Synthesis of highly functionalised dihydribenzofurans and indolines by Palladium-catalysed Mizoroki-Heck-heteroannulation cascade reactions of alkoxy-1,3-dienes

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Synthesis of Highly Functionalised Dihydrobenzofurans and Indolines
by Palladium Catalysed Mizoroki-Heck - Heteroannulation Cascade Reaction of Alkoxy-1,3-dienes

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Abstract

A Mizoroki – Heck – Heteroannulation cascade reaction has been used for the preparation of substituted dihydrobenzofurans and indolines in good yields. This has been done via a reaction between functionalised alkoxy-1,3-dienes and several o-iodophenols and protected o-iodoanilines depending on the starting material structure, the substitution on the aromatic ring and the amino protecting group.

Keywords: Mizoroki-Heck couplings, heteroannulation, cascade reactions, dihydrobenzofurans, indolines, alcoxydienes.

Introduction

The palladium catalysed annulation process is one of the most useful methods for the synthesis of highly functionalised heterocycles. In recent years this reaction has been exploited as a route to a wide variety of heterocycles and carbocycles using 1,2-, 1,3-, 1,4-dienes, as well as internal alkynes, which were reacted with aryl or vinyl halides and triflates.[1-3] We have previously described the synthetic use of the Heck coupling on 1-alkoxy-functionalised 1,3-dienes,[4, 5] and more recently we have turned our attention to protected 3-alkyl-1,2-dienols as synthetic precursors of α-arylated α,β-unsaturated aldehydes[6] and
substituted 3-alkenylindoles, 2-alkoxy 3-alkylidene-2,3-dihydrobenzofuranes and indolines.\[7\] The general reactivity of conjugated dienes and the direct formation of their palladium π-allyl complexes had already been described by Heck.\[8\] Grigg’s research group studied the palladium catalysed tandem cyclisation anion capture processes and the cases of carbon-, nitrogen- and oxygen- centered nucleophiles were described.\[9\] Larock and coworkers greatly contributed to the description of the chemistry of the Heck coupling of 1,2- and 1,3-dienes.\[3, 10-12\] They initially described the carbo- and heteroannulation of dienes and later the enantioselective version was also investigated.\[13\] More recently these authors reported the palladium-catalysed annulation of 1,3-dienes by \( o \)-iodoaryl acetates as an efficient approach to biologically interesting dihydrobenzofurans.\[14\] The reactivity of 1-alkoxy-\( \pi \)-allylpalladium complexes, obtained from the corresponding alkoxyallenes, has been explored and the dramatic effect of the alkoxy group on the regioselectivity of Pd(0) catalysed coupling reactions has been demonstrated. Actually, the most reactive position is adjacent to the alkoxy group.\[15\] The palladium catalysed methodologies which afford five- and six-membered fused heterocycles have been recently reviewed,\[16\] and of the described strategies, the multi-step syntheses of natural products, and the development and the use of multiple palladium catalysed transformations, performed in a domino fashion, occupy a special position.\[17-22\]

The 2,3-dihydrobenzofuran skeleton, is present in a vast array of natural products and numerous synthetic compounds with useful biological activity.\[23\] Dihydrobenzofuran containing natural products have been reported with activity against cancer,\[24-26\] tuberculosis,\[27\] malaria\[28\] and cataracts,\[29\] others show antioxidant and/or cytoprotective properties\[30\] and insecticidal activity.\[31\]

The importance of the indolinic moiety is also well established, especially in the alkaloid systems.\[32, 33\] For instance, correlated structures such as Toussaaintines have shown antimicrobial properties.\[34\] The Pauson-Khand reaction has been exploited for the synthesis of tri-\[35\] and tetracyclic\[36\] indolines correlated to the alkaloid asperparaline.

**Results and Discussion**

In this paper we wish to report the results obtained when studying the Pd(0) catalysed heteroannulation of functionalised 1-alkoxybuta-1,3-dienes with \( o \)-iodophenols and \( N \)-protected \( o \)-iodoanilines in order to obtain highly functionalised dihydro-2,3-benzofurans and indolines in a domino fashion. The possibility of
introducing several electrophiles to the dienic skeleton broaden the synthetic applications of the methodology. Moreover, the alkoxydic function is readily hydrolysed to the corresponding carbonylic group. Two alkoxybutadienes were prepared via the reaction between the \((E)\)-crotonaldehyde diethylacetal and 2 equiv of Schlosser’s superbase LIC-KOR (LIC, butyllithium, KOR, potassium tert-butoxide) respectively quenched with 1-iodobutane and propylene oxide (Scheme 1).

\[
\text{Scheme 1 Synthesis of } \text{(E)-4-ethoxyocta-1,3-diene (1a) and (E)-4-ethoxyocta-1,3-dien-ol (1b)}
\]

The reaction of \((E)\)-4-ethoxyocta-1,3-diene (1a) with 2-iodophenol was selected in order to optimise the process. This was done by evaluating the effect of the catalyst, solvent and base, as well as the influence of added phosphines and ionic liquids on the coupling yield and the diastereoselectivity. The results are reported in Table 1.

