Tandem Wittig-Diels-Alder reaction

Section IV

Tandem Wittig-Diels-Alder reaction: Synthesis of lignan and heterolignans

Introduction:
Haworth introduced the term 'lignan' in 1936 to describe a group of optically active extracts isolated from plant materials. These extracts contained dimeric compounds consisting of two phenypropanoid units linked \( \beta-\beta' \) (8-8') through the central carbons of their propane side chains as represented in Fig I. Several hundred lignans have been discovered in different parts of various plants, including wooden parts, roots, leaves, flowers, fruits and seeds.

The presence of C-C bonds and oxygen bridges in the bisphenylpropane structure has been used to structurally classify lignans in different groups (Fig II). Broadly they may be classified as: 1) Acyclic lignans and others containing no additional C-C bonds (1), such as substituted furans, furofurans, dibenzylbutyrolactones; 2) Arylnaphthalene derivatives (2), having a C6-C7 bond, which includes the
podophyllotoxins; and 3) Derivatives of dibenzocyclooctene skeleton (3), with a C6-C2' bond, which include the steganacins.2

The variations in the lignan structures have been mainly brought about by the modification of the substituents in the basic skeleton. Several modifications affecting the substitution pattern of the aromatic rings,3,4 the substituent at C7,5-9 the change of 9, 9' lactone into a 9, 9' lactam,10 and many other modification have been carried out.11

Fig II

Gottlieb extended the lignan family to include ‘neolignans’,12-14 a class of compounds created by the coupling of different phenylpropanoid units via carbon-oxygen bonds.

The term heterolignan was first introduced by Ramos et al.15 Heterolignans are those synthetic analogues of lignans designed as a result of replacing one or more carbon atoms of the propane moieties (C7-C9 and/ or replacing one or both benzene rings (C1-C6 and/or C1'-C6') by heteroaromatic system.

**Biogenesis:**

Biosynthetically, lignans are synthesized in plants via the shikimate pathway. This is a major metabolite pathway for the construction of many aromatic compounds. The biosynthesis of lignans in plants is hypothesized to occur via radical dimerization of phenylpropanoids catalysed by peroxidase enzymes.16 A representative example of the oxidative couplings of two cinnamic residue is given below (Scheme I).

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Biological activity of lignans:

Lignans have attracted attention due to its interesting pharmacological activities. A heterolignan substructure can also be found in pharmacologically promising new molecules such as potent dopamine D1 agonists used for the treatment of Parkinson's disease. The spectrum of biological activity includes anti-cancer activity, anti-inflammatory activity, analgesic activity, antifungal activity, anti-asthmatic activity, antirheumatic activity, antineoplastic properties. The furanone moiety is the structural feature of a number of biologically active lignans.

Several research groups have studied the *Podophyllum* lignans for their anticancer properties. Podophyllotoxin was first isolated from *Podophyllum peltatum*. Several derivatives of podophyllotoxin were synthesized (Fig III) and structure-activity relationships studied on their binding to tubulin. It was found that some analogues possessed comparable activity whereas some others were inactive. A semisynthetic derivative of etoposide, teniposide, (4), shows anticancer activity.
All the podophyllotoxin derivatives depicted in Fig III exhibited promising antitumour activity. Azatoxin (10), a hybrid molecule of ellipticine and etoposide is a DNA Topoisomerase II inhibitor.
Some of the naturally occurring lignans are shown below,

\[
\text{Me}_0
\]

\[
\text{Me}_0
\]

\[
\text{OMe}
\]

\[
\text{R} = \text{H}
\]

\[
\text{R} = \text{OH}
\]

\[
\text{Me}_0
\]

\[
\text{Me}_0
\]

\[
\text{OMe}
\]

\[
\text{R} = \text{OMe}
\]

\[
\text{R} = \text{OH}
\]

Plant source:

4-Deoxy-isodiphyllin (11) and isodiphyllin (12), *Umbellifera bupleurum frutiscens* L\(^{35}\)

5-Methoxyjusticidin A (13) *Protium unifoliolatum*\(^{36}\)

5-Hydroxyjusticidin A (14) *Mananthes patentiflora*\(^{37}\)
Plant source: 15, 16, 17, 18  *Mananthes patentiflora*\textsuperscript{37}

Plant source: Justicidin E  *Hypoestes purpurea* (19)\textsuperscript{38a,38b}

Plant source:

Justicidin B (20)  *Justicia procumbens*\textsuperscript{39a,39c,d}

Retrojusticidin (21)  *Phyllanthus myrtifolius*\textsuperscript{39b,39c,d}
Taiwanin C (22)  

Plant source  

Taiwanin C  

Taiwania cryptomerioide$^{40a}$

1,2,3,4-Dehydrodeoxypodophyllotoxin (23)  

Hernandia ovigera, L.$^{40b}$

**Synthesis of lignans:**

Lignans and heterolignans have been prepared by different methods. Some of the methods making pericyclic reaction are depicted below.

a) Charlton and Alauddin have synthesized (+)-isolariciresinol dimethyl ether using a cycloaddition reaction.$^{41a}$ The key synthetic step was the pericyclic extrusion of sulfur dioxide to yield the ortho-quinone-methide. This compound underwent a Diels-Alder cycloaddition with methyl fumarate to afford a 70% yield of the major adduct (Scheme II). Later from same laboratory$^{41b}$ has reported synthesis of (-)-a-dimethylretrodendrin.
Madalengoitia & Mcdonald have reported synthesis of 10-Aryl-3a,4,10,10a-tetrahydrofuro[3,4]carbazol-1-ones by an intramolecular Diels-Alder reaction. Exo/endo product ratios were found to be sensitive to both solvent and temperature. The synthesis of isoelliptitoxin, a hybrid molecule of ellipticine and 4'-demethylpodophyllotoxin is presented (Scheme III).

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**Scheme II**

(+-)isolariciresinol dimethyl ether
Ayres et al. synthesized 1-Arylnaphthalenes lignan related to podophyllotoxin (Scheme IV).
Gonzalez et al.\textsuperscript{14} have synthesized 4-deoxy-isodiphyllin by sequential condensation of sodium salt of 3,4-dimethoxyphenylpropionic acid and methylenedioxyccinnamyl chloride, intermolecular Diels-Alder reaction followed by oxidation (Scheme V).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) \includegraphics[width=0.4\textwidth]{reaction1.png};
\node (b) at (0.5,0) \includegraphics[width=0.4\textwidth]{reaction2.png};
\draw[->] (a) -- (b);
\end{tikzpicture}
\end{center}

\textbf{Scheme V}

Oppolzer et al.\textsuperscript{45} have shown the stereoselective synthesis of Benz[f]isoindoline derivative by intramolecular cycloaddition of styrenes to olefins (Scheme VI).
Scheme VI

