2.2. Part 2: Regioselective quadruple domino aldolization / aldol condensation / Michael addition / $S_N$Ar-cyclization: Construction of hexacyclic indeno-fused C-nor-D-homo-steroid frameworks$^1$
Part 2

Chapter 2

2.2.1 Introduction

2.2.1.1 Domino reaction

Today's approach in synthetic organic chemistry does not only mean to create complex molecules but to find the shortest, eco-compatible and frivolous route to reach the target. And to do so a periodic introduction of new synthetic methods (chemo-, regio-, diastereo- and enantioselective methods) has been done. The most important inclusion in this ever enhancing list is the domino method, is defined as the process where two or more bond-forming reactions take place under identical conditions in one-pot via the simultaneous transformation of the functionalities obtained in each of the penultimate steps.

Although, the domino synthesis seemed to be a new phenomenon to the synthetic laboratories, but in actual sense, it is very regular as Mother Nature has been using this domino approach for billions of years. One of the most prominent examples of this approach is the synthesis of fatty acids using a multi-enzyme complex starting from acetic acid derivatives, whereas the Mannich reaction is the first domino process developed by humankind (Scheme 2.2.1).

![Scheme 2.2.1. First domino reaction performed in laboratory.](image_url)

Domino strategies being a powerful subgroup of the broader category of one-pot reactions have emerged as one of the most intriguing synthetic tools due to their atom-/step-/cost-economy, and labor effectiveness. Several different approaches were introduced to classify domino reactions. The most relevant one is obviously by accounting the mechanism involved in each of the bond forming steps that are categorized as anionic, cationic, radical, pericyclic or the combination of two or more of the above category. Another way to term domino reaction is by the number of the real bond forming steps and the naming appears as double-, triple-, quadruple- domino reactions. Domino protocols are now a days frequently used in the synthesis of structurally complex bioactive molecules and natural products (alkaloids and steroids mainly).
2.2.1.2 C-nor-D-homo-steroids

Scheme 2.2.2. Skeletal difference of steroids and C-nor-D-homo-steroids.

C-nor-D-homo-steroids or [14(13→12)]-abeo-steroids are a small subgroup of steroids with an unusual 6-6-5-6 ring pattern rather than the 6-6-6-5 ring pattern of steroids (Scheme 2.2.2). Several alkaloids having the C-nor-D-homo-steroid skeleton were isolated from plants of the lily family and, in particular, of the veratrum schoenocaulone and zyadenous species. Among them the structurally diverse veratrum steroidal alkaloids cyclopamine is the most renowned one, acts as selective antagonist of transmembrane protein Smoothened and therefore has emerged as a novel and potent candidate for treatment of cancers dependent on hedgehog signaling. Steroidal alkaloids jervine, cytotoxic C-nor-D-homo-steroid nakiterpiosin and nakiterpiosinone (isolated from the Okinawan sponge Terpios hoshinota), proved to be potent antimitotic addressing the hedgehog pathway. Two new members of the class of C-nor-D-homo-steroid alkaloids are impane and dihydriompaine, have been isolated from Fritillaria Imperialis.

2.2.1.3 Review of literature (Synthesis of C-nor-D-homo-steroids)

One plausible approach to synthesize C-nor-D-homo-steroids is the expansion of the five membered ring D and contraction of the six membered ring C of the naturally occurring steroids. To achieve this goal, rearrangements or ring opening reactions, followed by cyclization must be performed. Among the scarcely available methods to synthesize C-nor-D-homo-steroid frameworks, intramolecular Horner-Wadsworth-Emmons and aldol condensations using the (+)-Wieland-Miescher ketone as a starting material, the Nazarov cyclization, and the degradation and rearrangement of abundantly available hecogenine are worthy to be mentioned. Tietze and co-workers synthesized a variety of hetero- and homo-steroids via domino Knoevenagel/hetero-Diels–Alder approach.

Athanassios Giannis and co-workers (2010) reported an interesting biomimetic conversion of “6-6-6-5”-steroids into their C-nor-D-homo-counterparts using Comins reagent along with DMAP as the promoter (Scheme 2.2.3).
L. Gui Donaruma and co-workers described synthesis of indeno-fused fluorene molecules \(39\) having structural resemblance with \(C\-nor\-D\)-homo-steroids from \(\alpha\)-phenylcinnamic acid derivatives \(38\) (Scheme 2.2.4).\(^{16}\) Both the carbonyl groups in these hexacyclic indeno-fused fluorene molecules exist in head to head orientation.