\[
\text{Table 1 Coupling reaction between } \text{(E)-4-ethoxyocta-1,3-diene (1a) and 2-iodophenol}^\text{a}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>1a : iodophenol</th>
<th>Base</th>
<th>Catalyst (%)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 : 1</td>
<td>an. NaOAc</td>
<td>Pd(OAc)(_2) (3)</td>
<td>DMSO/TBAB</td>
<td>2</td>
<td>23</td>
<td>99/1</td>
</tr>
<tr>
<td>2</td>
<td>2 : 1</td>
<td>an. NaOAc</td>
<td>Pd(OAc)(_2) (3)</td>
<td>DMSO/TBAB</td>
<td>2</td>
<td>28</td>
<td>99/1</td>
</tr>
<tr>
<td>3</td>
<td>1.2 : 1</td>
<td>an. NaOAc</td>
<td>Pd(OAc)(_2) (3)</td>
<td>DMSO/TBAB</td>
<td>2</td>
<td>54</td>
<td>99/1</td>
</tr>
<tr>
<td>4</td>
<td>1.2 : 1</td>
<td>an. NaOAc</td>
<td>Pd(OAc)(_2) (3)</td>
<td>(\text{DMSO})</td>
<td>4</td>
<td>18</td>
<td>99/1</td>
</tr>
<tr>
<td>5</td>
<td>1.2 : 1</td>
<td>an. NaOAc</td>
<td>Pd(OAc)(_2) (3)</td>
<td>DMSO/bmim\textsuperscript{+}Cl</td>
<td>16</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>1.2 : 1</td>
<td>an. NaOAc</td>
<td>Pd(OAc)(_2) (1)</td>
<td>DMSO/TBAB</td>
<td>16</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>1.2 : 1</td>
<td>an. NaOAc</td>
<td>Pd(OAc)(_2) (2)</td>
<td>DMSO/TBAB</td>
<td>16</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>1.2 : 1</td>
<td>an. NaOAc</td>
<td>Pd(PPh(_3))(_2) (3)</td>
<td>DMSO/TBAB</td>
<td>16</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>1.2 : 1</td>
<td>an. NaOAc</td>
<td>Pd(dba)(_2) (3)</td>
<td>DMSO/TBAB</td>
<td>16</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>1.2 : 1</td>
<td>(\text{Et}_3\text{N})</td>
<td>Pd(OAc)(_2) (3)</td>
<td>DMSO/TBAB</td>
<td>16</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>
Firstly, the reagents ratio was studied (entry 1–3), best results were obtained when a slight excess of alkoxydiene 1a was used. The presence of TBAB was crucial to increase the yields, in fact when it was absent (entry 4), or substituted with a different ionic liquid such as bmim+Cl (entry 5), little or no product was obtained. The substitution of Pd(OAc)$_2$ with Pd(PPh$_3$)$_4$ (entry 8) or Pd(dba)$_2$ (entry 9) afforded no products, while, a minimum amount of 3% allowed the coupling to be successful (see entry 6 and 7). Finally, only the use of NaOAc as the base afforded the desired product 2a, in acceptable yields. In all the cases a good regio- and diastereselectivity was afforded with the predominance of the E isomer. The diastereomeric ratio was determined by the $^1$H NMR spectrum, where the α position proton signals (with respect to the oxygen) were observed at 5.43 and 5.70 ppm respectively. The E configuration of the double bond was assigned via a NOESY experiment, where a correlation spot between the vinylic signal (H$_c$ in scheme 3, 4.65 ppm) and the CH$_2$ of the ethoxy group (H$_b$ in scheme 3, 3.72 ppm) was observed. The hypothesised reactivity pattern is illustrated in Scheme 2. The addition of an arylpalladium compound to alkoxy-1,3-diene 1 produced the π-allylpalladium intermediate A, and the subsequent intramolecular nucleophilic substitution afforded product 2. The regioselective outcome can be easily explained if we consider that the nucleophile attacks the diene γ-C, which is sterically hindered compared to the α-C, then in this case steric factors overcome electronic factors which would favour the nucleophilic attack on the α-carbon over the γ-carbon, because the first is more electrophilic due to the presence of the alkoxide function.

Scheme 2 Proposed mechanism for the Pd(0) catalysed heteroannulation of functionalised 1-alkoxy-1,3-butadienes with α-iodophenols and α-iodoprotected anilines
The optimised cross coupling reaction was then extended to different alkoxy-1,3-dienes, o-iodophenols and N-protected o-iodoanilines in order to evaluate the influence of the substituents present both on the aromatic ring and on the alkoxydiene, the nature of the heteroatom on the yields and the amino protecting group in the starting o-iodoanilines. The reaction was then successfully carried out on \((E)-4\)-ethoxyocta-1,3-diene (1a) and \((E)-4\)-ethoxyocta-1,3-dien-ol (1b) with o-iodophenol, 4-hydroxy-3-iodomethylbenzoate, 4-hydroxymethyl-o-iodophenol, N-methyl-o-iodoaniline and N-tosyl-o-iodoaniline. The annulation process led to the corresponding 2-(2ethoxyvinyl)-dihydrobenzofuran and indoline 2a-g (Scheme 3). The formation of the bicyclic structures was proven by the presence of the doublets, attributable to the olefinic proton \(H_c\), and the doublet of doublets pertinent to the \(H_b\) proton (see Scheme 3) in their \(^1\)H NMR spectra. Moreover, the signals relevant to \(H_a\) and \(H_a'\) showed the typical pattern of diastereotopic protons, which demonstrate the formation of a cycle which contained an asymmetric C. When o-iodophenols were employed, good yields were observed in all the cases, both when electronwithdrawing (2b) and electron donor substituent (2c) on the aromatic ring were present. In the latter case a slightly better yield was observed. Highest yields were obtained when \(N\)-tosyl-o-iodoaniline (2f and 2g) was employed, both with diene 1a and 1b, probably because of the bulky protecting group present on the amino group which helps the annulation process.
Scheme 3 Cross coupling between (E)-4-ethoxyocta-1,3-diene (1a) and (E)-4-ethoxyocta-1,3-dien-ol (1b) and substituted o-iodophenol, N-methyl-o-iodoaniline and N-tosyl-o-iodoaniline

The diastereomeric ratio of products 2a-g was deduced both by NMR analysis, comparing the areas of the signals pertinent to Hc and Hb and by gas chromatography. In cases 2a-d and 2f only (E) isomer was obtained whereas the data clearly indicate a lower diastereoselectivity when N-methyl-o-iodoaniline was used as a reagent (2e). This decrease could be explained by a possible post-reaction isomerisation process which would lead to the thermodynamic mixture. It would be promoted by a readdition of PdHL to the double bond.[40] The probability of this isomerisation, which would need a rotation of the substituents, is higher in the case of poor sterically demanding methyl group than in the tosyl group. Moreover it should be noticed that the ¹H NMR spectrum of derivative 2e shows a Hb typical chemical shift of 4.0 and 4.5 ppm for the two isomers respectively. In all other cases this signal is observed between approximately 5.5 ppm for the dihydrobenzofuran derivatives and 5.0 ppm for N-tosylindolines. This upfield shift could depend on a higher electron density on Hb proton in 2-(2-ethoxyhexa-1-enyl)-1-methylindoline (2e) which could facilitate the PdH elimination – addition process.

