This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Acetal initiated Prins bicyclization for the synthesis of hexahydrofuro-[3,4-c]furan lignans and octahydropyrano[3,4-c]pyran derivatives

B. V. Subba Reddy, a M. Ramana Reddy a B. Sridhar b and Kiran Kumar Singarapu c

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

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

Tetrahydrofuran core is frequently found in various biologically active natural products. In particular, furofuran lignans have attracted considerable interest over the years due to their promising biological activity. The sesamin, a furofuran lignan was isolated from Fagara plants and from sesame oil (Figure 1). It is used as a dietary supplement for fat-reduction and is also known to induce apoptosis in human lymphoid leukemia Molt 4B cells. It contains a substituted 3,7-dioxabicyclooctane core, the synthesis of which poses a challenging task. Of various approaches, Prins cyclization is a powerful method for the stereoselective construction of oxygen-containing heterocycles and has been employed successfully for the synthesis of several natural products. In particular, the intramolecular Prins cyclization is an attractive strategy for the stereoselective construction of fused heterocycles and tricycles. However, a few methods are reported to the synthesis of tetrahydrofuran derivatives through a Prins cyclization wherein a five-membered oxocarbenium ion is trapped with an external nucleophile. Furthermore, Prins cascade cyclization has not yet been explored to the stereoselective synthesis of furo[3,4-c]furan scaffolds.

In continuation of our interest on Prins cyclization and its application in total synthesis of natural products, we herein report a versatile method for the synthesis of 1,6-diarylhexahydrofuro[3,4-c]furan and 1,8-diahydropyrano[3,4-c]pyran derivatives through a Prins bicyclization strategy. Initially, we performed the reaction of (E)-2-strylpropane-1,3-diol (1) with 2-bromobenzaldehyde in the presence of 10 mol% p-TSA. To our surprise, no cyclization was observed under the above conditions (Table 1, entry a).

Table 1. Screening of acid catalysts in the formation of 2a/3a

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>2a:3a ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>10 mol % p-TSA</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>b</td>
<td>10 mol % Sc(OTf)</td>
<td>6</td>
<td>40</td>
<td>6:4</td>
</tr>
<tr>
<td>c</td>
<td>10 mol % In(OTf)</td>
<td>6</td>
<td>30</td>
<td>6:4</td>
</tr>
<tr>
<td>d</td>
<td>30 mol % Sc(OTf)</td>
<td>6</td>
<td>55</td>
<td>6:4</td>
</tr>
<tr>
<td>e</td>
<td>10 mol % Sc(OTf)</td>
<td>2</td>
<td>86</td>
<td>6:4</td>
</tr>
</tbody>
</table>

The reaction was performed on 0.5 mmol scale. Isolated yield. The ratio was determined from 1H NMR spectrum of the crude product.

Therefore, the next reaction was performed using 10 mol% Sc(OTf)3. Though the reaction proceeds under the above conditions, the desired product was obtained only in 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 by increasing the amount of Sc(OTf)3 from 10 mol% to 30 mol% (Table 1, entry d). Remarkably, the combination of Sc(OTf)3 and p-TSA gave the product in high yield in short reaction time (Table 1, entry e). From the above results, it was obvious that binary acid.
(Sc(OTf)3/p-TSA) is essential to perform the reaction successfully. These results are consistent with our earlier observation in which a binary acid exhibits remarkable synergistic effects. Therefore, the cooperative effect between Sc(OTf)3 and p-TSA provides high conversions and enhanced rates in a tandem process. Under optimized conditions, the expected product 2a/3a was obtained in 86% yield with 6:4 diastereoselectivity (Table 1, entry e). The ratio of the products (2:3) was confirmed by 1H NMR spectrum of 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 supporting information). Furthermore, the stereochemistry of 2a and 3a was confirmed by X-ray crystallography (Figure 2).