Georges J. Hoornaert et al. reported a photochemical transformation of truxones \(42\) (obtained by \(\text{AlCl}_3\) catalyzed dimerization of the corresponding indenones) to \(C\-nor\-D\)-homo-steroid ring systems \(43\) via exclusion of a carbon monoxide molecule (Scheme 2.2.5).\(^{17}\)

In view to the presence of a limited available methodologies a general synthetic strategy for the indeno-fused naphthalenes/quinolines having structural resemblance with \(C\-nor\-D\)-homo-steroid skeleton.
nor-D-homo-steroid skeleton is still elusive. In this regard, we utilized ortho-aroylacetophenones, which are easily accessible in moderate to good yields by the reported method (Thoroughly discussed Section 2 of this chapter, pages 36-47) in an anionic-quadruple-domino reaction that involves intramolecular-aldolization/aldol-condensation/intermolecular-Michael/S_{N}Ar-cyclization steps and synthesized complex hexa-carbo-/hetero-cyclic skeletons having structural similarity with the C-nor-D-homo-steroid nucleus, an interesting framework from the synthetic perspective.

2.2.2 Results and discussion

Initially, we attempted the desired domino reaction using ortho-benzoylacetophenone \( \text{1zc} \) (1.0 mmol) in DMSO (3.0 mL) in the presence of (S)-proline (0.3 mmol) at room temperature. Unfortunately, proline was found to be ineffective even to cyclize \( \text{1zc} \), and the starting material \( \text{1zc} \) was recovered as such after 24 h of stirring at room temperature (Table 2.2.1, entry 1). The above failure may be due to the inability to form the enamine intermediate, essential for the intramolecular alkylation because of steric hindrance.

Table 2.2.1. Base catalyzed conversion of \( \text{1zc} \).\(^{a}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mmol)</th>
<th>Solvent</th>
<th>Time</th>
<th>Product (yield in %)</th>
<th>( \text{2zc} )</th>
<th>( \text{44zc} )</th>
<th>( \text{45zc} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-Proline (0.30)</td>
<td>DMSO</td>
<td>24 h</td>
<td>nr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>50% aq. NaOH (0.30)</td>
<td>DMSO</td>
<td>3 h</td>
<td>-</td>
<td>-</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>50% aq. NaOH (4.00)</td>
<td>DMSO</td>
<td>4 h</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>50% aq. NaOH (0.05)</td>
<td>DMSO</td>
<td>2 min</td>
<td>-</td>
<td>-</td>
<td>93</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>NaOH (4.00)</td>
<td>Water</td>
<td>4 h</td>
<td>12</td>
<td>80</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NaOH (4.00)</td>
<td>DMSO</td>
<td>4 h</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>50% aq. KOH (0.05)</td>
<td>DMSO</td>
<td>5 min</td>
<td>92</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>50% aq. KOH (4.00)</td>
<td>DMSO</td>
<td>4 h</td>
<td>complex TLC</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>K(_2)CO(_3) (0.05)</td>
<td>DMSO</td>
<td>3 h</td>
<td>94</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
10 K₂CO₃ (4.00) DMSO 8 h complex TLC

\(^{a} 1\) mmol of 1zc was dissolved in 3 mL of solvent, appropriate proportion of promoter was added and stirred at rt. nr = no reaction.

To minimize the steric congestion arising in enamine formation, we investigated Brønsted bases such as NaOH, KOH, and K₂CO₃ as catalysts (Table 2.2.1). Thus, 1zc (1.0 mmol) in 3.0 mL of DMSO was treated with 0.024 mL (0.3 mmol NaOH) of aqueous NaOH solution (50% w/v) and the reaction mixture was stirred at room temperature (Table 2.2.1, entry 2). Notably, 1zc was completely consumed within 3 h. The work up of the reaction mixture provided 20zc in 47% yield, identified as 3-hydroxy-3-phenylindanone as the major product along with 3-phenylindenone 44zc in 16% yield and the desired 13b-phenylbenzo[a]indeno[1,2-c]fluorene-9,14-(8bH,13bH)-dione 45zc in 22% yield. The structure of 45zc was assigned on the basis of its satisfactory spectral and crystallographic analysis, and was found to have resemblance to the C-nor-D-homo-steroid nucleus (Figure 2.2.1).

![Figure 2.2.1. Crystal structures of 45zc, 45zd, 45zf and 45zh.](image)