A 50/50 diastereomeric mixture (2g) was also obtained when N-tosyl-o-iodoaniline was coupled with (E)-4-ethoxyocta-1,3-dien-ol (1b). In this case it was not obvious if the lack of stereoselectivity was due to the formation of a (E) or (Z) isomer mixture pertinent to the C1 double bond or to the presence of three stereocenters in the annulation product which would lead to different diastereoisomers. The first hypothesis might be confirmed by the fact that the mild acidic hydrolysis of 2-(2-ethoxyhexa-4-hydroxypent-1-yl)-1-tosylindoline (2g), as shown in Scheme 5, afforded only one product (3g). Since in the case of 2-((1E)-2-ethoxyhexa-1-enyl)-1-tosylindoline (2f), which differs from 2g by the presence of a linear butyl instead of a 2-hydroxypropyl group, only a diastereoisomer was recovered, it might be hypothesised a steric influence of this latter group together with the hindered tosyl group.
Diene 1b was reacted with both o-iodophenol and N-tosyl-o-iodoaniline and two different reactivity pattern were observed. In fact in the first case, the annulation process was followed by an E\textsubscript{2} elimination reaction affording the 2-((1\textit{E},3\textit{E})-2-ethoxypenta-1,3-dienyl)-2,3-dihydrobenzofuran 2d. The process was probably favored by the formation of the more stable conjugated system and the basic medium (Scheme 4) and afforded only the 1\textit{E},3\textit{E} isomer.

When N-tosyl-o-iodoaniline was used, the elimination process did not occur probably because of the steric hindrance of the tosyl group in the anti-periplanar conformation which did not favour the proton extraction, as evidenced in Figure 1. 2-((1\textit{E})-2-Ethoxyexa-4-hydroxypent-1-yl)-1-tosylinidine 2g was obtained, as as matter of fact both the \textsuperscript{1}H and the \textsuperscript{13}C spectra showed the typical signals of a CH bonded to an hydroxyl group at 4.1 and 66 ppm respectively.

Moreover, derivatives 2a-g can be converted into ketones by mild acidic treatment because of the presence of the vinyl ether function in accord to an \textit{umpolung} approach. They were then treated overnight with catalytic amounts of Amberlyst-15, in CH\textsubscript{2}Cl\textsubscript{2} at r.t. affording the corresponding carbonyl derivatives 3a-g in quantitative yield (Scheme 5). NMR data indicated the formation of a dyhydrobenzofuran or indoline structure bearing an oxomethylenic group in position 2. In fact, in the \textsuperscript{1}H NMR spectrum the signals corresponding to the olefinic proton disappeared, the \textsuperscript{13}C spectra showed a typical
carbonyl signal centered at approximately 210 ppm, according to the product structure. Finally all the product spectra (3a-g) showed four doublets of doublet typical of Ha, Ha’, Hc, Hc’ diastereomeric protons (see Scheme 5).

Scheme 5 Hydrolysis of derivatives 2a-g in mild acidic conditions

Conclusions

In summary, a Pd(0)-catalysed heteroannulation cascade process on differently functionalised alkoxy-1,3-diienes and substituted o-iodophenols and protected o-idoanilines has been reported. Several substituted dihydrobenzofurans and indolines were obtained in function of the starting alkoxy-1,3-diene, o-iodophenol and o-idoaniline, the substitution of the iodophenol aromatic ring and the protection of the amino group. The reaction was regio- and mainly stereoselective according to the heteroatom involved in the annulation process and its steric hindrance. Steric factors were predominant over electronic factors in determining the process regioselectivity. Finally, the presence of the enolether group extended the synthetic applications of
the cross-coupling because ketones can be obtained via simple hydrolysis in mild acidic conditions in quantitative yields.

**General**

Flasks and all equipments used for the generation and reaction of moisture-sensitive compounds were dried by electric heat gun under Ar. THF was distilled from sodium benzophenone ketyl, respectively. BuLi (1.6 M in hexanes) was obtained from Aldrich. All commercially obtained reagents and solvents were used as received. Products were purified by preparative column chromatography on Macherey Nagel silica-gel for flash chromatography, 0.04-0.063 mm/ 230-400 mesh. Alcoxy-1,3-dienes and N-protected o-iodoanilines were synthesised as previously reported.

Reactions were monitored by TLC using silica-gel on TLC-PET foils Fluka, 2-25 μm, layer thickness 0.2 mm, medium pore diameter 60 Å. 1H NMR spectra were recorded at 200 MHz, 13C NMR spectra at 50.2 MHz, in CDCl3. Data were reported as follows: chemical shifts in ppm from Me₄Si as an internal standard, integration, multiplicity, coupling constants (Hz), and assignment. 13C NMR spectra were measured with complete proton decoupling. Chemical shifts were reported in ppm from the residual pick solvent as an internal standard. GC-MS spectra were obtained on a mass selective detector HP 5970 B instrument operating at an ionizing voltage of 70 eV connected to a HP 5890 GC with a cross linked methyl silicone capillary column (25 m × 0.2 mm × 0.33 μm film tickness). IR spectra were recorded on a Perkin Elmer BX FT-IR. Enantiomeric purity of derivatives 1b and 2g was determined using a PerKin Elmer Autosystem GC equipped with a chiral column Cyclosil 6® (JW Scientific, 30 m × 0.25 mm × 0.25 μm film tickness).

**Procedure for the Palladium catalysed coupling of alcoxydienes and o-iodophenols or protected o-iodoanilines.** Pd(OAc)₂ (3% mol, 0.015 mmol, 3.36 mg) and TBAB (300 mg) were dissolved in anhydrous DMSO (3 mL) and the solution was degassed with Ar for 10 min. at r.t.. Then NaOAc (0.5 mmol, 41 mg), the suitable o-iodophenol or protected o-idoaniline (0.5 mmol), and the alcoxy-1,3-diene (0.55 mmol) were subsequently added. The reaction was stirred in a sealed
tube at 110 °C until the disappearance of the alcoxy-1,3-diene was observed by TLC and GC on a sample taken and partitioned between Et₂O and H₂O. Then H₂O was added and the mixture was extracted with Et₂O (2 × 20 mL), then washed with brine (2 × 20 mL), dried (K₂CO₃), filtered and evaporated under reduced pressure.