Sarkar et al.\textsuperscript{46} have described the Pummerer reaction of $\alpha$-benzoyl substituted pyridylmethyl sulfoxides which generates $\alpha$-thiocarbocations, the interception of which by the neighbouring keto functionality produces thio-substituted furo[3,4-\textit{c}] pyridine as transient intermediates. This undergoes [4+2] cycloaddition with an added dienophile. Base-induced ring opening of the cycloadducts followed by aromatization gives substituted isoquinolines related to heterocyclic analogues of 1-arylnaphthalene lignans (Scheme VII).
Jones and co-workers achieved a very efficient synthesis of (-)-podophyllotoxin (Scheme VIII) based on an asymmetric Diels-Alder addition to 1-aryl-2-benzopyran-3-one.48

![Chemical diagram](image)

Jana and Ghorai describes the synthesis of nitrogen containing heterocyclic analogues of 1-arylnaphthalene lignans using tandem furo[3,4-b]pyridines/furo[3,4-b]quinolines-Diels-Alder reaction. Furo[3,4-b]pyridines/furo[3,4-b]quinolines are synthesized from the coupling of alkynyl derivative with Fischer carbene complexes. This intermediate was trapped through Diels Alder reaction with dienophiles leading to the synthesis of lignan in a single step (Scheme IX).
Zheng et al.\textsuperscript{50} have showed the rearrangement of 1H-2,3-benzoxazine derivatives to the corresponding cyclic hemiaminal derivatives, which was trapped by various dienophiles to afford skeletal congeners of 1-arylnapthalene lignans (Scheme X).
The discovery of a new Pd-catalysed benzannulation reaction of bisbenzylidenedesuccinimide to arynaphthalene lignan aza-analogues (Scheme XI) is described by Mizufune et al.\textsuperscript{51}

\begin{center}
\textbf{Scheme XI}
\end{center}

Sugahara \textit{et al.}\textsuperscript{52} reported the acid catalysed transformation of pyridine substituted hydroxyl acetal to 1-pyridylisobenzofuran intermediate which undergoes rapid Diels-Alder reaction with dimethyl maleate to give mixture of \textit{exo} and \textit{endo} diastereomers. This on treatment with BF\textsubscript{3}.Et\textsubscript{2}O gave 1-pyridylnaphthalene lignan (Scheme XII).

\begin{center}
\textbf{Scheme XII}
\end{center}
Sato et al.\textsuperscript{53} have developed a novel method for the construction of arynaphthalene skeleton through a Pd catalysed [2+2+2] co-cyclisation of aryens and diynes. This co-cyclisation was the key step in the total synthesis of taiwanins C and E (Scheme XIII).
Present work:
Lignans and heterolignans being attractive targets due to their biological activities related to anticancer, we also could not resist evaluating our protocol of tandem Wittig-Diels-Alder reaction for their synthesis. Our strategy for their synthesis is depicted below (Scheme XIV).

Phosphorane “X” having a cinnamyl ester/amide linkage would undergo a Wittig reaction with aromatic/heteroaromatic aldehyde to give a unsaturated trans-ester/amide intermediate. This intermediate in situ would undergo a [4+2] addition reaction (Diels-Alder reaction). The cinnamyl part of the ester/amide would act as a diene and a newly formed unsaturated trans ester/amide as a dienophile. The Diels-Alder adduct would then undergo a 1,3-sigmatropic shift leading to lignan structure “Y”. The later part of the reaction being similar to Oppolzer et al.’s work (Scheme VI), a stereoselective product with all cis geometry was expected. It was also interesting to study the effect of triphenylphosphine oxide on this tandem process as it is observed to assist in [2+2] cycloaddition reaction. The required phosphorane was prepared according to scheme XV.
Cinnamyl aldehyde was converted to N-benzyl-3-phenprop-2-en-amine 24 by reductive amination. This was then acylated by bromoacetyl bromide followed by treatment of the resultant N-benzyl-2-bromo-N-[(2E)-3-phenylprop-2-in-1-yl]acetamide 25 with triphenylphosphine to obtain the corresponding phosphonium salt 26.

The compound 25 in its IR spectrum showed a band at 1643 cm$^{-1}$ indicating the presence of carbonyl group of amide.

In its $^1$H NMR (300 MHz, CDCl$_3$) spectrum one singlet (2H) was seen at $\delta$ 3.84 [3.92] which could be assigned to methylene attached to the bromine. The singlet (2H) at $\delta$ 4.63 [4.69] could be attributed to benzylic methylene protons. Doublet (2H, $J = 6.3$ Hz) at $\delta$ 4.0 [4.1] could be attributed to allylic methylene group. One multiplet (1H) and one doublet of doublet (1H, $J = 15.9$ Hz) was seen at $\delta$ 6.10 and 6.44 could be attributed to two olefinic protons of CH=CH-Ph group. One multiplet (10H) at $\delta$ 7.3 could be attributed to aromatic protons.
The peak at $\delta 26.23$ (t) in its $^{13}$C NMR spectrum is assigned to the CH$_2$ groups of CH$_2$Br group. Similarly, the peak at $48.53$ (t) could be attributed to carbon of allylic methylene group. Peak at $49.50$ (t) could be attributed to benzylic methylene carbon. Peaks at $123.24$ (d) and $123.46$ (d) could be attributed to two olefinic carbons. Peaks at $126.39$ (d), $127.55$ (d), $128.04$ (d), $128.66$ (d), $129.02$ (d), and $132.47$ (d), could be attributed to aromatic methine carbons. The quaternary carbons at $135.75$ (s) and $136.62$ (s) could be attributed to aromatic carbons. Peak at $167.17$ (s) could be due to carbonyl carbon of amide. The multiplicities of carbon signals mentioned were obtained from DEPT 135 experiment.

Thus on the basis of mode of formation & spectral properties N-benzyl-2-bromo-N-[(2E)-3-phenylprop-2-en-1-yl]acetamide (25) was assigned to it.

The salt 26 in its IR spectrum showed a band at 1640 cm$^{-1}$ indicating the presence of carbonyl group of amide.

In its $^1$H NMR (300 MHz, CDCl$_3$) spectrum doublet (2H, $J = 6$ Hz) at $\delta 4.10$ [4.67] could be attributed to allylic methylene group. Singlet (2H) at $\delta 5.15$ [5.24] could be due to benzylic methylene protons. The doublets (2H, $J = 15.6$ Hz) at $5.72$ [5.83] could be attributed to methylene attached to the phosphorous. One multiplet (1H) and two doublets ($J = 15.9$ Hz) at $\delta 6.10$ and $6.50$ could be attributed to two olefinic protons. Two multiplets (25 H) at $\delta 7.34$ and $7.88$ could be attributed to aromatic protons. The structure was further supported with $^{13}$C NMR and DEPT 135 spectra. Thus, peak at $34.1$ (t) could be assigned to carbon of methylene group attached to phosphorous. Peaks at $49.84$ (t) and $51.05$ (t) could be attributed to methylene carbon of allylic and benzylic methylene carbons. Peaks at $124.55$ (d)-$129.85$ (d), $130.0$ (d), $133.89$ (d), $134.45$ (d), $135.80$ (d) could be attributed to olefinic and aromatic methine carbons. The quaternary carbons appearing at $118.86$ (s), $120.06$ (s), $135.93$ (s), $136.23$ (s) could be attributed to aromatic carbons. The amide carbonyl carbon appeared at $164.66$ (s).