Attracted by this result, we attempted to optimize the yield of 45zc. The above reaction was stirred for a further period of time with continuous monitoring. It was found that the area and intensity of the TLC spot corresponding to 45zc increased continuously, whilst those of 20zc and 44zc decreased simultaneously. However, complete conversion was not observed even after 12 h. We next decided to increase the base proportion and with 0.32 mL (4 mmol NaOH) of aqueous NaOH (50% w/v) complete conversion of 1zc to the desired 45zc was observed in 86% isolated yield within 4 h. Hence, 4 equiv. of NaOH (50% w/v aq. solution) in 3 mL of DMSO at room temperature was recognized as the optimum conditions for the synthesis of 45 from 1 (Table 2.2.1, entry 3).
The scope and viability of this protocol was determined by using 12 different ortho-aroylacetophenones 1 with substitutions (both electron-donating and electron-withdrawing) at various positions. The reaction proceeded smoothly in most of the cases affording the desired product 45 in good yields (Table 2.2.2). However, when we used 0.004 mL (0.05 mmol NaOH) of aqueous NaOH (50% w/v) in DMSO at room temperature, 20zc was obtained in quantitative yield within 2 minutes (Table 2.2.1, entry 4 and Table 2.2.3). Next, when the reaction was performed using 4 equiv. of NaOH in water (3 mL), 44zc was obtained as the major product (80% isolated yield) along with 20zc. However, 45zc was not formed even in trace after 12 h of stirring (Table 2.2.1, entry 5). NaOH (4 mmol) in DMSO initially triggered the reaction and after 2 min 1zc was completely converted to 20zc, and a faint spot of desired product 45zc was observed. Further stirring of the reaction provided several spots on TLC, and after 4 h only a trace of 45zc was observed (Table 2.2.1, entry 6). Next, a catalytic amount of KOH or K₂CO₃ (0.05 equiv.) provided 20zc quite efficiently (Table 2.2.1, entries 7 and 9), but failed to produce 45zc, even after employing 4 mmol of these inorganic bases (Table 2.2.1, entries 8 and 10). Thus, from the above observations it may be suggested that NaOH as promoter and DMSO-H₂O mixture as solvent is specific for the completion of the desired domino reaction.

Table 2.2.2. Formation of 45 via anionic quadruple domino transformation of 1.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>45</th>
<th>Entry</th>
<th>1</th>
<th>45</th>
</tr>
</thead>
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<td><img src="image2.png" alt="image" /></td>
<td>1</td>
<td><img src="image3.png" alt="image" /></td>
<td><img src="image4.png" alt="image" /></td>
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<td><img src="image7.png" alt="image" /></td>
<td><img src="image8.png" alt="image" /></td>
</tr>
<tr>
<td>8</td>
<td><img src="image9.png" alt="image" /></td>
<td><img src="image10.png" alt="image" /></td>
<td>45zc 4 h, 86 %</td>
<td>Cl</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image11.png" alt="image" /></td>
<td><img src="image12.png" alt="image" /></td>
<td>1zi</td>
<td>Me</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td><img src="image13.png" alt="image" /></td>
<td><img src="image14.png" alt="image" /></td>
<td>45zi 24 h, 10 %</td>
<td>Cl</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image15.png" alt="image" /></td>
<td><img src="image16.png" alt="image" /></td>
<td>1zj</td>
<td>Me</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image17.png" alt="image" /></td>
<td><img src="image18.png" alt="image" /></td>
<td>45zi 24 h, 8 %</td>
<td>F</td>
<td></td>
</tr>
</tbody>
</table>
a1 mmol of 1 was dissolved in 3 mL of DMSO and 4 mmol of 50% aq. NaOH solution was poured and stirred at room temperature; bIsolated pure yield; cIntermediate Michael adduct 45MA was the major product.

Table 2.2.3. Formation of 20 via intramolecular aldolization of 1.a

\[
\begin{array}{c}
\text{R} \quad \text{Ar} \\
\text{1} \quad \text{H, Cl} \\
\text{20m (95)} \quad \text{20zn (94)} \\
\end{array}
\]

a1 mmol of 1 was dissolved in 3 mL of DMSO and 0.05 mmol of 50% aq. NaOH solution (0.004 mL) was added and the mixture stirred at room temperature; bIsolated pure yield.
To gain some mechanistic insight about the domino transformation we arranged 3 different set of reactions (Scheme 2.2.6). In the first set of reaction equimolar mixture of pure 20zc and 44zc was subjected under the optimized domino reaction conditions, that provided desired 45zc in 85% yield (Scheme 2.2.6, Set I). Similar result was found when isolated 20zc alone was used as the initial substrate (Scheme 2.2.6, Set II). But while 44zc was used as the initial substrate and subjected to the optimized domino reaction conditions, a complex TLC pattern showing several very close spots with no trace of the desired molecule 45zc was observed (Scheme 2.2.6, Set III). These observations discarded the possibility of Diels-Alder cycloaddition pathway of the formation of final product in the optimized reaction conditions and strengthened the assumption of the quadruple domino pathway of the reaction.

Scheme 2.2.6. Mechanistic cross check under optimized domino reaction conditions.