**2-((1E)-2-Ethoxyhexa-1-yl)-2,3-dihydrobenzofuran (2a)** As previously reported 110 mg (0.5 mmol) of o-iodophenol and 84.7 mg (0.55 mmol) of 4-ethoxyocta-1,3-diene 1a were suspended in the DMSO-TBAB mixture. After chromatographic purification (EP/EE 95/5) a pale yellow oil was obtained (65 mg, 54%). Found C, 77.98; H, 9.02%. Calc. for C₁₆H₂₂O₂: C, 78.01; H, 9.00%.

\[ \delta_H \text{ (200 MHz; CDCl}_3, \text{Me}_4\text{Si)} = 0.95 \text{ (3H, t, } J = 7.0 \text{ Hz, } \text{CH}_3\text{CH}_2CH_2) \]

\[ \delta_C \text{ (50.2 MHz; CDCl}_3, \text{Me}_4\text{Si)} = 13.8 \text{ (CH}_3, \text{14.4 (CH)}_3, \text{22.3 (CH}_2, \text{30.2 (CH}_2, \text{30.6 (CH}_2, \text{37.5 (CH}_3, \text{62.2 (CH}_2, \text{80.9 (CH), 97.4 (CH), 109.2 (CH), 119.9 (CH), 124.5 (CH), 127.2 (Cq), 127.8 (CH), 159.2 (Cq), 161.7 (Cq). MS (EI, 70 eV): } m/z \text{ (}% = 246 (M}^+ , 100), 217 (35), 133 (38), 131 (32), 85 (34). \]

**Methyl-2-((1E)-2-ethoxyhexa-1-yl)-2,3-dihydrobenzofuran-5-carboxylate (2b)** As previously reported 153 mg (0.5 mmol) of 4-hydroxy-3-iodomethylbenzoate and 79.2 mg (0.55 mmol) of 4-ethoxyocta-1,3-diene 1a were suspended in the DMSO-TBAB mixture. After chromatographic purification (EP/EE 95/5) a pale yellow oil was obtained (65 mg, 54%). Found C, 71.00; H, 7.93%. Calc. for C₁₈H₂₄O₄: C, 71.03; H, 7.95%.

\[ \delta_H \text{ (200 MHz; CDCl}_3, \text{Me}_3\text{Si)} = 0.96 \text{ (3H, t, } J = 7.0 \text{ Hz, } \text{CH}_3\text{CH}_2CH_2) \]

\[ \delta_C \text{ (50.2 MHz; CDCl}_3, \text{Me}_3\text{Si)} = 13.7 \text{ (CH}_3, \text{14.2 (CH}_3, \text{22.2 (CH}_2, \text{30.1 (CH}_2, \text{30.6 (CH}_2, \text{36.7 (CH}_2, \text{119.9 (CH), 124.5 (CH), 127.2 (Cq), 127.8 (CH), 159.2 (Cq), 161.7 (Cq). MS (EI, 70 eV): } m/z \text{ (}% = 246 (M}^+ , 100), 217 (35), 133 (38), 131 (32), 85 (34). \]
51.6 (CH₃), 62.3 (CH₂), 82.3 (CH), 96.8 (CH), 108.8 (CH), 122.0 (Cq), 126.3 (CH), 127.6 (Cq), 130.9 (CH), 162.3 (Cq), 163.4 (Cq), 166.9 (Cq). MS (EI, 70 eV): m/z (%) = 304 (M⁺, 100), 275 (23), 243 (22), 159 (16), 85 (14).

**2-((1E)-2-ethoxyhexa-1-enyl)-6-hydroxymethyl-2,3-dihydrobenzofuran (2c)** As previously reported 153 mg (0.5 mmol) of 4-hydroxymethyl-o-iodophenol and 79.2 mg (0.55 mmol) of 4-ethoxyocta-1,3-diene 1a were suspended in the DMSO-TBAB mixture. After chromatographic purification (EP/EE 80/20) a pale yellow oil was obtained (83 mg, 60%). Found C, 73.90; H, 8.73%. Calc. for C₁₇H₂₄O₃: C, 73.88; H, 8.75%.

δH (200 MHz; CDCl₃, Me₄Si) 0.96 (3H, t, J = 7.0 Hz, CH₃CH₂CH₂), 1.10-1.60 (7H, m, CH₃CH₂O, CH₃CH₂CH₂), 1.76 (1H, bs, OH), 2.26 (2H, m, CH₂C=CH), 2.93 (1H, dd, J = 15.4, 9.0 Hz, CH₂ ring), 3.40 (1H, dd, J = 15.4, 9.0 Hz, CH₂ ring), 3.71 (2H, q, J = 7.0 Hz, CH₂CH₂O), 4.63 (3H, m, CH₂OH, CH=CH), 5.48 (1H, q, J = 8.6 Hz, CHCH=CH), 6.82 (2H, m, Ar), 7.13 (1H, m, Ar).

δC (50.2 MHz; CDCl₃, Me₄Si) 13.7 (CH₃), 14.2 (CH₃), 22.2 (CH₂), 30.1 (CH₂), 30.6 (CH₂), 37.2 (CH₂), 62.2 (CH₂), 65.2 (CH₂), 81.2 (CH), 97.2 (CH), 107.9 (CH), 118.6 (CH), 124.4 (CH), 126.8 (Cq), 141.1 (Cq), 159.6 (Cq), 161.7 (Cq). MS (EI, 70 eV): m/z (%) = 276 (M⁺, 12), 148 (100), 131 (32), 119 (49), 86 (47).

**2-((1E,3E)-2-ethoxypenta-1,3-dienyl)-2,3-dihydrobenzofuran (2d)** As previously reported 110 mg o-iodophenol (0.5 mmol) and 85.2 mg (0.55 mmol) of 4-ethoxyepta-4,6-dien-2-ol 1b were suspended in the DMSO-TBAB mixture. After chromatographic purification (EP/EE 95/5) a pale yellow oil was obtained (37 mg, 32%). Found C, 78.25; H, 7.87%. Calc. for C₁₅H₁₈O₂: C, 78.23; H, 7.88%. v_max(neat)/ cm⁻¹ 2921, 1604, 1230, 963. δH (200 MHz; CDCl₃, Me₄Si) 1.32 (3H, t, J = 6.9 Hz, CH₂CH₂O), 1.82 (3H, m, CH₂CH=CH), 2.95 (1H, dd, J = 13.8, 8.0 CH₂ ring), 3.40 (1H, dd, J = 13.8, 8.0 Hz, CH₂ ring), 3.82 (2H, q, J = 6.9 Hz, CH₂CH₂O), 4.72 (1H, d, J = 8.0 Hz, CH=CH), 5.65 (1H, q, J = 8.0 Hz, CHCH=CH), 6.30 (2H, m, Ar), 7.15 (2H, m, Ar).

