, 40.5, 33.5, 33.4 ppm; IR (KBr): ν 2967, 2717, 1739, 1436, 1370, 1147, 1083, 756, 690 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 467; HRMS (EI): *m*/*z* calcd for $C_{20}H_{19}Br_2FO_2$: 467.9738; found: 467.9726.

(1*S*,4a*R*,8*R*,8a*R*)-1-(2-Bromophenyl)-8-(3,5-difluorophenyl)-octahydropyrano[3,4-*c*]pyran (8e). White solid, m.p. 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99–6.87 (m, 5H), 6.38–6.23 (m, 3H), 4.14–3.98 (m, 4H), 3.75–3.64 (m, 2H), 2.08 (q, J = 9.6 Hz, 1H), 1.90–1.64 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 160.3, 143.5, 139.2, 127.5, 127.3, 127.2, 110.7, 110.5, 102.4, 102.2, 102.0, 82.6, 81.5, 68.5, 68.5, 50.7, 40.4, 33.3, 33.2 ppm; IR (KBr): ν 3028, 2967, 1739, 1436, 1370, 1147, 1083, 1020, 983, 756, 697 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 408; HRMS (EI): *m*/*z* calcd for $C_{20}H_{19}BrF_2O_2$: 408.0532; found: 408.0529.

(1*S*,4a*R*,8*S*,8a*R*)-1-(2-Bromophenyl)-8-styryloctahydropyrano-[3,4-*c*]pyran (8f). White solid, m.p. 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.06 (m, 7H), 7.05–6.98 (m, 1H), 6.80–6.69 (m, 2H), 6.15 (d, J = 15.8 Hz, 1H), 5.25 (dd, J = 7.5, 15.8 Hz, 1H), 4.16–4.04 (m, 3H), 3.77–3.60 (m, 4H), 1.91 (q, J = 9.8 Hz, 1H), 1.73–1.54 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.7, 136.1, 131.1, 129.2, 128.1, 127.8, 127.5, 127.3, 126.7, 126.0, 82.5, 80.2, 68.5, 68.1, 51.2, 40.1, 33.3, 33.2 ppm; IR (KBr): ν 3062, 3028, 2924, 1739, 1370, 1147, 1083, 1020, 983, 756 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 398; HRMS (EI): *m*/*z* calcd for $C_{22}H_{23}BrO_2$: 398.0880; found: 398.0883.

(3a*S*,3a^1*S*,11b*R*,14a*S*)-1,2,3a,3a^1,11b,13,14,14a-Octahydro-3,12 dioxadibenzo[4,5:6,7]cyclohepta[1,2,3-*de*]naphthalene (9a). White solid, m.p. 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64–7.58 (m, 2H), 7.51–7.44 (m, 2H), 7.38–7.31 (m, 5H), 4.62 (d, J = 9.0 Hz, 2H), 4.21–4.12 (m, 2H), 3.91–3.81 (m, 2H), 1.88–1.70 (m, 4H), 1.50–1.36 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 135.5, 131.1, 127.0, 126.9, 126.6, 78.6, 67.3, 49.8, 40.5, 32.5 ppm; IR (KBr): ν 2924, 1726, 1447, 1379, 1259, 1121, 1070, 983, 755 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 292; HRMS (EI): *m*/*z* calcd for $C_{20}H_{20}O_2$: 292.1463; found: 292.1462.

(1*R*,3a*R*,6*R*,6a*S*)-1-(2-Bromophenyl)-6-phenylhexahydrofuro-[3,4-*c*]furan (2a). Solid, m.p. 102–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79–7.68 (m, 1H), 7.43–7.30 (m, 2H), 7.18–7.06 (s, 4H), 6.70–6.63 (m, 2H), 5.01 (d, J = 5.2 Hz, 1H), 4.38 (d, J = 8.3 Hz, 1H), 4.20–4.01 (m, 2H), 3.86 (q, J = 6.0 Hz, 1H), 3.65–3.57 (m, 1H), 3.49–3.39 (m, 1H), 3.30–3.17 (m, 1H), ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.1, 137.2, 131.7, 128.4, 127.8, 127.5, 126.9, 126.6, 125.8, 121.6, 82.5, 81.6, 74.2, 71.4, 55.0, 47.0 ppm; IR (KBr): ν 3035, 2954, 2862, 1494, 1253, 1048, 1023, 758 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 344; HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}BrO_2$: 344.0411; found: 344.0426.