Thus on the basis of mode of formation & spectral properties structure 26 was assigned to it.
The phosphorane 27 in its IR spectrum showed a band at 1663 cm\(^{-1}\) indicating the presence of carbonyl group of amide.

Its \(^1\)H NMR (300 MHz, CDCl\(_3\)) spectrum showed a doublet at \(\delta 2.20\) (1H, \(J = 13.8\) Hz) which could be attributed to ylidic proton of CH=P group. Doublet (2H, \(J = 6.3\) Hz) at \(\delta 4.0\) [4.18] could be attributed to allylic methylene group. Two singlet at \(\delta 4.44\) [4.64] and 4.55 [4.67] could be due to benzylic methylene protons. One multiplet (1H) and two overlapping doublets (1H, \(J = 15.6\) Hz) seen at \(\delta 6.10\) and 6.40 could be attributed to the two olefinic protons. Multiplet at \(\delta 7.40\)-7.70 could be attributed to aromatic protons.

The peak at \(\delta 25.4\) (d) in its \(^{13}\)C NMR spectrum is assigned to ylide carbon (CH=P). Peaks at 47.98 (t) and 50.73 (t) could be attributed to allylic carbon of methylene group and benzylic methylene carbon. Peaks at 126.38 (d)-128.95 (d), 131.93 (d) - 136.3 (d) could be attributed to olefinic carbons and aromatic methine carbons. The quaternary carbons appearing at 123.81 (s), 124.47 (s), 136.62 (s), 137.53 (s) could be attributed to aromatic carbons. Peak at 170.89 (s) attributed for carbonyl carbon of amide, as expected. HRMS data confirmed the elemental composition as C\(_{36}\)H\(_{32}\)NOP (Observed: \(m/z 526.2291\), calculated for [M+H]\(^+\) = 526.2300).

Thus on the basis of mode of formation & spectral properties structure 27 was assigned to it.

Initially, we tried 3,4,5-trimethoxybenzaldehyde as a substrate as this unit is present in podophyllotoxin (naturally occurring lignan). Thus 3,4,5-trimethoxy benzaldehyde 28 was treated with phosphorane 27 in refluxing diphenyl ether for 10 h (monitored by TLC). The usual chromatographic separation provided a solid compound (Scheme XVI).
Scheme XVI

Its IR spectrum had a strong peak at 1681 cm\(^{-1}\) indicating the presence of \(\gamma\)-lactam group (MP = 80-81°C, Yield = 62.10%).

\(^1\)H NMR (CDCl\(_3\), 300 MHz): (Fig 1a).

<table>
<thead>
<tr>
<th>(\delta)</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.70</td>
<td>m</td>
<td>3H</td>
</tr>
<tr>
<td>2.99</td>
<td>m</td>
<td>1H</td>
</tr>
<tr>
<td>3.10</td>
<td>m</td>
<td>1H</td>
</tr>
<tr>
<td>3.57</td>
<td>1s and 1m</td>
<td>3H and 1H</td>
</tr>
<tr>
<td>3.87</td>
<td>1s and 1m</td>
<td>3H and 1H</td>
</tr>
<tr>
<td>3.92</td>
<td>s</td>
<td>3H</td>
</tr>
<tr>
<td>4.48</td>
<td>s</td>
<td>1H</td>
</tr>
<tr>
<td>4.82</td>
<td>d ((J_{\text{gem}} = 15) Hz)</td>
<td>1H</td>
</tr>
<tr>
<td>6.63</td>
<td>m</td>
<td>3H</td>
</tr>
</tbody>
</table>
| 7.13    | m            | 8H         | Saturated carbon protons

- OCH\(_3\)
- CH\(_2\)Ph
- Ar-H
From the above PMR data the product obtained appeared like a mixture. So HPLC analysis of it was done. It was found that the product obtained is actually a mixture of two compounds in approximate ratio of 6:1. Repeated column chromatography or preparative TLC failed to separate the mixture.

The possible modes of cycloaddition are depicted below (Fig IV),

If the cyclization takes place by endo route it will give a product with cis-ring junction (cis-adduct) and if the cyclization takes place by exo route it will give product with trans-ring junction (trans-adduct).

The stereochemical structure for these possible products is depicted below (Fig V).
The other possible isomers which may arise if the unsaturated amide is having cis geometry (Fig VI).

The $^1$H NMR data suggested that the major product to be cis fused formed via endo transition state as in the shielded aromatic region at $\delta$ 6.63, three protons were seen. This could be due to the two protons from the benzene ring containing trimethoxy groups and the other proton could be from the fused benzene ring. This proton gets shielded due to the presence of $\pi$-cloud of benzene ring having trimethoxy group in the equatorial position (structure I). The fusion of the ring could not be decided by coupling constants as some other aliphatic proton signals were also overlapping in its place. The second minor product could be the trans adduct (structure II) formed by exo addition. The other possible products (III) and (IV) were also considered. Their formation required the cis geometry in the intermediate unsaturated amide. As normally stable Wittig reagent gives the trans product as the major product it was assumed that the geometry for the intermediate amide as trans amide (confirmed subsequently by carrying out Wittig reaction separately). Again if products (III) and (IV) were formed the equatorial protons shown in the figure should have appeared as a doublet ($J = 3 - 4$ Hz) at $\delta$ 4 - 4.5,
which was not observed. The only signals which were difficult to explain were from the benzylic methylene group appearing as a singlet at δ 4.48 and as a doublet at δ 4.82. The plausible explanation for this could be either the five membered ring is continuously flipping at room temperature to show the distinct nature of the two conformations or it is because the compound is tautomerizes to lactam & lactim form. Lastly the structure formed by the other possible Diels-Alder reactions (Scheme XVII) was not considered due to nature of the dienophile and diene though it cannot be entirely ruled out.