**Figure 2. ORTEP diagram of 2a**

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-nitrobenzaldehydes 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 works not only with aromatic aldehyde but also with aliphatic aldehyde. In case of n-propionaldehyde, the respective ethyl substituted cis-fused hexahydrofuro[3,4-c]furan was obtained slightly in low yield than aromatic counterpart (Table 2, entry h). On the other hand, α,β-unsaturated aldehyde afforded the styryl substituted furo[3,2-c]furan in excellent yield (Table 2, entry i). In addition, the reaction was also successful with heterocyclic aldehyde. For example, furfural gave the corresponding bicyclic ethers 2 and 3 in 76% yield with 7:3 selectivity (Table 2, entry j). It is entirely a new process for the direct conversion of homoallylic diol (1) into cis-fused furo[3,2-c]furan derivatives.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Products</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>2:3 Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CHO</td>
<td>1</td>
<td>4</td>
<td>86</td>
<td>60:40</td>
</tr>
<tr>
<td>b</td>
<td>CHO</td>
<td>1</td>
<td>4</td>
<td>75</td>
<td>60:40</td>
</tr>
<tr>
<td>c</td>
<td>CHO</td>
<td>1</td>
<td>3</td>
<td>90</td>
<td>50:50</td>
</tr>
<tr>
<td>d</td>
<td>CHO</td>
<td>1</td>
<td>3</td>
<td>80</td>
<td>55:45</td>
</tr>
<tr>
<td>e</td>
<td>CHO</td>
<td>1</td>
<td>4</td>
<td>82</td>
<td>62:38</td>
</tr>
<tr>
<td>f</td>
<td>CHO</td>
<td>1</td>
<td>4</td>
<td>78</td>
<td>60:40</td>
</tr>
<tr>
<td>g</td>
<td>CHO</td>
<td>1</td>
<td>3</td>
<td>90</td>
<td>58:42</td>
</tr>
<tr>
<td>h</td>
<td>CHO</td>
<td>1</td>
<td>3</td>
<td>70</td>
<td>60:40</td>
</tr>
<tr>
<td>i</td>
<td>CHO</td>
<td>1</td>
<td>3</td>
<td>85</td>
<td>60:35</td>
</tr>
<tr>
<td>j</td>
<td>CHO</td>
<td>1</td>
<td>3</td>
<td>78</td>
<td>70:30</td>
</tr>
</tbody>
</table>

The reactions were performed on 0.5 mmol scale. Yield refers to pure products after column chromatography. Diastereomeric ratio was determined from 1H NMR spectrum of the crude product.

The reaction proceeds via the formation of an oxocarbenium ion generated from the acetal which is formed in situ from aldehyde and homoallylic diol 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 a flexibility in terms of C-C bond rotation therefore which can result in the formation of 2 and 3. In contrast, a thermodynamically more stable diastereomer 2 forms predominantly. However, the formation of 4 was not observed due to elimination of the proton (Scheme 1).
To support the reaction mechanism, we carried out the cyclization of (E)-2-(4-methoxyphenyl)-5-steryl-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-phenylhexahydrofurano[3,4-c]pyran was obtained in 95% yield with 6:4 diastereoselectivity. It 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 a sole product in 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 (Figure 3).

![Figure 3. ORTEP diagram of 7a](image)

**Table 3. Synthesis of octahydropyrano[3,4-c]pyrans derivatives**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scheme</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td><img src="image" alt="Scheme 1" /></td>
<td>95</td>
</tr>
<tr>
<td>51</td>
<td><img src="image" alt="Scheme 2" /></td>
<td>90</td>
</tr>
<tr>
<td>52</td>
<td><img src="image" alt="Scheme 3" /></td>
<td>80-92</td>
</tr>
<tr>
<td>53</td>
<td><img src="image" alt="Scheme 4" /></td>
<td>85-90</td>
</tr>
<tr>
<td>54</td>
<td><img src="image" alt="Scheme 5" /></td>
<td>85-95</td>
</tr>
<tr>
<td>55</td>
<td><img src="image" alt="Scheme 6" /></td>
<td>80-90</td>
</tr>
<tr>
<td>56</td>
<td><img src="image" alt="Scheme 7" /></td>
<td>80-95</td>
</tr>
<tr>
<td>57</td>
<td><img src="image" alt="Scheme 8" /></td>
<td>80-90</td>
</tr>
<tr>
<td>58</td>
<td><img src="image" alt="Scheme 9" /></td>
<td>80-95</td>
</tr>
<tr>
<td>59</td>
<td><img src="image" alt="Scheme 10" /></td>
<td>80-90</td>
</tr>
<tr>
<td>60</td>
<td><img src="image" alt="Scheme 11" /></td>
<td>80-95</td>
</tr>
</tbody>
</table>

The above results provided a gateway to extend this process to other substrate such as (E)-3-(2-bromostyryl)pentane-1,5-diol (6). The scope of the reaction is 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 the octahydropyrano[3,4-c]pyran in good to high yields (80-92%). Similarly, α,β-unsaturated aldehyde also worked well in this reaction to produce the styryl substituted pyran3,4-c]pyran (8f) in excellent yield. The structure and stereochemistry of 8d were established by detailed 1D and 2D NMR experiments (see supporting information). In all cases, the corresponding trans-fused octahydropyrano[3,4-c]pyrans were obtained in good yields with high selectivity (Table 3). Thus this method provides a direct approach for the conversion of γ,δ-unsaturated diols into trans-fused pyranopyrans.