(1*S*,3a*S*,6*R*,6a*R*)-1-(2-Bromophenyl)-6-phenylhexahydrofuro-[3,4-*c*]furan (3a). Liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53–7.42 (m, 2H), 7.37–7.22 (m, 7H), 7.15–7.07 (m, 1H), 5.31 (d, J = 4.5 Hz, 1H), 5.01 (d, J = 4.5 Hz, 1H), 4.35 (m, 1H), 4.19 (q, J = 6.7 Hz, 1H), 3.91–3.83 (m, 2H), 3.23–3.11 (m, 1H), 3.05–2.96 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.7, 140.4, 132.5, 128.5, 127.9, 127.1, 127.1, 126.8, 125.8, 121.5, 85.3, 84.3, 73.4, 72.1, 61.0, 46.6 ppm; IR (KBr): ν 2954, 2860, 1466, 1252, 1040, 750, 699, 574 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 344; HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}BrO_2$: 344.0411; found: 344.0415.

5-((1*R*,3a*R*,6*R*,6a*S*)-6-Phenylhexahydrofuro[3,4-*c*]furan-1-yl)-benzo[*d*][1,3]dioxole (2b). Semi solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.21 (m, 4H), 7.12–7.10 (m, 1H), 6.84–6.73 (m, 3H), 5.96–5.88 (m, 2H), 4.93–4.89 (m, 1H), 4.87–4.83 (m, 1H), 4.36–4.33 (m, 1H), 4.20–4.16 (m, 1H), 3.84–3.77 (m, 2H), 3.23–3.13 (m, 1H), 3.01–2.94 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.7, 140.8, 132.5, 127.1, 126.5, 126.1, 120.4, 107.1, 107.0, 100.4, 83.0, 82.3, 72.4, 67.7, 58.0, 45.1 ppm; IR (KBr): ν 2875, 1731, 1616, 1494, 1442, 1387, 1245, 1038, 931, 810, 770 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 310; HRMS (EI): *m*/*z* calcd for $C_{19}H_{18}O_4$: 310.1205; found: 310.1213.

5-((1*S*,3a*S*,6*R*,6a*R*)-6-Phenylhexahydrofuro[3,4-*c*]furan-1-yl)-benzo[*d*][1,3]dioxole (3b). Semi solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.22 (m, 4H), 7.16–7.12 (m, 1H), 6.82 (s, 1H), 6.79–6.72 (m, 2H), 5.95–5.90 (m, 2H), 4.93–4.90 (m, 1H), 4.86–4.81 (m, 1H), 4.39–4.34 (m, 1H), 4.23–4.17 (m, 1H),

4.02–3.98 (m, 1H), 3.85–3.74 (m, 2H), 3.24–3.09 (m, 1H), 3.04–2.95 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3, 146.5, 140.5, 134.4, 128.1, 127.7, 127.6, 127.1, 125.8, 125.3, 119.0, 107.9, 106.2, 100.8, 85.1, 84.7, 72.7, 72.5, 61.5, 46.7 ppm; IR (KBr): ν 2870, 1616, 1494, 1387, 1246, 930, 810, 770 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 310; HRMS (EI): *m*/*z* calcd for $C_{19}H_{18}O_4$: 310.1205; found: 310.1213.