δC (50.2 MHz; CDCl₃, Me₄Si) 14.3 (CH₃), 18.1 (CH₃), 37.4 (CH₂), 62.4 (CH₂), 79.6 (CH), 99.5 (CH), 109.2 (CH), 119.9 (CH), 122.1 (CH), 124.5 (CH), 127.0 (Cq), 127.8 (CH), 129.5 (CH), 155.5 (Cq), 159.0 (Cq). MS (EI, 70 eV): m/z (%) = 230 (M⁺, 100), 215 (24), 201 (24), 187 (49), 131 (29), 69 (53).
2-(2-Ethoxyhexa-1-enyl)-1-methylindoline (2e) As previously reported 116 mg (0.5 mmol) of N-methyl-o-iodoaniline and 84.7 mg (0.55 mmol) of 4-ethoxyocta-1,3-diene 1a were suspended in the DMSO-TBAB mixture. After chromatographic purification (EP/EE 90/10) a pale yellow oil was obtained (58 mg, 45%). Diastereomeric mixture 60:40: \( \delta_H \) (200 MHz; CDCl\textsubscript{3}, Me\textsubscript{4}Si): 0.94 (3H, m, \( CH_3CH_2CH_2 \)), 1.19-1.65 (7H, m, \( CH_3CH_2O, CH_3CH_2CH_2 \)), 2.30 (2H, t, \( J = 7.0 \) Hz, \( CH_3C=CH \)), 2.68 (3H, s, NCH\textsubscript{3}), 3.05 (1H, m, \( CH_2 \) ring), 3.12 (1H, m, \( CH_2 \) ring), 3.77 (2H, q, \( J = 7.0 \) Hz, \( CH_3CH_2O \)), 4.00 (1H, d, \( J = 9.7 \) Hz, NCH, minor isomer), 4.38 (1H, q, \( J = 9.7 \) Hz, NCH, major isomer). Diastereomeric mixture 60:40: \( \delta_H \) (200 MHz; CDCl\textsubscript{3}, Me\textsubscript{4}Si): 0.96 (3H, t, \( J = 7.0 \) Hz, \( CH_3CH_2CH_2 \)), 1.20 (3H, t, \( J = 7.0 \) Hz, \( CH_3CH_2O \)), 1.26-1.66 (4H, m, \( CH_3CH_2CH_2 \)), 2.20 (2H, m, \( CH_3C=CH \)), 2.32-2.68 (1H, m, \( CH_2 \) ring), 2.3 (3H, s, \( CH_3Ar \)), 3.12 (1H, dd, \( J = 16.0, 6.8 \) Hz, \( CH_2 \) ring ), 3.40 (2H, m, \( CH_3CH_2O \)), 4.38 (1H, d, \( J = 9.4 \) Hz, \( C=CH \)), 5.45 (1H, td, \( J = 9.4, 3.0 \) Hz, \( CHCH=C \)), 6.96-7.27 (5H, m, Ar), 7.45-7.75 (3H, m, Ar). \( \delta_C \) (50.2 MHz; CDCl\textsubscript{3}, Me\textsubscript{4}Si) \( \delta \) (ppm): 13.9 (CH\textsubscript{3}), 14.3 (CH\textsubscript{3}), 21.3 (CH\textsubscript{3}), 22.4 (CH\textsubscript{2}), 29.9 (CH\textsubscript{2}), 30.4 (CH\textsubscript{2}), 32.1 (CH\textsubscript{2}), 61.0 (CH\textsubscript{3}), 61.9 (CH\textsubscript{3}), 98.4 (CH), 115.8 (CH), 123.6 (CH), 125.0 (CH), 126.9 (CH), 127.5