\[ \text{Scheme XVII} \]

\[ \text{\begin{align*} \text{H}_2\text{CO} & \quad \text{H}_2\text{CO} \\ \text{H}_2\text{CO} & \quad \text{H}_2\text{CO} \\ \text{\text{N}Bn} & \quad \text{\text{N}Bn} \end{align*}} \]

\[ \text{13C NMR spectrum (Fig 1a) of the mixture had a peak at 30.0 (t), which could be assigned to the CH}_2\text{ group of six membered ring. Peak at 46.16 (t) could be attributed to methylene carbon of lactam ring. Peak at 52.30 (t) could be assigned to benzylic methylene carbon. Peaks at 33.91 (d), 41.51 (d), 41.57 (d) could be attributed to three methine carbons of six membered ring. Peaks at 56.03 (q), 60.83 (q), and 60.97 (q) could be attributed to three methyl carbons attached to the oxygen of OCH}_3\text{ group. Peaks at 108.14 (d), 126.18 (d)-128.70 (d) could be attributed to the aromatic methine carbons. The quaternary carbons appearing at 123.07 (s), 132.49 (s), 135.64 (s), 140.84 (s), 142.05 (s), 151.88 (s), and 152.52 (s) could be due to the aromatic carbons. Peak at 176.38 (s) could be due to carbonyl carbon of lactam. HRMS data confirmed the elemental composition as C}_{28}\text{H}_{29}\text{O}_4\text{N} (Observed: m/z 444.2177, calculated for [M+H]^+ = 444.2175).} \]

In order to confirm the geometry of the intermediate unsaturated amide. 3,4,5-Trimethoxy benzaldehyde was condensed with \text{N}-benzyl-N-[(2E)-3-phenylprop-2-en-1yl]-2-(triphenylphosphoranylidene)acetamide in refluxing chloroform (Scheme XVIII).
Scheme XVIII

Based on the mode of formation and spectral properties mentioned below, structure 29 was assigned to the compound. The high coupling constant \( J = 15.3 \text{ Hz} \) of vinyl protons indicated \textit{trans} geometry of the product (yield = 84.96%).

\[ \text{IR} (\nu_{\text{max}}): 1649 \text{ cm}^{-1} (\text{CO}). \]

\[ ^1\text{H NMR} (300 \text{ MHz, CDCl}_3): \]

<table>
<thead>
<tr>
<th>( \delta )</th>
<th>Multiplicity</th>
<th>( \text{J} )</th>
<th>( \text{H} )</th>
<th>( \text{Assignments} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.86 [3.88]</td>
<td>s</td>
<td>9H</td>
<td>3 X OCH(_3)</td>
<td></td>
</tr>
<tr>
<td>4.20 [4.31]</td>
<td>d (( \text{J} = 4.5 \text{ Hz} ))</td>
<td>1H</td>
<td>-CH(_2)-CH=CH</td>
<td></td>
</tr>
<tr>
<td>4.56 [4.64]</td>
<td>s</td>
<td>2H</td>
<td>CH(_2)-Ph</td>
<td></td>
</tr>
<tr>
<td>6.1-6.29</td>
<td>m</td>
<td>1H</td>
<td>CH(_2)-CH=CH</td>
<td></td>
</tr>
<tr>
<td>6.49 [6.55]</td>
<td>d (( \text{J} = 9.0 \text{ Hz} ))</td>
<td>1H</td>
<td>CH(_2)-CH=CH</td>
<td></td>
</tr>
<tr>
<td>6.67</td>
<td>s</td>
<td>1H</td>
<td>Ar-H</td>
<td></td>
</tr>
<tr>
<td>6.75</td>
<td>s</td>
<td>1H</td>
<td>Ar-H</td>
<td></td>
</tr>
<tr>
<td>6.76 [6.84]</td>
<td>d (( \text{J} = 15.3 \text{ Hz} ))</td>
<td>1H</td>
<td>CH=CH-CO</td>
<td></td>
</tr>
<tr>
<td>7.31</td>
<td>m</td>
<td>5H</td>
<td>Ar-H</td>
<td></td>
</tr>
<tr>
<td>7.74 [7.77]</td>
<td>d (( \text{J} = 15.3 \text{ Hz} ))</td>
<td>1H</td>
<td>CH=CH-CO</td>
<td></td>
</tr>
</tbody>
</table>

\[ ^{13}\text{C NMR and DEPT 135} \]: \( \delta 48.27 \) (t, CH\(_2\)-CH=CH), \( 49.13 \) (t, CH\(_2\)Ph), \( 56.18 \) (q, 2 X OCH\(_3\)), \( 60.94 \) (q, OCH\(_3\)), \( 105.16 \) (d, C-2 and C-6), \( 116.80 \) (d, -CO-CH=CH-), \( 124.55 \) (d, Ph-CH=CH-), \( 126.42-129.00 \) (d, C\(_{\text{ArH}}\)), \( 130.90 \) (s), \( 132.17 \) (d, -CH=CH-Ph), \( 137.55 \) (s), \( 139.73 \) (s), \( 143.57 \) (d, -CH=CH-CO), \( 153.40 \) (s), \( 166.97 \) (s, CO).
The *trans* unsaturated amide 29 was then heated in refluxing diphenyl ether for 10 h under nitrogen atmosphere, followed by chromatography gave diastereomers in 65.00%. 

![Fig 1a](image1)

![Fig 1b](image2)
Having successful synthesised, one terahydronaphthalene lignan we thought of extending this methodology for the synthesis of heterolignans.

Indole-3-carboxyaldehyde was heated with phosphorane 29 in xylene for 12 h. Purification of the crude mixture by flash column chromatography gave compound 34 (Scheme XIX). Compound 34 on HPLC analysis indicated to be a single pure compound.

The solid compound 34, MP = 244-246°C (Yield = 62.30%), in its IR spectrum showed bands at 1678 and 3300 cm\(^{-1}\) indicating the presence of carbonyl group of lactam ring and nitrogen of indole group respectively.

In its \(^1\)HNMR (300 MHz, CDCl\(_3\)) (Fig 2a) spectrum a multiplet (1H) seen at δ 2.5 could be attributed to proton of 9a-H. One multiplet at δ 2.75 (1H) could be attributed to proton of 6a-H group. One multiplet (1H) at δ 2.90 could be attributed to proton of 6-H. Multiplet (3H) seen at δ 3.10-3.60 could be attributed to protons of 9-H\(_2\) and 6-H group. One doublet was seen at δ 4.07 (1H, J = 10.5 Hz) which could be attributed to methine proton of 10-H. One doublet seen at δ 4.35 [4.64] (2H, J = 15 Hz) could be attributed to benzylic methylene protons. In the aromatic region two multiplets were seen at δ 7.14-7.37 (13H) and 7.60 (1H) could be
attributed to aromatic protons. The coupling constants were attributed based on the decoupling experiment.
The possible cyclisation mode of the intermediate Wittig products is given below (Fig VIIa)
Hydrogen should be shielded due to the presence of equatorial indole.

Fig VIIa

OR

Fig VIIb
Based on which diene system acts as a dienophile, mixture of products was possible (Fig VIIa,b). In one case, if unsaturated amide acts as a diene then it could give 34 (regioisomeric mixture) or it may act as a dienophile as observed in the earlier example of trimethoxy benzaldehyde leading to 30 (regioisomeric mixture). Both the possibilities with the endo and exo transition states are depicted in Fig VIIa,b.