4-((1*R*,3a*R*,6*R*,6a*S*)-6-Phenylhexahydrofuro[3,4-*c*]furan-1-yl)-benzonitrile (2c). Solid, m.p. 86–88 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.19–7.09 (m, 3H), 6.68–6.62 (m, 2H), 4.96 (d, *J* = 5.5 Hz, 1H), 4.41 (t, *J* = 8.4 Hz, 1H), 4.15–4.04 (m, 2H), 3.91 (dd, *J* = 6.4, 9.4 Hz, 1H), 3.61 (dd, *J* = 6.9, 8.8 Hz, 1H), 3.35–3.26 (m, 1H), 3.20–3.13 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 139.9, 131.5, 127.8, 127.3, 126.6, 126.1, 118.4, 110.8, 82.6, 81.5, 74.3, 71.9, 57.7, 47.3 ppm; IR (KBr): ν 3055, 2861, 2228, 1735, 1604, 1218, 1602, 932, 826 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 291; HRMS (EI): *m*/*z* calcd for $C_{19}H_{17}NO_2$: 291.1259; found: 291.1254.

4-((1*S*,3a*S*,6*R*,6a*R*)-6-Phenylhexahydrofuro[3,4-*c*]furan-1-yl)-benzonitrile (3c). Solid, m.p. 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.42–7.34 (m, 5H), 7.32–7.29 (m, 3H), 4.98 (dd, *J* = 4.7, 13.2 Hz, 2H), 4.26–4.21 (m, 2H), 3.88–3.80 (m, 2H), 3.22–3.15 (m, 1H), 2.98–2.94 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.9, 139.7, 131.7, 128.1, 127.2, 125.6, 125.1, 118.1, 85.0, 84.2, 73.0, 72.5, 62.0, 46.8 ppm; IR (KBr): ν 3055, 2922, 2228, 1735, 1604, 1218, 1062, 932, 828, 714 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 291; HRMS (EI): *m*/*z* calcd for $C_{19}H_{17}NO_2$: 291.1259; found: 291.1254.

(1*R*,3a*R*,6*R*,6a*S*)-1-(4-Chlorophenyl)-6-phenylhexahydrofuro-[3,4-*c*]furan (2d). Solid, m.p. 106–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.24 (m, 4H), 7.20–7.13 (m, 2H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.70–6.67 (m, 1H), 6.57 (d, *J* = 8.3 Hz, 1H), 4.93–4.86 (m, 1H), 4.39 (t, *J* = 8.3 Hz, 1H), 4.27–4.17 (m, 1H), 4.11–4.01 (m, 1H), 3.91–3.78 (m, 1H), 3.65–3.56 (m, 1H), 3.32–3.20 (m, 1H), 3.12–2.95 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 140.1, 131.6, 128.6, 127.7, 127.4, 125.8, 125.7, 121.4, 84.9, 84.5, 72.8, 72.5, 61.6, 46.5 ppm; IR (KBr): ν 2924, 2854, 1739, 1636, 1459, 1376, 1071, 1017, 755 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 300; HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}ClO_2$: 300.0917; found: 300.0919.

(1*S*,3a*S*,6*R*,6a*R*)-1-(4-Chlorophenyl)-6-phenylhexahydrofuro-[3,4-*c*]furan (3d). Semi solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.22 (m, 9H), 4.97–4.87 (m, 2H), 4.27–4.17 (m, 2H), 3.85–3.77 (m, 2H), 3.24–3.17 (m, 1H), 3.03–2.89 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.0, 127.9, 127.6, 127.4, 127.3, 127.0, 126.5, 125.1, 84.8, 84.5, 72.7, 72.5, 61.7, 46.8 ppm; IR (KBr): ν 2924, 2854, 1739, 1636, 1459, 1376, 1071, 821, 755 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 300; HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}ClO_2$: 300.0917; found: 300.0919.