On the basis of the above experimental results together with the related reports, a plausible reaction scenario for this domino reaction is outlined in Scheme 2.2.7. The first step in the mechanism is believed to be intramolecular aldolization of 1zc to produce 20zc. Part of 20zc undergoes dehydration to complete aldol condensation furnishing 44zc, which further undergoes Michael addition with the enolic form (20'zc) of 20zc to provide the Michael adduct 45MA2zc via dehydration of 45'MA'2zc. The Michael adduct 45MA2zc undergoes consecutive SNAr cyclization, and oxidative aromatization to furnish the desired product 45zc. Intermediates 20zc and 44zc were isolated at the initial stage of the reaction. With the progress of the reaction these intermediates diminished and converted to the desired product 45zc.
Scheme 2.2.7. Mechanism of the concerned anionic multiple domino reaction.

To verify the regioselectivity of step ‘E’ in Scheme 2.2.7 of the quadruple domino reaction, we used 1ze, 1zh, 1zi and 1zd as initial substrates (Scheme 2.2.7). Exclusive formation of 45zh offers a proof in favour of specific intramolecular nucleophilic attack of in situ generated enolic nucleophile in the Michael adduct 45MA_{zh} to the less hindered para-position with respect to the chloro group of 3-chlorophenyl ring. A similar result was obtained in case of substrate 1ze, where regioisomer 45ze was formed exclusively. The observed steric effect domination of the product formation is mirrored in the yield, 45zg greater than 45zh.

In case of substrate 1zd the nucleophilic attack occurs exclusively at C-2 of the pyridine ring in the intermediate 45MA_{zd} leading to the exclusive formation of 45zd. A similar trend of regioselectivity was observed in case of formation of 45zm and 45zn (Scheme 2.2.7).

Scheme 2.2.8. Regioselectivity in final domino SNAr step.
Structure of the exact regioisomers (45ze, 45zh, 45zl, 45zm and 45zn) has been fully characterized by their satisfactory spectral (\(^1\)H & \(^{13}\)C NMR and HRMS) studies along with crystallographic analysis of one of the representative molecule 45zh (Figure 2.2.1). In the case of substrate 1zk a lower yield of desired product 45zk was obtained as the final S\(_{\text{NAr}}\) step is somewhat less favorable due to increase of electron density and steric crowding in the aromatic ring.

However, when we used 1zi as the initial substrate, Michael adduct 45MAzi was formed after 6 h, which was isolated and characterized. Interestingly, when the reaction was continued for another 18 h, 13b-(2-chlorophenyl)benzo[a]indeno[1,2-c] fluorene-9,14-(8bH,13bH)-dione (45zi) was obtained in very low yield by intramolecular S\(_{\text{NAr}}\) reaction via chloride displacement. The similar trend was observed in the case of substrate 1zj also. Despite having positive electronic factor as the chloride is better leaving group than hydride the inefficiency of the desired product formation in the above two cases is assumed to be the restricted rotation of C–C bond due to steric hindrance that limits the scope to attain the favorable conformation essential for cyclization (Scheme 2.2.9).

![Scheme 2.2.9. Inefficiency of 1zi and 1zj towards desired domino reaction.](image)

### 2.2.3 Conclusion

We prepared some novel indeno-fused naphthalene and quinoline molecules that have structural similarity with the C-nor-D-homo-steroid nucleus. This anionic quadruple-domino strategy consists of intramolecular-aldolization/aldol condensation/intermolecular-Michael/S\(_{\text{NAr}}\)-cyclization steps. This domino transformation where simple Brønsted base NaOH is sufficient to trigger four complex reaction steps to construct four new bonds is the first of its kind. Investigation of each step of the domino reaction was explored experimentally to propose a reasonable mechanistic sequence. Furthermore, specificity of
NaOH as promoter and DMSO-H$_2$O mixture as solvent for the completion of the desired domino reaction is established.

2.2.4 Experimental section

2.2.4.1 General Remarks

$^1$H and $^{13}$C NMR spectra were recorded at 300 and 75 MHz respectively. Chemical shift ($\delta$) values are given in parts per million (ppm) with reference to tetramethylsilane (TMS) as the internal standard. Coupling constant ($J$) values are given in Hertz (Hz). High resolution mass spectra were recorded using ESI method. Organic solvents used were dried by standard methods wherever necessary. Commercially obtained reagents were used as such without further purification. All the reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 F$_{254}$ precoated plates. Column chromatography was carried out using silica gel with 100-200 mesh or with anhydrous alumina. Mixture of hexane/ethyl acetate or MeOH/DCM in appropriate proportion (determined by TLC analysis) was used as eluent solvent system.

2.2.4.2 Typical procedure for the synthesis of 45

1 mmol of 1 was taken in a round bottom flask and dissolved in DMSO (3 mL), 4 mmol (0.32 mL) of freshly prepared 50% aqueous NaOH (2.5 g in 5 mL distilled water) was added and stirred at room temperature. After completion of the reaction (monitored by TLC) 30 mL water was added to it and product was extracted with ethyl acetate (20 mL × 3). Combined organic layer was washed with water and brine solution and dried over anhydrous Na$_2$SO$_4$. Ethyl acetate was evaporated and crude was purified by column chromatography using EtOAc/Hexane mixture as eluent (45zc-45zk). In case of synthesis of 45zd-45zn extraction was performed using solvent DCM instead of EtOAc and column was done with MeOH/DCM solvent system in appropriate proportion using neutral allumina as stationary phase.