Decoupling experiment indicated anti-anti relationship of the hydrogen of the cyclohexene ring ($J = 12 \& 10$ Hz). This excluded the two possible compounds A and C, to be formed via endo transition state. The other two possible products could be B and D to be formed by exo transition state. If compound D was formed it was expected that one of the aromatic proton (Fig VIIb) of the tetrahydronaphthalene should have appeared at upfield around $\delta 6.7$ as a doublet which was not seen in the spectrum. Also proton on nitrogen of indole was observed at comparative upfield region at $\delta 7.5$ suggesting structure B (34) over structure D for the product obtained. The chemical shift of the axial benzylic methine proton ($\delta 4.07$) could be due to its diallylic nature. However the possibility that the proton is not equatorial (Fig VIIc, structure E) was ruled out based on coupling constant and the geometrical requirements for the transition state. For the formation of E the double bond of the dienophile should be cis and stable Wittig reagents give mostly exclusively trans-product.

The structure of compound 34 was further supported by its $^{13}$C NMR and DEPT 135 spectra (Fig 2b). Thus, the peak at 21.90 (t) could be assigned to the methylene carbon of six membered ring. Peak at 46.78 (t) could be assigned to methylene carbon of lactam ring. Peak at 49.40 (t) could be attributed to benzylic methylene
Peaks at 45.55 (d), 45.59 (d) and 46.61 (d) could be assigned to three methine carbons of six membered ring. Peaks at 110.87 (d), 118.41 (d), 119.67 (d), 121.97 (d), 127.26 (d) - 129.14 (d) could be attributed to aromatic methine carbons. The quaternary carbons appearing at 111.35 (s), 127.27 (s), 135.51 (s), 136.40 (s), 136.64 (s), and 140.21 (s) could be attributed to aromatic carbons. Peak at 174.86 (s) could be assigned to carbonyl carbon of lactam. HRMS data confirmed the elemental composition as C_{27}H_{24}ON_2 (Observed: m/z 416.1819, calculated for [M+Na]^+ = 416.1865).

Thus on the basis of mode of formation & spectral properties, structure 34 was assigned to it.

The successful synthesis of the indole heterolignan by tandem Wittig reaction and Diels Alder reaction methodology opened new possibilities for the preparation of many analogues of heterolignan. We have extended this methodology for the synthesis of furano lignans. Thus, 2-furyl aldehyde was condensed with phosphorane 27 in refluxing diphenyl ether for 8 h. The crude reaction mixture when subjected to column chromatography gave a liquid compound (Scheme XX).
The liquid compound 38 in its IR spectrum showed a band at 1670 cm\(^{-1}\) indicating the presence of carbonyl carbon of lactam ring. Its \(^1\)H NMR spectrum had signals at \(\delta\) 2.2-3.2 (m, 6H) could be assigned to 4a-H, 5-H\(_2\), 7a-H, 8-H\(_2\) group. One broad doublet at \(\delta\) 3.7 (1H, \(J = 10.5\) Hz) could be attributed for the methine proton attached to the furan ring. One doublet of doublet (2H, \(J = 14.7\) Hz) at \(\delta\) 4.4-4.5 could be attributed for benzylic methylene group. One doublet at \(\delta\) 5.93 (1H, \(J = 1.8\) Hz) could be attributed to 3-H of furan ring. In aromatic region one multiplet at \(\delta\) 7.3 (11H) could be attributed to benzene protons and 2-H of furan ring. In addition to these major peaks, some minor peaks were observed close by the major ones. This suggested that this is in fact a mixture of two regioisomers. The ratio of the two compounds based on the NMR spectrum is calculated to be 1:2.5 (yield = 70.10).

The possible mode of cycloaddition is depicted below (fig VIIIa,b)
Depending upon the mode of cyclisation (endo and exo) and the nature of diene and dienophile four isomeric products were visualized (Fig VIIIa,b). Products 39a and 39b were expected to show two doublets ($J = 3.6 \, \text{Hz}$) for the C-3 & C-4 protons for furan ring at around $\delta \, 6.0$, where as 38a and 38b were expected to show one doublet ($J = 1.8 \, \text{Hz}$) for one C-3 proton. As the spectrum showed a doublet ($J = 1.8 \, \text{Hz}$) at $\delta \, 5.93$ for one proton the product is a mixture of 38a and 38b. This was further supported by $^{13}$C NMR spectrum where it shows only two methine furan carbons. From NMR values we could not decide the major and the minor product. We were also not able to separate the isomers by chromatographic methods. We assumed the endo product 38a as a major product and exo 38b as the minor product based on literature precedence for the endo cyclisation of similar Diels-Alder reaction products.

The $^{13}$C NMR and DEPT of the product obtained are mentioned below.

\[
\begin{align*}
\delta & \quad 24.14 \, (t, \, C-8), \, 41.38 \, (d, \, C-4a), \, 45.12 \, (d, \, C-7a), \, 46.70 \, (d, \, C-4), \, 48.43 \, (t, \, C-5), \\
& \quad 49.28 \, (t, \, \text{CH}_2-\text{Ph}), \, 109.85 \, (d, \, C-3), \, 121.50 \, (s), \, 126.8-128.63 \, (d, \, \text{CArH}), \, 136.41 \, (s), \\
& \quad 140.95 \, (s), \, 141.7 \, (d, \, C-2), \, 150.39 \, (s), \, 174.07 \, (s, \, \text{CO}).
\end{align*}
\]

HRMS data confirmed the elemental composition as C$_{23}$H$_{21}$NO$_2$ (Observed: $m/z$ 366.1474, calculated for [M+Na]$^+$ = 366.1470).

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We have also carried out the synthesis of 38a-b in stepwise manner (Scheme XXI). Thus 2-furylaldehyde was condensed with phosphorane 27 in refluxing chloroform. The usual work up and purification produced a thick liquid.

Based on the mode of formation & spectral properties mentioned below, structure 37 was assigned to the liquid obtained. The coupling constant of the vinyl protons (J = 15.3 Hz) indicated trans geometry to the product (yield = 86.80%).

\[
\text{IR (v}_{\text{max}}\text{): 1655 cm}^{-1} \text{ (CO).}
\]

\[
\begin{array}{|c|c|c|}
\hline
\delta & \text{NMR} (\text{CDCl}_3, 300 \text{ MHz}) & \\
\hline
4.17 [4.26] & \text{d (J = 5.1 Hz)} & 2H & \text{CH}_2-\text{CH}= \\
4.71 [4.78] & \text{s} & 2H & \text{CH}_2-\text{Ph} \\
6.20 & \text{m} & 1H & \text{CH}_2-\text{CH}= \\
6.46-6.58 & \text{m} & 3H & 3-H, 4-H, \& =\text{CH-CO} \\
6.81-6.86 & 2 \times \text{d (J = 15.3 Hz)} & 1H & \text{CH=CH-Ph} \\
7.34-7.44 & \text{m} & 11H & 5-H \& \text{Ar-H} \\
7.58-7.63 & \text{d (J = 15.3 Hz)} & 1H & \text{CH=CHCO} \\
\hline
\end{array}
\]

\[
\text{IR (v}_{\text{max}}\text{): 1655 cm}^{-1} \text{ (CO).}
\]

\[
\text{1H NMR (CDCl}_3, 300 \text{ MHz):}
\]

Thus, trans unsaturated amide 37 was then heated in refluxing diphenyl ether for 8 h under nitrogen atmosphere, followed by chromatography separation gave \(\gamma\)-lactams 38a-b in 80.00%.
We also prepared the regioisomer of 38a-b. Thus, 3-turyl aldehyde was heated with phosphorane 27, in refluxing diphenyl ether. The product was separated from triphenylphosphine oxide by flash chromatography (Scheme XXII).