(1*R*,3a*R*,6*R*,6a*S*)-1-(4-Bromophenyl)-6-phenylhexahydrofuro-[3,4-*c*]furan (2e). Solid, m.p. 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.38 (m, 2H), 7.36–7.24 (m, 2H), 7.1–7.10 (m, 3H), 6.71–6.66 (m, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 4.91–4.84 (m, 1H), 4.39 (t, *J* = 8.3 Hz, 1H), 4.29–4.16 (m, 1H), 4.08–4.01 (m, 1H), 3.90–3.77 (m, 1H), 3.65–3.56 (m, 1H), 3.31–3.21 (m, 1H), 3.15–3.01 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 140.2, 128.2, 127.8, 127.0, 126.4, 123.3, 82.6, 81.4, 74.2, 71.9, 57.6, 47.0 ppm; IR (KBr): ν 2926, 2855, 1737, 1487, 1238, 1073, 1010, 756, 700 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 344; HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}BrO_2$: 344.0411; found: 344.0426.

(1*S*,3a*S*,6*R*,6a*R*)-1-(4-Bromophenyl)-6-phenylhexahydrofuro-[3,4-*c*]furan (3e). Semi solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.42 (m, 2H), 7.37–7.24 (m, 6H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.94 (d, *J* = 4.7 Hz, 1H), 4.89 (d, *J* = 4.8 Hz, 1H), 4.25–4.19 (m, 2H), 3.84–3.79 (m, 2H), 3.22–3.19 (m, 1H), 2.99–2.93 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.8, 141.1, 132.7, 129.7, 128.8, 128.6, 126.9, 122.7, 86.6, 86.2, 74.6, 74.3, 63.5, 48.6 ppm; IR (KBr): ν 3028, 2926, 2855, 1729, 1487, 1221, 1069, 1008, 770 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 344; HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}BrO_2$: 344.0411; found: 344.0426.

(1*R*,3a*S*,6*R*,6a*R*)-1-(4-Methoxyphenyl)-6-phenylhexahydrofuro-[3,4-*c*]furan (2f). Solid, m.p. 80–82 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.15 (m, 5H), 6.89–6.81 (m, 3H), 6.68–6.59 (m, 1H), 4.90–4.87 (m, 1H), 4.85 (d, *J* = 4.7 Hz, 1H), 4.39–4.27 (m, 1H), 4.22–4.17 (m, 1H), 4.02 (d, *J* = 9.1 Hz, 1H), 3.79 (s, 3H), 3.78–3.73 (m, 1H), 3.27–3.15 (m, 1H), 3.04–2.95 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 154.4, 132.6, 128.9, 127.7, 124.4, 120.6, 116.7, 113.2, 83.0, 81.5, 88.0, 55.1, 47.8, 38.1 ppm; IR (KBr): ν 2870, 1621, 1490, 1442, 1387, 1245, 1038, 931, 770 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 296; HRMS (EI): *m*/*z* calcd for $C_{19}H_{20}O_3$: 296.1412; found: 296.1409.

(1*S*,3a*S*,6*R*,6a*R*)-1-(4-Methoxyphenyl)-6-phenylhexahydrofuro-[3,4-*c*]furan (3f). Semi solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.23 (m, 5H), 7.13–7.10 (m, 1H), 6.89–6.81 (m, 2H), 4.93–4.87 (m, 2H), 4.40–4.35 (m, 1H), 4.26–4.18 (m, 1H), 4.04–4.00 (m, 1H), 3.87–3.74 (m, 4H), 3.26–3.15 (m, 1H), 3.06–2.99 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 141.4, 131.1, 129.3, 127.9, 127.5, 127.0, 126.8, 126.3, 113.3, 83.0, 82.4, 72.3, 67.7, 57.6, 55.2, 45.0 ppm; IR (KBr): ν 2875, 1731, 1616, 1494, 1245, 1308, 931, 810, 770 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 296; HRMS (EI): *m*/*z* calcd for $C_{19}H_{20}O_3$: 296.1412; found: 296.1408.