![Scheme 3. Heck reaction of 7a for the construction of biaryl derivative 9a](image)
To demonstrate the synthetic utility of this method, we applied this protocol to generate allocolchicine analogues. Accordingly, the compound 7a was transformed into polycyclic compound 9a in 76% yield via ary-aryl bond formation using Pd(OAc)$_2$ (10 \text{ mol\%}), triphenylphosphine (10 \text{ mol\%}), and K$_2$CO$_3$ (2 equiv) in DMA at 130 °C (Scheme 3). The 6-7-6-carboyclic framework is a common structural core in allocolchicine (A) and N-acetyl colchino-8-ethyl ether (NCME) (B). The allocolchines are seven-membered biaryl derivatives of naturally occurring colchicines, which are potent tubulin inhibitors.\(^\text{16}\)

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 a direct access to furan lignan analogues which are reported as potent antitumor, antimicrobial, and antiviral agents. This method generates two heterocyclic rings with four new stereocenters in a one-pot operation.

Experimental

General Remarks
IR spectra were recorded on FT-IR spectrometer (KBr) and in reciprocating centimeters (cm$^{-1}$). $^1$HNMR spectra were recorded at 500 MHz, 300 MHz and $^{13}$C NMR at 125 MHz, 75 MHz. For $^1$H NMR, tetramethylsilane (TMS) was used as internal standard (δ = 0) and the 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, CDC$_1$ (δ = 77.27) was used as 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 salisaldehyde, acetophenone, and TMSOTf was used without further purification. DCE were distilled from CaH$_2$ under 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 Table 2 and 3. The resulting mixture was stirred at the temperature specified in Table 2 and 3 under nitrogen atmosphere. After completion, as indicated by TLC, the reaction mixture was quenched with saturated NaHCO$_3$ solution (1.0 mL) and extracted with dichloromethane (2x 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography using ethyl acetate/hexane as eluent to afford the pure product.

($3aS,3a'S,5,11bR,14aS$)-1,2,3a,3a'd,11b,13,14,14a-octahydro-3,12-dioxadibenzo[4,5,6,7]cyclohepta[1,2,3-de]naphtalene (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$_2$CO$_3$ (276 mg, 2 equiv) at room temperature under 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 75% yield as a solid.

(1R,4aS,8aS,8a'S)-1-(2-Bromophenyl)-8-phenyloctahydropyran[3,4-c]-pyran (7a):
White solid, m.p.110-112 °C; $^1$H 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 ppm; 40.6, 33.5, 33.4 ppm; IR (KBr): v 2923, 2890, 2851, 2221, 1145, 1109, 983, 833, 764 cm$^{-1}$; MS (EI): v/m/z ([M]$: 372; HRMS (EI): v/m/z calcd for C$_{23}$H$_{18}$BrO: 372.0725; found: 372.0732.

(4R,8aS,8a'S)-1-(Furan-2-yl)-8-phenyloctahydropyran[3,4-c]-pyran (7c):
White solid, m.p.186-188 °C; $^1$H 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): v 2925, 2890, 2851, 2221, 1453, 1092, 983, 833, 764 cm$^{-1}$; MS (EI): v/m/z ([M]$: 319; HRMS (EI): v/m/z calcd for C$_{19}$H$_{14}$NO: 319.1572; found: 319.1577.

(1R,4aS,8aS,8a'S)-1,8-Diphenyloctahydropyran[3,4-c]-pyran (7d):
White solid, m.p.104-106 °C; $^1$H NMR (300 MHz, CDCl$_3$): δ 6.80-6.69 (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): v 2933, 2717, 1731, 1455, 1149, 1081, 818, 766 cm$^{-1}$; MS (EI): v/m/z ([M]$: 284; HRMS (EI): v/m/z calcd for C$_{24}$H$_{18}$O: 284.1412; found: 284.1425.