2.2.4.3 Typical procedure for the synthesis of 20

1 mmol of 1 was taken in a round bottom flask and dissolved in DMSO (3 mL), 0.05 mmol (0.004 mL) of freshly prepared 50% aqueous NaOH (2.5 g in 5 mL distilled water) was added and stirred at room temperature. After completion of the reaction (monitored by TLC), 30 mL water was added to it and product was extracted with ethyl acetate (20 mL × 3).
Combined organic layer was washed with water and brine solution and dried over anhydrous Na$_2$SO$_4$. Ethyl acetate was evaporated and crude was purified by column chromatography using EtOAc/Hexane mixture as the mobile phase and silica gel (100/200 mesh) as the stationary phase to afford pure 20.

2.2.4.4 Characterization data of the synthesized molecules

3-Hydroxy-3-phenylindanone (20zc)

Yellow gelly; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.67 (d, $J$ = 7.5 Hz, 1H), 7.56 (t, $J$ = 7.05 Hz, 1H), 7.41-7.31 (m, 2H), 7.24-7.18 (m, 5H), 3.04 (s, 2H), 2.90 (broad, 1H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 203.8, 158.2, 145.1, 135.7, 129.3, 128.4, 127.3, 127.2, 125.2, 125.1, 124.9, 123.0, 78.3, 55.9.

3-hydroxy-6-methyl-3-phenyl-2,3-dihydro-1H-inden-1-one (20zd)

Yellow gelly; $^1$H-NMR (300 MHz, CDCB) $\delta$ 7.58 (s, 1H), 7.48 (d, $J$ = 7.8 Hz, 1H), 7.34-7.25 (m, 6H), 3.16 (s, 2H), 2.50 (s, 1H), 2.44 (s, 3H); $^{13}$C-NMR (75 MHz, CDCB) $\delta$ 203.9, 155.9, 145.4, 139.5, 136.8, 135.9, 128.3, 127.1, 124.9, 122.8, 78.0, 56.3, 21.1; HRMS (ESI-TOF) of C$_{16}$H$_{14}$O$_2$ = 261.0886 [M+Na$^+$] (calculated 261.0886).

3-(4-chlorophenyl)-3-hydroxy-2,3-dihydro-1H-inden-1-one (220zg)

Light yellow sticky solid; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.64-7.56 (m, 2H), 7.44 (t, $J$ = 7.2 Hz, 1H), 7.36 (d, $J$ = 7.5 Hz, 1H), 7.26-7.23 (m, 4H), 4.04 (s, 1H), 3.09 (dd, $J_1$ = 19.05 Hz, $J_2$ = 29.9 Hz, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 203.8, 157.9, 143.7, 135.8, 135.4, 133.0, 129.4, 128.4, 126.4, 125.1, 123.0, 77.8, 55.7.

3-(3-Chlorophenyl)-3-hydroxy-2,3-dihydro-1H-inden-1-one (20zh)

Orange sticky solid; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.67-7.57 (m, 2H), 7.46-7.35 (m, 3H), 7.21-7.09 (m, 3H), 3.94 (s, 1H), 3.10 (dd, $J_1$ = 18.9 Hz, $J_2$ = 27 Hz, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 203.7, 157.8, 147.3, 135.9, 135.5, 134.3, 129.6, 129.6, 127.4, 125.3, 125.1, 123.3, 123.1, 77.8, 55.7; HRMS (ESI-TOF) of C$_{15}$H$_{11}$ClO$_2$ = 281.0340 [M+Na$^+$] (calculated 281.0340).
6-Chloro-3-hydroxy-3-(pyridin-3-yl)-2,3-dihydro-1H-inden-1-one (20zm)

Brown sticky solid; \( ^1H \)-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.52 (broad, 1H), 8.35 (broad, 1H), 7.70-7.59 (m, 3H), 7.34-7.26 (m, 3H), 3.26 (dd, \( J_1 = 19.2 \text{ Hz}, \ J_2 = 32.1 \text{ Hz}, \text{2H}\)); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \) 201.3, 155.5, 148.2, 146.3, 140.9, 137.2, 136.4, 136.0, 133.3, 126.6, 123.5, 123.1, 76.5, 56.0; HRMS (ESI-TOF) of C\(_{14}\)H\(_{10}\)ClNO\(_2\) = 260.0471 [M+H\(^+\)] (calculated 260.0473).