IR (v max): 1673 cm⁻¹ (CO).

\(^1\)H NMR (300 MHz, CDCl₃):

<table>
<thead>
<tr>
<th>δ</th>
<th>2.20-3.40</th>
<th>m</th>
<th>6H</th>
<th>4-H₂, 4a-H, 7-H₂, 7a-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>3.93</td>
<td>brd (J = 9.6 Hz)</td>
<td>1H</td>
<td>8-H</td>
</tr>
<tr>
<td>δ</td>
<td>4.30 [4.60]</td>
<td>d (J = 14.7 Hz)</td>
<td>2H</td>
<td>CH₂Ph</td>
</tr>
<tr>
<td>δ</td>
<td>6.30</td>
<td>d (J = 1.8 Hz)</td>
<td>1H</td>
<td>3-H</td>
</tr>
<tr>
<td>δ</td>
<td>6.84-7.20</td>
<td>m</td>
<td>11H</td>
<td>Ar-H &amp; 2-H</td>
</tr>
</tbody>
</table>
CNMR and DEPT 135 (CDCl3): δ 22.58 (t, C-4), 41.76 (d, C-7a), 45.44 (d, C-4a), 46.41 (d, C-8), 46.72 (t, C-7), 49.70 (t, CH₂Ph), 110.59 (d, C-3), 118.95 (s), 127.36-128.65 (d, C₆H₅), 136.40 (s), 139.57 (s), 142.13 (d, C-2), 151.06 (s), 174.28 (s, CO).

HRMS data confirmed the elemental composition as C₂₃H₂₁NO₂ (Observed: m/z 366.1464, calculated for [M+Na]⁺ = 366.1470). The yield of the compound was found to be 67.90%.

Again from the PMR spectrum, we could not assign the stereochemistry at the ring junction due to overlapping signals. The product is a mixture in the ratio 1:2.5. We assumed the major product obtained cis fused (42a) formed via endo transition state. The other minor product could be product obtained from exo transition state (trans fused, 42b).

The other possible structures 43a & 43b (Fig IX) were discarded as the PMR spectrum had only one proton at δ 6.33. If compounds 43a and 43b were formed, additional signals in the region 6.0-6.5 would have been present. Besides, its ¹³C NMR spectrum were also devoid of additional furan methine carbon signals. The formation of product 42a & 42b was assumed to be formed from trans unsaturated amide intermediate.

![Fig IX](image_url)

To confirm the structure of the intermediate we separately isolated the Wittig product (trans unsaturated amide) and carried out (4+2) intramolecular Diels-Alder reaction (Scheme XXIII).
Based on mode of formation and spectral properties mentioned below, structure 41 was assigned to the compound. The high coupling constant \((J = 15.6 \text{ Hz})\) of the vinyl protons indicated trans geometry to the product (yield = 88.20%).

**IR \((v_{\text{max}})\):** 1658 cm\(^{-1}\) (CO).

**\(^1\text{H NMR (CDCl}_3, 300 \text{ MHz)}\):**

<table>
<thead>
<tr>
<th>(\delta)</th>
<th>Multiplicity</th>
<th>J (Hz)</th>
<th>Number</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.15 [4.28]</td>
<td>brd</td>
<td></td>
<td>2H</td>
<td>(\text{CH}_2\text{-CH=})</td>
</tr>
<tr>
<td>4.69 [4.77]</td>
<td>s</td>
<td></td>
<td>2H</td>
<td>(\text{CH}_2\text{-Ph})</td>
</tr>
<tr>
<td>6.19</td>
<td>m</td>
<td></td>
<td>1H</td>
<td>(\text{CH}_2\text{-CH=})</td>
</tr>
<tr>
<td>6.48-6.58</td>
<td>m</td>
<td></td>
<td>3H</td>
<td>(\text{CH}=\text{CH-Ph, 4-H}) &amp; (\text{CH}=\text{C}=\text{O})</td>
</tr>
<tr>
<td>7.28-7.36</td>
<td>m</td>
<td></td>
<td>11H</td>
<td>(\text{Ar-H &amp; 5-H})</td>
</tr>
<tr>
<td>7.65</td>
<td>brs</td>
<td></td>
<td>1H</td>
<td>2-H</td>
</tr>
<tr>
<td>7.98</td>
<td>d (J = 15.6 Hz)</td>
<td></td>
<td>1H</td>
<td>(\text{CH}=\text{CHCO})</td>
</tr>
</tbody>
</table>

**\(^{13}\text{C NMR and DEPT 135 (CDCl}_3\):** \(\delta\) 48.70 (t, \(\text{CH}_2\text{-CH=}\)), 48.90 (t, \(\text{CH}_2\text{Ph}\)), 107.49 (d, -\(\text{CHCO}\)), 116.91 (d, C-4), 123.06 (s), 126.44 (d, \(\text{CH}=\text{CHPh}\)), 127.70-128.97 (d, \(\text{C}_{\text{ArH}}\)), 132.125 (d, \(\text{CH}=\text{CH-CO-}\)), 133.66 (d, \(\text{CH}=\text{CH-Ph}\)), 144.19 (d, C-2 \& C-5), 167.02 (s, CO).
Thus, *trans* unsaturated amide 41 upon, refluxing in diphenyl ether for 8 h, followed by purification of crude product by flash chromatography gave compound 42 in 79.10% yield, and they were formed in 1:2.5 ratio.

For the synthesis of furanoindole lignans, indole-3-carboxyaldehyde was condensed with the phosphorane 44 in refluxing diphenyl ether for 8 h. Separation of reaction mixture by flash chromatography gave a solid compound (Scheme XXIV).

![Scheme XXIV](image)

HPLC analysis of the compound indicated that it's a mixture of two compounds in a ratio of 1:3.

The solid compound 46, MP =212-214°C, (Yield = 60.30%) IR showed bands at 1750 and 3230 cm⁻¹ indicating the presence of carbonyl group of lactone and nitrogen proton of indole group respectively.