2-((1E)-2-Ethoxyhexa-1-enyl)-1-tosylinodline (2f) As previously reported 191 mg (0.5 mmol) of N-tosyl-o-iodoaniline and 84.7 mg (0.55 mmol) of 4-ethoxyocta-1,3-diene 1a were suspended in the DMSO-TBAB mixture. After chromatographic purification (EP/EE 95/5) a pale yellow oil was obtained (143 mg, 72%). Found C, 69.17; H, 7.30, N, 3.50, S, 8.04%. Calc. for \( C_{23}H_{29}NO_3S \): C, 69.14; H, 7.32; N, 3.51; S, 8.03%. \( \nu_{max} \) (neat)/ cm\textsuperscript{-1}: 2959, 1660, 1600, 1479, 1167. \( \delta_H \) (200 MHz; CDCl\textsubscript{3}, Me\textsubscript{4}Si) 0.96 (3H, t, \( J = 7.0 \) Hz, \( CH_3CH_2CH_2 \)), 1.20 (3H, t, \( J = 7.0 \) Hz, \( CH_3CH_2O \)), 1.26-1.66 (4H, m, \( CH_3CH_2CH_2 \)), 2.20 (2H, m, \( CH_3C=CH \)), 2.32-2.68 (1H, m, \( CH_2 \) ring), 2.3 (3H, s, \( CH_3Ar \)), 3.12 (1H, dd, \( J = 16.0, 6.8 \) Hz, \( CH_2 \) ring ), 3.40 (2H, m, \( CH_3CH_2O \)), 4.38 (1H, d, \( J = 9.4 \) Hz, \( C=CH \)), 5.45 (1H, td, \( J = 9.4, 3.0 \) Hz, \( CHCH=C \)), 6.96-7.27 (5H, m, Ar), 7.45-7.75 (3H, m, Ar). \( \delta_C \) (50.2 MHz; CDCl\textsubscript{3}, Me\textsubscript{4}Si) \( \delta \) (ppm): 13.9 (CH\textsubscript{3}), 14.3 (CH\textsubscript{3}), 21.3 (CH\textsubscript{3}), 22.4 (CH\textsubscript{2}), 29.9 (CH\textsubscript{2}), 30.4 (CH\textsubscript{2}), 32.1 (CH\textsubscript{2}), 61.0 (CH\textsubscript{3}), 61.9 (CH\textsubscript{3}), 98.4 (CH), 115.8 (CH), 123.6 (CH), 125.0 (CH), 126.9 (CH), 127.5
2-(-2-Ethoxyexa-4-hydroxypent-1-yl)-1-tosylindoline (2g) As previously reported 191 mg (0.5 mmol) of N-tosyl-o-iodoaniline and 85.2 mg (0.55 mmol) of 4-ethoxyepta-4,6-dien-2-ol 1b were suspended in the DMSO-TBAB mixture. After chromatographic purification (EP/EE 50/50) a pale yellow oil was obtained (143 mg, 72%). Diastereomeric mixture 50:50: δH (200 MHz; CDCl3, Me4Si): 1.25 (7H, m, CH3CHOH, CH3CH2O, OH), 2.36 (3H, s, CH3ArSO2), 2.50–2.61 (3H, m, CH2=CH, CH2 ring), 3.06 (1H, dd, J = 16.0, 9.6 Hz, CH2 ring ), 3.51 (2H, m, CH3CH2O), 4.11 (1H, m, CHOH), 4.58 (1H, d, J = 9.8 Hz, C=CH, isomer a), 4.63 (1H, d, J = 9.6 Hz, C=CH, isomer b), 6.50 (1H, m, CHCH=C), 7.03 (5H, m, Ar), 7.60 (3H, m, Ar). Diastereomeric mixture δC (50 MHz, CDCl3, Me4Si) 14.2 (CH3), 21.2 (CH3), 22.9 (CH3), 23.2 (CH3), 37.0 (CH2), 37.1 (CH2), 39.6 (CH2), 40.0 (CH2), 60.7 (CH), 62.1 (CH2), 66.0 (CH), 100.9 (CH), 101.3 (CH), 115.8 (CH2), 115.9 (CH), 123.8 (CH), 123.9 (CH), 125.0 (CH), 126.8 (CH), 126.9 (CH), 128.5 (CH), 129.3 (CH), 129.4 (CH), 131.0 (Cq), 131.1 (Cq), 135.6 (Cq), 136.1 (Cq), 140.9 (Cq), 141.0 (Cq), 143.5 (Cq), 143.6 (Cq), 155.2 (Cq), 155.4 (Cq). MS (EI, 70 eV): m/z (%) isomer a= 357 (M⁺ - EtOH, 36), 202 (100), 174 (26), 130 (52), 91 (30). MS (EI, 70 eV): m/z (%) minor isomer b= 357 (M⁺ - EtOH, 7), 272 (100), 271 (22), 155 (54), 91 (42).

**General procedure for the acid catalysed hydrolysis of ethoxysubstituted dihydrobenzofurans and indolines.** In a 50 mL round bottom flask, the suitable substrate (0.5 mmoles) was dissolved in 3 mL of CH2Cl2, then 0.1 g of Amberlyst 15 were added. The solution was stirred overnight at r. t. filtered and the solvent evaporated under reduced pressure.

1-(2,3-dihydrobenzofuran-2-yl)-hexan-2-one (3a) As previously reported 123 mg (0.5 mmol) of 2-((1E)-2-ethoxyhexa-1-enyl)-2,3-dihydrobenzofuran 2a were dissolved in CH2Cl2 and stirred overnight in the presence of Amberlyst 15. After filtration and the solvent evaporation a pale yellow oil was obtained in quantitative yield (109 mg). Found C, 77.06; H, 8.30%. Calc. for
C_{14}H_{18}O_2: C, 77.03; H, 8.31%. \( \nu_{\text{max}}(\text{neat})/\text{cm}^{-1} \) 2958, 1714, 1598, 1480, 1230. \( \delta_H \) (200 MHz; CDCl₃, Me₄Si) 0.90 (3H, t, \( J = 7.7 \) Hz, CH₃CH₂CH₂), 1.31 (2H, sest, \( J = 7.7 \), CH₃CH₂CH₂), 1.61 (2H, quint, \( J = 6.4 \), CH₃CH₂CH₂), 2.48 (2H, t, \( J = 7.2 \) Hz, COCH₂), 2.73 (1H, dd, \( J = 16.6 \), 6.4, CH₂ ring), 2.84 (1H, dd, \( J = 15.6 \), 8.0, CH₂CO), 3.05 (1H, dd, \( J = 16.6 \), 6.8, CH₂ ring), 3.44 (1H, dd, \( J = 15.8 \), 9.0, CH′CO), 5.19 (1H, m, CHCH₂CO), 6.85 (2H, m, Ar), 7.15 (2H, m, Ar). \( \delta_C \) (50.2 MHz; CDCl₃, Me₄Si) 13.7 (CH₃), 22.1 (CH₂), 25.5 (CH₂), 35.4 (CH₂), 43.2 (CH₂), 48.4 (CH₂), 78.5 (CH), 109.3 (CH), 120.3 (CH), 124.8 (CH), 126.1 (Cq), 127.8 (CH), 158.9 (Cq), 208.8 (Cq). MS (EI, 70 eV): \( m/z \) (%) = 218 (M⁺, 13), 119 (15), 118 (100), 91 (11), 57 (9).