3-Phenyl-1H-inden-1-one (44zc)

Yellow oil; \(^1H\)-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.48-7.46 (m, 2H), 7.36-7.32 (m, 4H), 7.21-7.12 (m, 3H), 5.82 (s, 1H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \) 196.6, 162.5, 143.7, 132.8, 132.6, 132.1, 130.3, 129.0, 128.7, 127.0, 122.8, 122.6, 122.4, 121.4.

13b-Phenylbenzo[a]inden[1,2-c]fluorene-9,14(8bH,13bH)-dione (45zc)

Orange red solid; mp 254-257 °C; \(^1H\)-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.19-8.15 (m, 2H), 7.85-7.77 (m, 2H), 7.71 (t, \( J = 7.35 \text{ Hz, 1H}\), 7.53-7.43 (m, 6H), 7.29-7.23 (m, 4H), 7.14 (d, \( J = 6.3 \text{ Hz, 2H}\), 3.98 (s, 1H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \) 201.4, 194.7, 156.8, 151.8, 143.2, 141.3, 137.0, 134.8, 134.1, 133.7, 133.0, 132.4, 131.7, 131.2, 130.7, 129.0, 128.8, 127.8, 127.1, 126.6, 125.6, 123.4, 122.6, 122.4, 110.0, 100.6, 66.0, 51.6; CCDC 875292.

2,11-Dimethyl-13b-phenylbenzo[a]inden[1,2-c]fluorene-9,14(8bH,13bH)-dione (45zd)

Red solid; mp 262-264 °C; \(^1H\)-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.14 (d, \( J = 7.5 \text{ Hz, 1H}\)), 8.05 (d, \( J = 8.1 \text{ Hz, 1H}\), 7.66-7.63 (m, 2H), 7.54-7.42 (m, 4H), 7.23-7.19 (m, 5H), 7.13 (d, \( J = 6.6 \text{ Hz, 2H}\), 3.95 (s, 1H), 2.42 (s, 3H), 2.33 (s, 3H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \) 201.6, 195.1, 154.5, 151.7, 143.6, 139.4, 138.5, 138.0, 137.2, 136.1, 134.2, 133.4, 132.9, 132.8, 131.6, 131.2, 130.4, 128.8, 128.3, 127.8, 127.0, 126.7, 125.7, 123.7, 123.4, 122.3, 66.2, 51.3, 21.2, 21.0; CCDC 898556.
6-Methyl-13b-(m-tolyl)benzo[a]indenol1,2-c]fluorene-9,14(8bH,13bH)-dione (45ze)

Orange red solid; mp 256-258 °C; \(^1H\)-NMR (300 MHz, CDCl₃) \(\delta 8.17\) (d, \(J = 7.8\) Hz, 1H), 7.96 (s, 1H), 7.83 (t, \(J = 7.35\) Hz, 2H), 7.70 (t, \(J = 7.35\) Hz, 1H), 7.42-7.24 (m, 6H), 7.15 (t, \(J = 7.95\) Hz, 1H), 7.02 (d, \(J = 7.2\) Hz, 1H), 6.90 (broad, 2H), 3.94 (s, 1H), 2.46 (s, 3H), 2.23 (s, 3H); \(^13C\)-NMR (75 MHz, CDCl₃) \(\delta 201.9, 194.7, 157.1, 151.8, 143.2, 141.4, 138.4, 137.5, 136.9, 134.7, 133.8, 132.9, 132.4, 132.0, 131.5, 131.2, 130.7, 129.0, 128.6, 128.0, 127.9, 127.7, 127.1, 126.3, 123.8, 123.4, 122.5, 122.4, 65.7, 51.7, 21.5, 21.5; HRMS (ESI-TOF) of C\(_{32}\)H\(_{22}\)O\(_2\) = 439.1691 [M+H\(^+\)] (calculated 439.1693).

2,11-Dichloro-13b-phenylbenzo[a]indenol1,2-c]fluorene-9,14(8bH,13bH)-dione (45zf)

Orange red solid; mp 285-287 °C; \(^1H\)-NMR (300 MHz, CDCl₃) \(\delta 8.10\) (d, \(J = 8.1\) Hz, 2H), 7.79-7.38 (m, 7H), 7.25 (broad, 4H), 7.10-7.08 (m, 2H), 4.00 (s, 1H); \(^13C\)-NMR (75 MHz, CDCl₃) \(\delta 200.1, 193.1, 154.7, 151.8, 142.4, 139.1, 138.5, 135.5, 134.8, 134.7, 134.0, 133.6, 133.2, 132.2, 131.9, 131.8, 129.0, 128.1, 127.6, 127.4, 126.5, 125.7, 123.3, 123.2, 66.2, 51.3; CCDC 891987.