In its ¹HNMR (300 MHz, CDCl₃) spectrum showed three multiplets at δ 2.7 (3H), 3.4 (1H), 4.3 (3H) which could be attributed to the protons of six membered ring and lactam ring. Multiplet (9H) seen at δ 7.14 - 7.64 could be attributed to aromatic protons. One singlet at δ 8.40 could be attributed to indole nitrogen proton.
The structure was further supported by its $^{13}$C NMR and DEPT spectra. Thus, a peak at 21.12 (t) could be assigned to the methylene carbon of six membered ring. Peaks at 42.72 (d), 46.00 (d), 48.39 (d) could be assigned to methine carbons of six membered ring. Peak at 68.99 (t) could be assigned to methylene carbon of lactam ring. Peaks at 111.10 (d), 117.43 (d), 118.44 (d), 119.58 (d), 120.99 (d), and 125.32 (d) -129.85 (d) could be attributed to aromatic methine carbons. The quaternary carbons appearing at 134.75 (s), 136.51 (s), 139.33 (s), 141.80 (s) could be attributed to aromatic carbons. The peak at 176.62 (s) could be assigned to carbonyl carbon of γ-lactam.

HRMS data confirmed the elemental composition as $\text{C}_{20}\text{H}_{17}\text{O}_2\text{N}$ (Observed: $m/z$ 326.1157, calculated for $[\text{M+Na}]^+ = 326.1142$).

The possible cyclisation mode of the intermediate Wittig products is given below (Fig Xa)
Based on our previous assumption for indolepyrallo lignan which have anti-anti relationship of the hydrogen of cyclohexene ring. We assumed similar stereochemistry for this compound. Our attempts to carry out decoupling failed to conclusively establish the stereochemistry.
We assumed trans adduct (46b) is formed via exo transition state and the minor product 46a (cis adduct) formed from endo transition state. The other two possibilities 47a & 47b were eliminated due to the absence of expected additional signal in the region in PMR at around δ 6.3 (d, J = 8 Hz) due to the benzene protons being shielded by equatorial indole ring.

To confirm the geometry of the intermediate, we separately prepared the Wittig product and then carried out the cyclisation reaction (Scheme XXV).

Based on the mode of formation & spectral properties mentioned below, structure 45 was assigned as Wittig product. Based on the coupling constant of the vinyl protons (J = 15.9 Hz) indicated the trans geometry to the product (yield = 70.20%).

IR (ν_max): 1658 cm⁻¹ (CO).

¹H NMR (CDCl₃, 300 MHz): (Fig 3a)

<table>
<thead>
<tr>
<th>δ</th>
<th>Assignment</th>
<th>2H</th>
<th>CH₂-CH=CH</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.9</td>
<td>d (J = 5.7 Hz)</td>
<td>1H</td>
<td>CH₂-CH=CH</td>
</tr>
<tr>
<td>6.38</td>
<td>m</td>
<td>1H</td>
<td>CH-CHO-</td>
</tr>
<tr>
<td>6.53</td>
<td>d (J = 15.9 Hz)</td>
<td>1H</td>
<td>CH₂-CH=CH</td>
</tr>
<tr>
<td>6.75</td>
<td>d (J = 16.2 Hz)</td>
<td>1H</td>
<td>CH₂-CH=CH</td>
</tr>
<tr>
<td>7.25-7.53</td>
<td>m</td>
<td>9H</td>
<td>Ar-H</td>
</tr>
<tr>
<td>7.95</td>
<td>brs</td>
<td>1H</td>
<td>2-H</td>
</tr>
<tr>
<td>8.01</td>
<td>d (J = 15.9 Hz)</td>
<td>1H</td>
<td>CH=CH=CO-</td>
</tr>
<tr>
<td>8.50</td>
<td>brs</td>
<td>1H</td>
<td>NH</td>
</tr>
</tbody>
</table>
$^{13}$C NMR and DEPT 135 (Fig 3b): $\delta$ 64.79 (CH$_2$-CH=), 111.7 (d, C-7), 113.10 (d, CH-CO), 113.67 (s), 120.50 (d, C-4), 121.57 (d, C-6), 123.38 (d, C-5), 123.77 (d, C-2), 125.30 (s), 126.62 (d, CH=CH-Ph), 127.95-128.88 (d, CAH), 133.88 (d, CH=CH-Ph), 136.38 (s), 137.07 (s), 138.68 (d, CH=CH-CO$^-$), 167.98 (s, CO).

The $\textit{trans}$ unsaturated ester 45 was heated in refluxing diphenyl ether for 8 h, followed by purification by chromatography gave tetracyclic $\gamma$-lactams in 62.5%.
Conclusion:

1) We have successfully synthesized the podophyllotoxin analogues by using tandem Wittig Diels-Alder reaction.

2) By using tandem sequence we have synthesized four different heterolignans.
Experimental section:

Expt. 2.4.1: Preparation of N-benzyl-3-phenylprop-2-en-1-amine (24).

\[
\begin{align*}
\text{H}_2\text{N} &\quad \text{Ph} \\
\text{NaBH}_4 &\quad \text{DCM, MeOH} \\
\text{Mol. Seives} &\quad \text{24}
\end{align*}
\]

Benzyl amine (1.95 mL, 18.18 mmol) was added to a stirred solution of cinnamaldehyde (2 g, 15.15 mmol), sodium borohydride (0.84 g, 22.7 mmol) in dichloromethane (50 mL) containing 4 Å molecular sieves (0.4 g). The mixture was stirred for 2 h. The reaction mixture was cooled to 0°C. Methanol (5 mL) was added and stirring continued at 0°C for 10 min. The reaction mixture was allowed to come to room temperature and further stirred for 30 min. It was then filtered and the residue washed with ethyl acetate (25 mL). The combined filtrate was concentrated and ether (50 mL) and water (25 mL) were added. The ether layer was separated, dried over sodium sulphate and concentrated. Purification by silica gel column chromatography (ethyl acetate and hexanes, 8:2) gave a desired liquid product (2.3 g, 68.70%).


\[
\begin{align*}
\text{NH} &\quad \text{Ph} \\
\text{bromoacetyl bromide} &\quad \text{K}_2\text{CO}_3, \text{CHCl}_3 \\
\text{25}
\end{align*}
\]

A solution of N-benzyl-3-phenylprop-2-en-1-amine (1.8 g, 8.14 mmol) and potassium carbonate (1.1 g, 8.14 mmol) in dry chloroform (20 mL) was cooled to 0°C. Bromoacetyl bromide (1.6 g, 8.14 mmol) was added dropwise with stirring over a period of 10 min. The mixture was stirred for 1 h at 0°C and further at room temperature for 1 h. To the reaction mixture water (15 mL) was added and extracted in chloroform (2 x 20 mL). The chloroform layer was dried over sodium
sulphate and was removed under vacuum pump to give yellow liquid (2.4 g, 86.33%).