(1R,4aS,8aS,8a'S)-1-(4-Chlorophenyl)-8-phenyloctahydropyran[3,4-c]-pyran (7e):
White solid, m.p.124-126 °C; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.01-6.70 (m, 10H), 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): v 3064, 2924, 2837, 1731, 1492, 1149, 910, 891, 756 cm$^{-1}$; MS (EI): v/m/z calcd for C$_{24}$H$_{16}$ClO: 324.0619; found: 324.0623.
White solid, m.p.218-220 °C; 1H NMR (300 MHz, CDCl₃): 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); 13C NMR (75 MHz, CDCl₃): δ 146.7, 145.6, 138.9, 128.1, 127.4, 127.1, 126.8, 121.9, 82.4, 81.3, 68.5, 65.1, 40.5, 32.5, 32.5 ppm; IR (KBr): ν 3083, 2925, 2846, 1517, 1346, 1084, 972, 755 cm⁻¹; MS (EI): m/z ([M⁺]): 339; HRMS (EI): m/z calecd for C₇₈H₇₀O₂: 339.1470; found: 339.1472.

(1S,4aR,8bR,8aS)-1-Pentyl-8-phenyloctahydropyrano[3,4-c]pyran (7h):

White solid, m.p.218-220 °C; 1H NMR (300 MHz, CDCl₃): 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); 13C NMR (75 MHz, CDCl₃): δ 146.7, 145.6, 138.9, 128.1, 127.4, 127.1, 126.8, 121.9, 82.4, 81.3, 68.5, 65.1, 40.5, 32.5, 32.5 ppm; IR (KBr): ν 3083, 2925, 2846, 1517, 1346, 1084, 972, 755 cm⁻¹; MS (EI): m/z ([M⁺]): 339; HRMS (EI): m/z calecd for C₇₈H₇₀O₂: 339.1470; found: 339.1472.

(1S,4aR,8bR,8aS)-1-Ethyl-8-phenyloctahydropyrano[3,4-c]pyran (7h):

White solid, m.p.218-220 °C; 1H NMR (300 MHz, CDCl₃): 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); 13C NMR (75 MHz, CDCl₃): δ 146.7, 145.6, 138.9, 128.1, 127.4, 127.1, 126.8, 121.9, 82.4, 81.3, 68.5, 65.1, 40.5, 32.5, 32.5 ppm; IR (KBr): ν 3083, 2925, 2846, 1517, 1346, 1084, 972, 755 cm⁻¹; MS (EI): m/z ([M⁺]): 339; HRMS (EI): m/z calecd for C₇₈H₇₀O₂: 339.1470; found: 339.1472.

(1S,4aR,8bR,8aS)-1-(2-Bromophenyl)-8-(thiophen-2-yl)octahydropyrano[3,4-c]pyran (8a):

White solid, m.p.78-80 °C; 1H NMR (300 MHz, CDCl₃): 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); 13C NMR (125 MHz, CDCl₃): δ 143.0, 139.6, 127.3 127.1, 126.6, 125.8, 124.5, 124.2, 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 calecd for C₉₇H₇₄Br₂O₄: 378.0289; found: 378.0297.

(1S,4aR,8bR,8aS)-1-(2-Bromophenyl)-8-(furany-2-yl)octahydropyrano[3,4-c]pyran (8b):

White solid, m.p.85-87 °C; 1H NMR (300 MHz, CDCl₃): 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); 13C NMR (75 MHz, CDCl₃): 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 calecd for C₉₈H₇₂Br₂O₄: 362.0518; found: 362.0513.
Solid, m.p.102-104 °C; 1H NMR (300 MHz, CDCl3): 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; 13C NMR (125 MHz, CDCl3): 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): υ 3055, 2954, 2862, 1494, 1253, 1048, 7235 cm⁻¹; MS (EI): m/z [M⁺]: 291; HRMS (EI): m/z calc'd for C_{10}H_{12}NO: 291.0259; found: 291.0254.

1-(3a,6S,6aR)-1-(2-Bromomethyl)-6-phenyhexahydrofuro[3,4-c]furan-1-ylbenzo[d][1,3]dioxole (2a): Liquid, 1H NMR (500 MHz, CDCl3): 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; 13C NMR (125 MHz, CDCl3): 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): υ 2975, 1731, 1616, 1494, 1442, 1387, 1245, 1058, 931, 810, 770 cm⁻¹; MS (EI): m/z [M⁺]: 310; HRMS (EI): m/z calc'd for C_{10}H_{12}O: 310.0250; found: 310.0213.