7-Chloro-13b-(4-chlorophenyl)benzo[a]indenol1,2-c]fluorene-9,14(8bH,13bH)-dione (45zg)

Orange red solid; mp 228-230 °C; \(^1H\)-NMR (300 MHz, CDCl₃) \(\delta 8.15-8.07\) (m, 2H), 7.86 (d, \(J = 7.5\) Hz, 1H), 7.73 (t, \(J = 7.95\) Hz, 2H), 7.44 (broad, 5H), 7.32-7.22 (m, 3H), 7.06 (d, \(J = 8.4\) Hz, 2H), 3.87 (s, 1H); \(^13C\)-NMR (75 MHz, CDCl₃ & DMSO-d\(_6\)) \(\delta 201.1, 191.2, 157.8, 152.1, 139.2, 137.5, 137.2, 136.5, 136.4, 135.0, 134.6, 133.4, 133.2, 132.8, 131.0, 129.8, 128.8, 128.4, 127.6, 127.5, 126.2, 125.8, 123.1, 123.0, 121.9, 121.1, 64.7, 52.3; HRMS (ESI-TOF) of C\(_{30}\)H\(_{16}\)Cl\(_2\)O\(_2\) = 517.0339 [M+K\(^+\)] (calculated 517.0159).
6-Chloro-13b-(3-chlorophenyl)benzo[a]indenol[1,2-c]fluorene-9,14(8bH,13bH)-dione (45zh)

Red solid; mp 290 °C; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 8.21-8.14 (m, 2H), 7.89 (d, $J = 7.8$ Hz, 1H), 7.79-7.72 (m, 2H), 7.54-7.41 (m, 5H), 7.35-7.19 (m, 3H), 7.11-7.01 (m, 2H), 3.94 (s, 1H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 200.4, 194.1, 155.7, 150.5, 145.1, 140.6, 136.7, 135.2, 134.8, 134.0, 133.4, 132.8, 132.0, 131.9, 131.0, 130.6, 130.2, 129.4, 129.3, 128.3, 127.6, 126.7, 125.6, 124.9, 123.8, 123.0, 122.4, 65.1, 51.4; CCDC 898787.

13b-(2-Chlorophenyl)benzo[a]indenol[1,2-c]fluorene-9,14(8bH,13bH)-dione (45zi)

Red solid; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 8.80 (d, $J = 8.1$ Hz, 1H), 8.61- 8.58 (m, 2H), 8.25 (d, $J = 7.8$ Hz, 1H), 8.04 (d, $J = 7.5$ Hz, 1H), 7.77-7.64 (m, 2H), 7.53-7.43 (m, 4H), 7.32-7.29 (m, 1H), 7.24-7.14 (m, 3H), 7.04 (d, $J = 7.5$ Hz, 1H), 5.08 (s, 1H); ESI MS: m/z = 467 [M+Na]$^+$.  

13b-(2-Fluorophenyl)benzo[a]indenol[1,2-c]fluorene-9,14(8bH,13bH)-dione (45zj)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 8.83 (d, $J = 8.4$ Hz, 1H), 8.61 (d, $J = 8.1$ Hz, 1H), 8.26 (d, $J = 6.6$ Hz, 2H), 8.05 (d, $J = 7.2$ Hz, 1H), 7.76-7.67 (m, 2H), 7.56-7.45 (m, 5H), 7.34-7.25 (m, 4H), 5.42 (s, 1H).

7-Methoxy-13b-(4-methoxyphenyl)benzo[a]indenol[1,2-c]fluorene-9,14(8bH,13bH)-dione (45zk)

Red solid; mp 238-240 °C; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 8.20 (d, $J = 7.8$ Hz, 1H), 8.11 (d, $J = 9$ Hz, 1H), 7.82 (d, $J = 7.5$ Hz, 1H), 7.74-7.65 (m, 2H), 7.44-7.36 (m, 4H), 7.27-7.23 (m, 1H), 7.06-6.95 (m, 3H), 6.79 (d, $J = 8.7$ Hz, 2H), 3.89 (s, 4H), 3.73 (s, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 201.4, 195.3, 162.0, 158.5, 141.3, 136.7, 136.6, 135.5, 134.8, 132.8, 132.6, 131.3, 130.7, 130.6, 129.0, 127.8, 127.7, 127.3, 127.3,
123.4, 122.2, 121.1, 118.5, 117.2, 114.1, 113.5, 66.5, 55.4, 55.1, 51.1; HRMS (ESI-TOF) of C_{32}H_{22}O_{4} = 471.1596 \text{ [M+H]^+} (calculated 471.1591).