(1*R*,3a*R*,6*R*,6a*S*)-1-(4-Nitrophenyl)-6-phenylhexahydrofuro-[3,4-*c*]furan (2g). Solid, m.p. 78–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.3 Hz, 3H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.19–7.08 (m, 3H), 6.70–6.64 (m, 2H), 5.01 (d, *J* = 6.0 Hz, 1H), 4.42 (d, *J* = 8.3 Hz, 1H), 4.16–4.06 (m, 2H), 3.96–3.89 (m, 1H), 3.63 (q, *J* = 6.7 Hz, 1H), 3.38–3.16 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 139.4, 127.6, 127.1, 126.4, 125.8, 122.7, 82.5, 81.4, 74.3, 72.0, 57.8, 47.4 ppm; IR (KBr): ν 2926, 2850, 1720, 1602, 1520, 1345, 1220, 1067, 850, 770 cm^{-1}; MS (EI): *m*/*z* ([M]$^+$): 311; HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}NO_4$: 311.1157; found: 311.1154.

(1*S*,3a*S*,6*R*,6a*R*)-1-(4-Nitrophenyl)-6-phenylhexahydrofuro-[3,4-*c*]furan (3g). Solid, m.p. 82–84 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.6 Hz, 3H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.40–7.24 (m, 7H), 5.04 (d, *J* = 4.7 Hz, 1H), 4.99 (d, *J* = 4.7 Hz, 1H), 4.30–4.20 (m, 2H), 3.91–3.80 (m, 2H), 3.26–3.14 (m, 1H), 3.02–2.93 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.9, 139.7, 131.7, 128.1, 127.2, 125.6, 125.1, 85.0, 84.2, 73.0, 72.5, 62.0, 46.8 ppm; IR (KBr): ν 2926, 2857, 1729, 1602, 1520, 1345,

1607, 850, 771 cm^{-1}; MS (EI): *m*/*z* ($[M]^+$): 311; HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}NO_4$: 311.1157; found: 311.1154.

(1*S*,3a*R*,6*R*,6a*S*)-1-Ethyl-6-phenylhexahydrofuro[3,4-*c*]furan (2h). Semi solid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.41–7.25 (m, 5H), 4.66 (d, *J* = 7.7 Hz, 1H), 4.35 (t, *J* = 8.5 Hz, 1H), 4.14–4.10 (m, 1H), 3.85–3.81 (m, 1H), 3.67 (dd, *J* = 6.5, 2.9 Hz, 1H), 3.62–3.52 (m, 2H), 3.19–3.11 (m, 1H), 2.90–2.85 (m, 1H), 1.84–1.75 (m, 1H), 1.62–1.53 (m, 1H), 0.87 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 128.5, 127.8, 127.1, 83.1, 81.6, 74.3, 71.5, 55.9, 46.8, 23.4, 11.5 ppm; IR (KBr): ν 2922, 2228, 1604, 1218, 1602, 826, 770, 700 cm^{-1}; MS (EI): *m*/*z* ($[M]^+$): 218; HRMS (EI): *m*/*z* calcd for $C_{14}H_{18}O_2$: 218.1306; found: 218.1317.

(1*R*,3a*R*,6*R*,6a*S*)-1-Ethyl-6-phenylhexahydrofuro[3,4-*c*]furan (3h). Semi solid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.24 (m, 6H), 4.66 (d, *J* = 7.7 Hz, 1H), 4.28–4.38 (m, 1H), 4.84–4.81 (m, 1H), 3.69–3.52 (m, 3H), 3.18–3.11 (m, 1H), 2.90–2.74 (m, 1H), 2.34–2.29 (m, 1H), 2.08–1.98 (m, 1H), 1.83–1.76 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.9, 128.3, 128.0, 127.4, 82.6, 81.2, 72.2, 67.0, 55.0, 44.8, 27.0, 8.9 ppm; IR (KBr): ν 2924, 1729, 1480, 1001, 770, 701 cm^{-1}; MS (EI): *m*/*z* ($[M]^+$): 218; HRMS (EI): *m*/*z* calcd for $C_{14}H_{18}O_2$: 218.1306; found: 218.1317.