**Methyl-2-(2-oxyhexyl)-2,3-dihydrobenzofuran-5-carboxylate (3b)** As previously reported 152 mg of methyl-2-((1E)-2-ethoxyhexa-1-enyl)-2,3-benzodihydrofuran-5-carboxylate 2b (0.5 mmol) were dissolved in CH₂Cl₂ and stirred overnight in the presence of Amberlyst 15. After filtration and the solvent evaporation a pale yellow oil was obtained in quantitative yield (138 mg). Found C, 69.57; H, 7.32%. Calc. for C_{16}H_{20}O₄: C, 69.54; H, 7.30%. \( \nu_{\text{max}}(\text{neat})/\text{cm}^{-1} \) 2958, 1715, 1613, 1489, 1270. \( \delta_H \) (200 MHz; CDCl₃, Me₄Si) 0.92 (3H, t, \( J = 7.2 \) Hz, CH₃CH₂CH₂), 1.17-1.49 (2H, m, CH₃CCH₂CH₂), 1.47-1.76 (2H, m, CH₃CH₂CH₂), 2.48 (2H, t, \( J = 7.3 \) Hz, COCH₂), 2.75 (1H, dd, \( J = 16.0 \), 6.0 Hz, CH₂ ring), 2.85 (1H, dd, \( J = 16.0 \), 8.0 Hz, CH₂CO), 3.06 (1H, dd, \( J = 18.0 \), 8.0 Hz, CH₂ ring), 3.46 (1H, dd, \( J = 15.9 \), 10.1 Hz, CH′CO), 3.87 (3H, s, OCH₃), 5.28 (1H, m, CHCH₂CO), 6.76 (1H, d, \( J = 9.0 \) Hz, Ar), 7.85 (2H, bs, Ar). \( \delta_C \) (50.2 MHz; CDCl₃, Me₄Si) \( \delta \) (ppm): 13.6 (CH₃), 22.0 (CH₂), 25.4 (CH₂), 34.8 (CH₂), 43.2 (CH₂), 48.2 (CH₂), 51.7 (CH₃), 79.7 (CH), 109.0 (CH), 122.6 (Cq), 126.6 (CH), 131.0 (CH), 163.0 (Cq), 166.7 (Cq), 208.0 (Cq). MS (EI, 70 eV): \( m/z \) (%) = 276 (M⁺, 13), 177 (100), 176 (67), 145 (53), 105 (14).

**6-Hydroxymethy-2-(2-oxyhexyl)-2,3-dihydrobenzofuran (3c)** As previously reported 138 mg of 2-((1E)-2-ethoxyhexa-1-enyl)-6-hydroxymethyl-2,3-dihydrobenzofuran 2c (0.5 mmol) were dissolved in CH₂Cl₂ and stirred overnight in the presence of Amberlyst 15. After filtration and the solvent evaporation a pale yellow oil was obtained in quantitative yield (100 mg). Found C, 72.53; H, 8.13%. Calc. for C_{15}H_{20}O₃: C, 72.55; H, 8.12%. \( \nu_{\text{max}}(\text{neat})/\text{cm}^{-1} \) 3352, 2961.
1705, 1408, 1260, 1017. δH (200 MHz; CDCl₃, Me₄Si) 0.92 (3H, t, J = 7.2 Hz, CH₃CH₂CH₂), 1.31-1.66 (5H, m, CH₃CH₂CH₂OH), 2.48 (2H, t, J = 7.2 Hz, COCH₂), 2.75 (1H, dd, J = 16.6, 6.6 Hz, CH₂ ring), 2.83 (1H, dd, J = 16.6, 8.8 Hz, CH₂CO), 3.06 (1H, dd, J = 16.9, 6.7 Hz, CH₂ ring), 3.48 (1H, dd, J = 16.6, 9.2 Hz, CH'₂CO), 4.62 (2H, s, CH₂OH), 5.20 (1H, m, CH₂CH₂), 6.82 (2H, m, Ar), 7.13 (1H, d, J = 7.4 Hz, Ar).

δC (50.2 MHz; CDCl₃, Me₄Si) δ (ppm): 15.0 (CH₃), 22.0 (CH₂), 25.4 (CH₂), 35.1 (CH₂), 43.2 (CH₂), 48.4 (CH₂), 65.6 (CH₂), 78.8 (CH), 108.0 (CH), 119.0 (CH), 124.7 (Cq), 125.6 (CH), 141.3 (Cq), 159.3 (Cq), 209.0 (Cq).

MS (EI, 70 eV): m/z (%) = 248 (M⁺, 8), 148 (100), 147 (19), 131 (22), 119 (24).

(E)-1-(2,3-dihydrobenzofuran-2-yl)-penta-3-en-2-one (3d) As previously reported 115 mg of 2-((1E,3E)-2-ethoxypenta-1,3-dienyl)-2,3-dihydrobenzofuran 2d (0.5 mmol) were dissolved in CH₂Cl₂ and stirred overnight in the presence of Amberlyst 15. After filtration and the solvent evaporation a pale yellow oil was obtained in quantitative yield (124 mg). Found C, 77.18; H, 6.99%. Calc. for C₁₁H₁₂O₂: C, 77.20; H, 6.98%. νmax(neat)/cm⁻¹ 2925, 1674, 1481, 1232, 971, 750.

δH (200 MHz; CDCl₃, Me₄Si) 0.92 (3H, dd, J = 6.8, 1.4 Hz, CH₃CH=CH), 2.92-2.80 (2H, bdd, CH₂ ring, CH'₂CO), 3.20 (1H, dd, J = 16.6, 6.4 Hz, CH₂ ring), 3.43 (1H, dd, J = 16.6, 9.2 Hz, CH₂CO), 5.23 (1H, dd, J = 16.6, 9.2 Hz, CH₂CO), 6.18 (1H, dm, J = 15.8, 1.6 Hz, COCH=CH), 6.75-6.99 (3H, m, Ar, COCH=CH), 7.13 (2H, m, Ar).

δC (50.2 MHz; CDCl₃, Me₄Si) δ (ppm): 18.2 (CH₃), 35.5 (CH₂), 45.6 (CH₂), 78.7 (CH), 109.3 (CH), 120.3 (CH), 124.9 (CH), 125.2 (Cq), 127.9 (CH), 132.1 (CH), 143.7 (CH), 159.0 (Cq), 197.0 (Cq).

MS (EI, 70 eV): m/z (%) = 202 (M⁺, 18), 118 (100), 84 (30), 69 (41), 41 (13).

1-(N-Methylindolin-2-yl)-hexan-2-one (3e) As previously reported 130 mg of 2-((1E)-2-ethoxyhexa-1-ethyl)-1-methylindoline 2e (0.5 mmol) were dissolved in CH₂Cl₂ and stirred overnight in the presence of Amberlyst 15. After filtration and the solvent evaporation a pale yellow oil was obtained in quantitative yield (116 mg). Found C, 77.85; H, 9.14, N, 6.03%.