14b-(Pyridin-3-yl)diindeno[1,2-f:1',2'-h]quinoline-5,14(5aH,14bH)-dione (45z)

Brown solid; mp 148-150 °C; \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 8.69-8.68 (broad, 1H), 8.44-8.43 (broad, 1H), 8.35-8.33 (m, 2H), 8.06 (d, \( J = 7.8 \) Hz, 1H), 7.83 (d, \( J = 7.5 \) Hz, 1H), 7.68-7.62 (m, 2H), 7.50-7.37 (m, 5H), 7.27-7.18 (m, 2H), 4.21 (s, 1H); \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 199.0, 193.8, 154.7, 154.0, 151.5, 150.7, 147.6, 147.4, 147.3, 140.2, 138.8, 137.0, 135.4, 135.3, 133.5, 132.5, 131.8, 131.4, 130.1, 129.8, 128.5, 124.0, 123.7, 123.2, 123.0, 122.2, 67.6, 50.4; HRMS (ESI-TOF) of C_{28}H_{16}N_{2}O_{2} = 435.1103 \text{ [M+Na]^+} (calculated 435.1104).

3,12-Dichloro-14b-(pyridin-3-yl)diindeno[1,2-f:1',2'-h]quinoline-5,14(5aH,14bH)-dione (45zm)

Brown solid; mp 120-122 °C; \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 8.75 (broad, 1H), 8.49 (broad, 1H), 8.36 (broad, 2H), 8.09-8.02 (m, 1H), 7.84 (s, 1H), 7.69-7.63 (m, 2H), 7.42 (broad, 5H), 4.31 (s, 1H); \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 197.9, 192.5, 153.0, 151.9, 151.7, 150.7, 149.0, 139.3, 139.2, 138.6, 138.1, 136.3, 135.6, 135.4, 135.3, 134.3, 134.2, 133.5, 132.7, 132.5, 131.5, 124.0, 123.9, 123.8, 123.6, 123.4, 114.04, 67.9, 50.2; HRMS (ESI-TOF) of C_{28}H_{14}Cl_{2}N_{2} = 481.0516 \text{ [M+H]^+} (calculated 481.0505).

3,12-Dimethyl-14b-(pyridin-3-yl)diindeno[1,2-f:1',2'-h]quinoline-5,14(5aH,14bH)-dione (45zn)

Brown solid; mp 122-124 °C; \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 8.75 (d, \( J = 3.9 \) Hz, 1H), 8.48 (d, \( J = 3.6 \) Hz, 1H), 8.40 (t, \( J = 6.15 \) Hz, 1H), 8.00 (d, \( J = 7.8 \) Hz, 1H), 7.68 (s, 1H), 7.57-7.40 (m, 3H), 7.25-7.19 (m, 4H), 4.26 (s, 1H); \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 199.4, 194.2, 154.4, 154.2, 152.6, 151.2, 150.5,
148.4, 148.2, 140.2, 138.7, 138.6, 134.6, 133.3, 132.5, 132.3, 129.9, 124.3, 123.9, 123.7, 122.9, 122.0, 67.9, 50.2, 21.3, 21.0; HRMS (ESI-TOF) of C$_{30}$H$_{20}$N$_2$O$_2$ = 441.1606 [M+H$^+$] (calculated 441.1598).

1,3'-Bis(2-chlorophenyl)-3-hydroxy-1H,1'H-[1,2'-biinden]-1'-one (45MA$_{z1}$)

Orange Solid; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.65 (d, $J = 7.2$ Hz, 1H), 7.41-6.76 (m, 15H), 6.66 (d, $J = 6.9$, 1H), 6.39 (s, 1H); $^{13}$C-NMR (75MHz, CDCl$_3$) $\delta$ 196.0, 173.2, 153.0, 145.2, 143.5, 143.1, 138.5, 133.4, 132.4, 132.2, 131.8, 131.4, 131.2, 130.1, 130.0, 129.9, 129.9, 129.8, 129.7, 128.7, 128.4, 127.4, 127.0, 126.3, 122.7, 122.6, 121.8, 26.6. ESI MS: m/z = 519 [M+K]$^+$; Anal. Calcd. For C$_{30}$H$_{18}$Cl$_2$O$_2$: C, 74.85; H, 3.77. Found: C, 74.82; H, 3.19.

1,3'-Bis(2-fluorophenyl)-3-hydroxy-1H,1'H-[1,2'-biinden]-1'-one (45MA$_{zj}$)

Orange Solid; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 8.14 (d, $J = 7.5$ Hz, 1H), 8.05 (d, $J = 7.8$ Hz, 1H), 7.83-7.77 (m, 2H), 7.66 (t, $J = 7.5$ Hz, 1H), 7.54-7.38 (m, 6H), 7.31-7.25 (m, 3H), 7.13 (t, $J = 7.8$ Hz, 1H), 7.04 (t, $J = 7.5$ Hz, 2H), 4.30 (s, 1H).
$^1$H and $^{13}$C NMR of 45zc
${}^1$H and ${}^{13}$C NMR of 45zI
\(^1\)H and \(^{13}\)C NMR of 45MA\(_{zl}\)
2.2.5 References


Part 2

Chapter 2