(1*R*,3a*R*,6*S*,6a*S*)-1-Phenyl-6-styrylhexahydrofuro[3,4-*c*]furan (2i). Semi solid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.21 (m, 10H), 6.63 (d, *J* = 15.7 Hz, 1H), 6.24 (dd, *J* = 6.4, 16.0 Hz, 1H), 4.44–4.40 (m, 2H), 4.20–4.16 (m, 2H), 3.72 (dd, *J* = 4.8, 9.1 Hz, 1H), 3.17–3.11 (m, 1H), 2.73–2.68 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.6, 130.9, 128.1, 127.7, 127.4, 127.2, 126.1, 125.4, 84.8, 84.1, 72.8, 72.3, 59.7, 46.5 ppm; IR (KBr): ν 2973, 1815, 1696, 1613, 1075, 832, 787 cm^{-1}; MS (EI): *m*/*z* ($[M]^+$): 292; HRMS (EI): *m*/*z* calcd for $C_{20}H_{20}O_2$: 292.1463; found: 292.1471.

(1*R*,3a*R*,6*R*,6a*S*)-1-Phenyl-6-styrylhexahydrofuro[3,4-*c*]furan (3i). Semi solid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39–7.23 (m, 10H), 6.64 (d, *J* = 15.4 Hz, 1H), 6.23 (dd, *J* = 6.4, 16.0 Hz, 1H), 4.83 (d, *J* = 4.7 Hz, 1H), 4.55 (t, *J* = 5.1 Hz, 1H), 4.26–4.16 (m, 2H), 3.79–3.74 (m, 2H), 3.21–3.14 (m, 1H), 2.89–2.83 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.9, 130.9, 128.2, 127.8, 127.4, 126.1, 83.7, 72.5, 58.0, 46.1 ppm; IR (KBr): ν 2993, 1834, 1667, 1563, 1016, 875, 735 cm^{-1}; MS (EI): *m*/*z* ($[M]^+$): 292; HRMS (EI): *m*/*z* calcd for $C_{20}H_{20}O_2$: 292.1463; found: 292.1471.

(1*R*,3a*S*,6*R*,6a*R*)-1-(Furan-2-yl)-6-phenylhexahydrofuro[3,4-*c*]-furan (2j). Semi solid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.73–7.70 (m, 2H), 7.55–7.53 (m, 2H), 7.40–7.33 (m, 2H), 6.34–6.28 (m, 2H), 5.02 (d, *J* = 3.2 Hz, 1H), 4.77 (d, *J* = 5.7 Hz, 1H), 4.31–4.16 (m, 3H), 3.85–3.74 (m, 2H), 3.31–3.16 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 137.8, 130.1, 129.5, 128.1, 127.9, 125.2, 107.2, 78.0, 71.9, 68.2, 62.2, 52.3, 39.2 ppm; IR (KBr): ν 2982, 1765, 1604, 1542, 1064, 837, 763 cm^{-1}; MS (EI): *m*/*z* ($[M]^+$): 256; HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}O_3$: 256.1098; found: 256.1096.

(1*S*,3a*S*,6*R*,6a*R*)-1-(Furan-2-yl)-6-phenylhexahydrofuro[3,4-*c*]-furan (3j). Semi solid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.28 (m, 4H), 6.34 (s, 2H), 5.97 (d, *J* = 3.1 Hz, 1H), 4.94 (d, *J* = 5.8 Hz, 1H), 4.66 (d, *J* = 6.6 Hz, 1H), 4.38–4.30 (m, 1H), 4.05–3.88 (m, 2H), 3.74–3.65 (m, 1H), 3.46–3.25 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.3, 142.3, 129.8, 128.4, 126.8, 125.5, 109.9, 107.6, 78.4, 72.7, 68.2, 54.2, 38.9 ppm; IR (KBr): ν 2895, 1761, 1642, 1502, 1134, 898, 754 cm^{-1}; MS (EI): *m*/*z* ($[M]^+$): 256; HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}O_3$: 256.1098; found: 256.1097.

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