Calc. for C₁₃H₂₁NO: C, 77.88; H, 9.15, N, 6.05%. νmax(neat)/cm⁻¹ 2958, 1713, 1609, 1486, 1376, 1270, 748. δH (200 MHz; CDCl₃, Me₄Si) 0.92 (3H, t, J = 6.8, CH₃CH₂CH₂), 1.26-1.67 (4H, m, CH₃CH₂CH₂CH₂), 2.48 (2H, t, J = 7.0, COCH₂CH₂), 2.63 (2H, m, CH₂ ring, CH₂CO), 2.71 (3H, s, N-CH₃), 2.96 (1H, dd, J = 16.8, 6.6 Hz, CH₂ ring), 3.29 (1H, dd, J = 15.6, 8.4 Hz, CH'₂CO), 3.73 (1H, m, CH₂CH₂CO), 4.12 (2H, t, J = 7.0, OCH₂CH₂), 4.60 (2H, s, CH₂OCH₂), 4.98 (2H, s, CH₂OCH₂), 7.13 (1H, d, J = 7.4 Hz, Ar).
6.47 (1H, d, J = 7.8 Hz, Ar), 6.69 (1H, td, J = 7.2, 0.8 Hz, Ar), 7.05 (2H, m, Ar). δ_C (50.2 MHz; CDCl₃, Me₄Si) δ (ppm): 13.7 (CH₃), 22.1 (CH₂), 25.6 (CH₂), 34.2 (CH₃), 35.6 (CH₂), 43.4 (CH₂), 46.6 (CH₂), 62.6 (CH), 107.1 (CH), 117.9 (CH), 124.0 (CH), 127.2 (CH), 128.5 (Cq), 152.6 (Cq), 209.6 (Cq). MS (EI, 70 eV): m/z (%) = 231 (M⁺, 16), 132 (100), 131 (27), 130 (19), 117 (14).

1-(N-Tosylindolin-2-yl)-hexan-2-one (3f) As previously reported 200 mg of 2-((1E)-2-ethoxyhexa-1-etyl)-1-tosylindoline 2f (0.5 mmol) were dissolved in CH₂Cl₂ and stirred overnight in the presence of Amberlyst 15. After filtration and the solvent evaporation a pale yellow oil was obtained in quantitative yield (185 mg). Found C, 67.93; H, 6.79, N, 3.75, S 8.64%. Calc. for C₂₁H₂₃NO₃S: C, 67.89; H, 6.78, N, 3.77, S 8.63%. ν_max(neat)/cm⁻¹ 3010, 2958, 1711, 1479, 1355, 1168. δ_H (200 MHz; CDCl₃, Me₄Si) 0.91 (3H, t, J = 7.2, CH₂CH₂CH₂), 1.26-1.37 (2H, m, CH₂CH₂CH₂), 1.49-1.60 (2H, m, CH₂CH₂CH₂), 2.36-2.51 (6H, m, COCH₂CH₂CH₂ ring, CH₂Ar), 2.83-3.03 (2H, m, CH₂ ring, CH₂CO), 3.25 (1H, dd, J = 17.8, 3.2 Hz, CH₂CO), 4.58 (1H, m, CHCH₂CO), 7.02 (2H, dd, J = 4.2 Hz, Ar), 7.17 (3H, m, Ar), 7.55 (2H, m, J = 7.8 Hz, Ar), 7.70 (1H, m, Ar). δ_C (50.2 MHz; CDCl₃, Me₄Si) δ (ppm): 13.6 (CH₃), 21.3 (CH₃), 22.1 (CH₂), 25.6 (CH₂), 35.0 (CH₂), 42.9 (CH₂), 49.6 (CH₂), 58.0 (CH), 116.8 (CH), 124.4 (CH), 125.1 (CH), 126.9 (CH), 127.6 (CH), 129.4 (CH), 131.2 (Cq), 134.3 (Cq), 140.9 (Cq), 143.8 (Cq), 209.0 (Cq). MS (EI, 70 eV): m/z (%) = 371 (M⁺, 2), 271 (96), 216 (100), 132 (43), 91 (41).

4-Hydroxy-1-(N-tosylindolin-2-yl)-pentan-2-one (3g) As previously reported 202 mg of 2-(2-ethoxyhexa-4-hydroxy-1-pentyl)-1-tosylindoline 2g (0.5 mmol) were dissolved in CH₂Cl₂ and stirred overnight in the presence of Amberlyst 15. After filtration and the solvent evaporation a pale yellow oil was obtained in quantitative yield (187 mg). Found C, 64.35; H, 6.19, N, 3.76, S 8.60%. Calc. for C₂₀H₂₅NO₄S: C, 64.32; H, 6.21, N, 3.75, S 8.59%. ν_max(neat)/cm⁻¹ 3543, 3056, 2973, 1705, 1599, 1351, 814. δ_H (200 MHz; CDCl₃, Me₄Si) 1.19 (3H, d, J = 6.2, CH₂CHOH), 2.35 (3H, s, CH₂Ar), 2.43-3.10 (7H, m, CH₂ ring, CH₂CO, CH₂COOH, OH), 4.28 (1H, m, CH₂CHOH), 4.58 (1H, m, CHCH₂CO), 7.02 (2H, bd, J = 4.3 Hz, Ar), 7.19 (3H, m, Ar), 7.55 (2H, d, J = 8.1 Hz, Ar), 7.70 (1H, d, J = 8.1 Hz, Ar). δ_C (50.2 MHz; CDCl₃, Me₄Si) δ (ppm): 21.3 (CH₃), 22.5 (CH₃), 35.0 (CH₂), 51.2 (CH₂),
53.0 (CH$_2$), 57.8 (CH), 63.6 (CH), 116.8 (CH), 124.6 (CH), 125.1 (CH), 126.9 (CH), 127.6 (CH), 129.5 (CH), 131.2 (Cq), 134.1 (Cq), 140.8 (Cq), 144.0 (Cq), 209.0 (Cq). MS (EI, 70 eV): m/z (%) = 329 (M$^+$ - C$_2$H$_4$O, 8), 271 (95), 174 (100), 132 (80), 91 (49).

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Supporting informations $^1$H, $^{13}$C and DEPT spectra of products 2a-g and 3a-g. NOESY spectra of product 2