5-(1R,3aR,6R,6aS)-6-Phenyhexahydrofuro[3,4-c]furan-1-ylbenzo[d][1,3]dioxole (2b): Solid, 1H NMR (500 MHz, CDCl3): 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; 13C NMR (125 MHz, CDCl3): δ 147.3, 146.5, 140.5, 134.1, 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): υ 2970, 1616, 1494, 1387, 1246, 930, 810, 770 cm⁻¹; MS (EI): m/z [M⁺]: 310; HRMS (EI): m/z calc'd for C_{10}H_{12}O: 310.0250; found: 310.1213.

4-(1R,3aS,6R,6aS)-7-Phenyhexahydrofuro[3,4-c]furan-1-ylbenzonitrile (3e): Solid, m.p.86-88 °C; 1H NMR (500 MHz, CDCl3): 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; 13C NMR (125 MHz, CDCl3): δ 142.6, 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): υ 3055, 2861, 2228, 1735, 1604, 1218, 1002, 932, 826 cm⁻¹; MS (EI): m/z [M⁺]: 291; HRMS (EI): m/z calc'd for C_{10}H_{12}NO: 291.0259; found: 291.0254.
(1R,3aS,6R,6aR)-1-(4-Methoxyphenyl)-6-phenylhexahydrofurano[3,4-c]furan (2f)

Solid, m.p.80-82 °C; 1H NMR (500 MHz, CDCl3): 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, 1H), 3.78-3.73 (m, 1H), 3.27-3.15 (m, 1H), 3.04-2.95 (m, 1H) ppm; 13C NMR (75 MHz, CDCl3): 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): v 2780, 1621, 1490, 1442, 1387, 1245, 1038, 931, 770 cm⁻¹; MS (EI): m/z ([M⁺]): 296; HRMS (EI): m/z calculated for C19H12O2: 296.0954; found: 296.0957.

(1S,3aS,6R,6aR)-1-(4-Nitrophenyl)-6-phenylhexahydrofurano[3,4-c]furan (3f)

Solid, m.p.78-80 °C; 1H NMR (500 MHz, CDCl3): δ 7.54-7.28 (m, 7H), 7.13-7.10 (m, 1H), 6.89-6.81 (m, 2H), 4.93-4.87 (m, 2H), 4.40-4.35 (m, 2H), 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; 13C NMR (75 MHz, CDCl3): δ 159.2, 141.4, 131.1, 129.3, 127.9, 127.5, 127.0, 126.8, 126.3, 113.3, 83.0, 84.2, 72.3, 67.7, 57.6, 55.2, 45.0 ppm; IR (KBr): v 2926, 1735, 1719, 1494, 1245, 1308, 931, 810, 770 cm⁻¹; MS (EI): m/z ([M⁺]): 296; HRMS (EI): m/z calculated for C19H12NO2: 296.0918; found: 296.0917.

(1R,3aR,6R,6aS)-1-Ethyl-6-phenylhexahydrofurano[3,4-c]furan (3b)

Semi solid; 1H NMR (500 MHz, CDCl3): 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; 13C NMR (75 MHz, CDCl3): δ 141.9, 128.3, 128.0, 127.4, 82.6, 81.2, 72.2, 67.0, 54.8, 44.8, 27.8, 9.89 ppm; IR (KBr): v 2924, 2792, 1740, 1001, 770, 701 cm⁻¹; MS (EI): m/z ([M⁺]): 218; HRMS (EI): m/z calculated for C18H14O2: 218.1306; found: 218.1317.

Acknowledgments

M.R.R thankful to CSIR for the award of a fellowship. B.V.S. thanks CSIR, New Delhi for financial support as part of XII five year plan program under title ORIGIN (CSC-0108).
Notes and References

‘Natural Product Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, India. Fax: 91-40-27160512; Tel: 91-40-27193333; E-mail: baisreddy@ict.res.in

†Laboratory of X-ray Crystallography, CSIR-Indian Institute of Chemical Technology, Hyderabad, India.

*Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data, NOE experiments, X-ray crystal co-ordinate and CIF file format of 2a and 7a. See DOI: 10.1039/b000000x/