**Expt. 2.4.3: Preparation of N-benzyl-N-[(2E)-3-phenylprop-2-en-1-yl]-2-(triphenylphosphoranylidene) acetamide (27).**

![Chemical structure of 25](image)

![Chemical structure of 27](image)

The solution of N-benzyl-2-bromo-N-[(2E)-3-phenylprop-2-en-1-yl]acetamide (1.5 g, 4.4 mmol) & triphenyl phosphine (1.2 g, 4.4 mmol) in dry benzene (10 mL) was stirred overnight at RT. The salt formed was dissolved in water (50 mL), benzene (40 mL) was added and 2N sodium hydroxide solution was added to the solution with stirring to phenolphthalein end point. The benzene layer was separated and the aqueous layer was extracted with benzene (2 X 20 mL). The combined benzene layer was dried over anhy. sodium sulphate and the solvent removed under vacuum pump to give N-benzyl-N-[(2E)-3-phenylprop-2-en-1-yl]-2-(triphenylphosphoranylidene) acetamide (27) (1.7 g, 73.90%).

**Expt. 2.4.4: Preparation of (2E)-3-phenylprop-2-en-1-yl bromoacetate.**

![Chemical structure of 218](image)

A solution of cinnamyl alcohol (2.0 g, 14.39 mmol) & pyridine (1.1 mL, 14.39 mmol) in dry chloroform (20 mL) was cooled to 0°C. Bromoacetyl bromide (2.9 g, 14.39 mmol) was added dropwise with stirring over a period of 15 min. The mixture was stirred for 1 h at 0°C and further at room temperature for 1 h. To the reaction mixture water (20 mL) was added and extracted in chloroform (2 X 25 mL). The organic layer was washed with 2N HCl (2 X 15 mL), sat. sodium
bicarbonate (2 X 20 mL) and finally with water (20 mL). The chloroform layer was dried over sodium sulphate and was evaporated under vaccuo to give yellow liquid (3.7 g, 92.5%).

Expt. 2.4.5: Preparation of (2E)-3-phenylprop-2-en-1-yl (triphenylphosphoranylidene)acetate (44).

![Conversion reaction](image)

The solution of (2E)-3-phenylprop-2-en-1-yl bromoacetate (2.1 g, 7.6 mmol) & triphenylphosphine (2 g, 7.6 mmol) in dry benzene (20 mL) was stirred overnight at RT. The salt formed was filtered and dissolved in methanol (5 mL). To this water (20 mL), benzene (40 mL) was added and then 2N sodium hydroxide solution was added with stirring to phenolphthalein end point. The benzene layer was separated and the aqueous layer was extracted with benzene (2 X 20 mL). The combined benzene layer was dried over anhy. sodium sulphate and the solvent removed under vaccum pump to give (2E)-3-phenylprop-2-en-1-yl (triphenylphosphoranylidene)acetate (2.5 g, 71.42%).

Expt. 2.4.6: General procedure for the synthesis of unsaturated amides and ester.

A solution of aromatic/heteroaomatic aldehyde (1 mmol) & N-benzyl-N-[((2E)-3-phenylprop-2-en-1-yl]-2-(triphenylphosphoranylidene)acetamide (27)/phosphorane 44 (1.5 mmol) in chloroform/xylene (10 mL) was refluxed for 1 to 5 h. The solvent was evaporated under reduced pressure to leave crude product which was subjected to column chromatography over silica gel using hexanes and ethyl acetate (9:2) as solvent.
Expt. 2.4.7: Tandem Wittig-Diels Alder reaction: Preparation of tricyclic γ-lactam/lactone.

A solution of aromatic/heteroaromatic (1 mmol) & N-benzyl-N-[2E]-3-phenylprop-2-en-1-yl)-2-(triphenylphosphoranylidene)acetamide (1.5 mmol) in diphenyl ether/xylene (10 mL) was refluxed under nitrogen atmosphere for 8 to 12 h. The crude mixture was subjected to flash column chromatography over silica gel using hexanes to remove diphenyl ether first and further elution with 30-50% ethylacetate and hexanes to afford diastereomeric γ-lactams/lactone.
<table>
<thead>
<tr>
<th>Expt. No</th>
<th>Substrate</th>
<th>Product</th>
<th>Nature</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4.7.1</td>
<td>(\text{H}_3\text{C}0\text{CHO})</td>
<td><img src="image1.png" alt="Product 1" /></td>
<td>Solid (m.p. 80-81°C)</td>
<td>62.10%</td>
</tr>
<tr>
<td>2.4.7.2</td>
<td>(\text{CHO})</td>
<td><img src="image2.png" alt="Product 2" /></td>
<td>Solid (m.p. 244-246°C)</td>
<td>62.30%</td>
</tr>
<tr>
<td>2.4.7.3</td>
<td>(\text{CHO})</td>
<td><img src="image3.png" alt="Product 3" /></td>
<td>Liquid</td>
<td>70.10%</td>
</tr>
<tr>
<td>2.4.7.4</td>
<td>(\text{CHO})</td>
<td><img src="image4.png" alt="Product 4" /></td>
<td>Liquid</td>
<td>67.90%</td>
</tr>
<tr>
<td>2.4.7.5</td>
<td>(\text{CHO})</td>
<td><img src="image5.png" alt="Product 5" /></td>
<td>Solid (m.p. 212-214°C)</td>
<td>60.30%</td>
</tr>
</tbody>
</table>
Expt. 2.4.8: Preparation of tricyclic γ-lactam/lactone from amides/ester.

Unsaturated amide/esters was refluxed in diphenyl ether (10 mL) for 8 to 10 h under nitrogen atmosphere. The crude mixture was subjected to column chromatography using hexanes to remove diphenyl ether first and further elution with 30-40% ethylacetate and hexanes to afford diastreomeric γ-lactams/lactone.

<table>
<thead>
<tr>
<th>Expt. No</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4.8.1</td>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td><img src="image2.png" alt="Product 1" /></td>
<td>65%</td>
</tr>
<tr>
<td>2.4.8.3</td>
<td><img src="image3.png" alt="Substrate 2" /></td>
<td><img src="image4.png" alt="Product 2" /></td>
<td>80%</td>
</tr>
<tr>
<td>2.4.8.4</td>
<td><img src="image5.png" alt="Substrate 3" /></td>
<td><img src="image6.png" alt="Product 3" /></td>
<td>79%</td>
</tr>
<tr>
<td>2.4.8.5</td>
<td><img src="image7.png" alt="Substrate 4" /></td>
<td><img src="image8.png" alt="Product 4" /></td>
<td>62%</td>
</tr>
</tbody>
</table>
References:


18) a) MacRae, W. D.; Toweres, G. H. N. *Phytochemistry* 1984, 23, 1207.


30) Rao, C. B. S. *Chemistry of lignan; Andra University press; Waltair, 1978.*


